Development of a Pharmacoeconomic model to compare the cost-effectiveness of low versus high dose colistin in the treatment of nosocomial pneumonia caused by Multi-Drug Resistant (MDR) Gram Negative Bacteria in Saudi Arabia

Student name

Abdul Karim Suleman Cara

(214515660)

UNIVERSITY OF KWAZULU-NATAL

INYUVESI YAKWAZULU-NATALI

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Supervisor

Prof. Fatima Suleman

Co-supervisor

Dr. Syed Tabish Razi Zaidi

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PREFACE

This dissertation is presentation in article format. The findings are presented in chapter 3 in manuscript format as required by the regulations of the University of KwaZulu-Natal. The manuscript was submitted for publication in the International Journal of Clinical Pharmacy.

DECLARATION 1 - PLAGIARISM

I, Abdul Karim Suleman Cara, declare that:

1. The research reported in this thesis, except where otherwise indicated, and is my original work.
2. The work described in this dissertation has not been submitted for any degree or examination at any other university.
3. This dissertation does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written resources have been quoted, then:

a) Their words have been re-written but the general information attributed to them has been referenced.

b) Where their exact words have been used, then their writing has been placed inside quotation marks, and referenced.

4. This dissertation does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the thesis and in the reference sections.

Signed:  Name: Abdul Karim Suleman Cara Date 28 July 2017

This is to certify that the contents of this thesis are the original work of Abdulkarim Suleman Cara and as the candidate's supervisor; I have approved this thesis for submission.

1. Signed: Tabish Zaidi Name: Dr. Syed Tabish Razi Zaidi Date: 17/04/2018

2. Signed: Fatima Suleman Name: Prof. Fatima Suleman Date: 17/04/2018

DECLARATION 2 – ETHICS APPROVAL

The study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments and in compliance with International Conference on Harmonization, Good Clinical Practices, and all applicable regulatory guidelines.

Full ethical approval for the study was obtained from King Abdullah International Medical Research Centre (HAS-16-437780-10741) on 19 January 2016 (Annexure 1) and from the Humanities and Social Sciences Research Ethics Committee of the University of KwaZulu-Natal (HSS/0975/015M) on 29 January 2016 – (Annexure 2).

Patient confidentiality was maintained always and no patient hospital numbers, names or date of birth/identification numbers were reported in the data sets.

DECLARATION 3 – MANUSCRIPT PUBLICATION

1. My contribution to the project was as follows:

   Abdul Karim Suleman Cara: Principle Investigator – contributed to the project by performing all literature reviews, data and statistical analyses, interpretation of the results as well as manuscript preparation and writing of dissertation.

2. The contributions of others to the project were as follows:

   Prof. Fatima Suleman: Supervisor – supervision of the concept of the study and review of the dissertation and manuscript.

   Dr. Syed Tabish Razi Zaidi: Co-Supervisor – supervision of the concept of the study and review of the dissertation and manuscript.

DEDICATION

I dedicate this thesis to my mom and offer gratitude to my dad, sisters, children and especially my wife Fiona, without whose support, understanding and encouragement, this paper would not have been possible.

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Mr. Syed Ahmed for his assistance in collecting laboratory data.

ACRONYMS AND ABBREVIATIONS

AB	:	Acinetobacter Baumannii
CBA	:	Cost-benefit analysis
CBC	:	Complete blood count
CEA	:	Cost-effectiveness analysis
CMA	:	Cost-minimization analysis
COPD	:	Chronic obstructive pulmonary disease
CUA	:	Cost-utility analysis
GW	:	General ward
HAP	:	Hospital Acquired Pneumonia
HDC	:	High dose colistin
ICU	:	Intensive Care Unit
KAH	:	King Abdulaziz Hospital
KP	:	Klebsiella Pneumoniae
KSA	:	Kingdom of Saudi Arabia
LDC	:	Low dose colistin
LOS	:	Length of stay
MDR-GNB	:	Multi-Drug Resistant Gram Negative Bacteria
NP	:	Nosocomial Pneumonia
PA	:	Pseudomonas Aeruginosa
PE	:	Pharmacoeconomics
QOL	:	Quality of Life
SAR	:	Saudi Arabian Riyal
VAP	:	Ventilator Associated Pneumonia
WBC	:	White blood cell count

ABSTRACT

Introduction

The emergence of multi-drug resistant bacteria has led to higher treatment failure and a subsequent increase in patient mortality. Limited treatment options are available for Gram-negative bacteria (GNB) that are resistant to carbapenam antibiotics. Colistin is considered as the last resort treatment options for the carbapenamase producing GNB, though occasional reports of colistin resistance has been noted in the literature. Available studies show efficacy with both doses and with variable levels of adverse effects. In the absence of consensus regarding a dosing strategy for colistin, a model comparing low and high dose colistin in the treatment of nosocomial pneumonia will serve as a useful tool in decision making.

Methods

A decision–analytic model using data obtained from a retrospective review of patients treated for nosocomial pneumonia at King Abdulaziz Hospital, Saudi Arabia, was developed to compare the costs and outcomes of low dose versus high dose colistin in the treatment of nosocomial pneumonia caused by colistin-only sensitive bacteria. Outcome measures used in the analysis were length of antibiotics use, length of hospital stay, cure and nephrotoxicity in order to calculate the mean total cost of treatment, incremental costs, cost effectiveness ratios and incremental cost effectiveness ratios.

Results

There was a total of 171 patients that received colistin during the study period of which 96 met the inclusion criteria. Of the remaining patients 33 received high dose and 63 received low dose colistin. Low dose colistin was associated with a non-significant 9% lower cure rate than high dose colistin (21% vs 30%, respectively; p=0.292). Low dose colistin was associated with a 22% lower incidence of nephrotoxicity than HDC (30% vs 8%, respectively) which was found to be significant (p=0.004), respectively. Low dose colistin was associated with similar cure rates and greater cost savings resulting from nephrotoxicity being avoided compared to high dose colistin (ICER = -SAR 13, 894.66 per nephrotoxicity avoided).

Conclusion

Low dose colistin was not inferior to high dose colistin in terms of clinical cure and had a lower incidence of nephrotoxicity resulting in significant cost avoidance. The cost–benefit profile suggests that low dose colistin could be considered a more cost-effective option than high dose colistin in the treatment of patients with pneumonia caused by MDR-GNB in Saudi Arabia. King Abdulaziz Hospital should adopt the low dose colistin strategy for treatment of nosocomial pneumonia caused by colistin-only sensitive gram negative bacteria while taking cognizance of local resistance patterns.

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CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

Hospital Acquired Pneumonia (HAP) is the second most common nosocomial infection in United States(1). Rates of HAP due to multidrug-resistant gram-negative bacteria (MDR-GNB) have escalated in recent years and are a major concern(2). Gram negative pathogens are increasingly resistant to commonly used first line antibiotics and colistin is in most cases the only medicine available against MDR GNB. There are no definite dosing recommendations for colistin with very limited information available comparing the effectiveness of low versus high dose colistin. Given the reported efficacy of low dose colistin in the treatment of MDR GNB(3–5) and the financial burden that Nosocomial Pneumonia (NP) places on the healthcare systems worldwide, it makes good sense to construct an economic model that will allow for the comparison of low and high dose colistin in the treatment of pneumonia caused by colistin-only sensitive MDR GNB. This model will add significantly to the medical literature and assist healthcare professionals in making decisions related to colistin prescribing in critically ill patients.

1.2 BACKGROUND AND RATIONALE

1.2.1 Background

Nosocomial Pneumonia (NP) is defined as pneumonia that occurs after healthcare contact. NP encompasses hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)(1,6). HAP is a lung infection that occurs in non-intubated hospitalized patients 48 hours or more after admission as compared to VAP which occurs 48 hours or more after endotracheal intubation. In the United States of America, HAP is estimated to occur in 5 to 10 patients per 1,000 hospital admissions(1). The incidence of NP is up to twenty times greater in patients receiving ventilator support(7). The incidence of VAP according to the CDC National Healthcare Safety Network report of 2010 is between 0 and 5.8 per 1,000 ventilator days(8). The incidence of VAP in developing countries, however, ranges from 16.7 to 73.4 per 1,000 ventilator-days in adult ICUs(9,10).

For HAP outside the intensive care unit, the mortality is reported to be up to 27.7%(11) and mortality due to VAP, on the other hand has been reported between 24% and 76% depending on the causative organism(12,13). El-Saed et al found that the rates of VAP in three Arabian countries was 4.8/1000 ventilator days(14). The financial burden due to VAP is greater than other nosocomial infections(15) and according to the World Health Organization (WHO), Healthcare Associated Infections (HCAI) contribute 16 million extra days to hospital stay in Europe. The direct cost associated with the disease is approximately $7 billion. In 2004, the cost of HCAI in the US translated into approximately US$ 6.5 billion(16). Estimates of the costs of VAP per patient; range from $12,000 to $25,000. The effect of MDR bacterial infections have been studied and demonstrate an increase in overall costs(17).

Bacterial causes of HAP may include *Klebsiella Pneumonia* (KP), *Enterobacter*, *Serratia* (KES), *Pseudomonas Aeruginosa* (PA), *Acinetobacter species* (AB), *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Methicillin Sensitive Staphylococcus aureus* (MSSA) and *Methicillin resistant Staphylococcus aureus* (MRSA), *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Legionella pneumophila*. Of these MRSA and gram-negative bacilli are the most common bacterial causes of HAP. MRSA frequently causes nosocomial pneumonia, and though this is problematic for the clinician, there are a number of available options such as linezolin and ceftaroline.

Gram negative pathogens are increasingly resistant to commonly used first line antibiotics. The increasing incidence of pneumonia in critically ill patients caused by MDR-GNB resistant to carbapenem antibiotics means that treatment options are quite limited for such patients(2,18,19). MDR-GNB for the purposes of this study is defined as bacteria resistant to aminoglycosides, anti-pseudomonas penicillins, carbapenems, cephalosporins and fluoroquinolones.

Colistin is perhaps one of a few and in most cases the only medicine available against MDR GNB and is recommended by the ATS guidelines(20). Colistin, also known as Polymixin E, is a relatively old antibiotic that was abandoned due to high risk of nephron- and neurotoxicity(21). Despite the toxicities, this old medicine has recently gained favor due to nosocomial infections caused by the emergence of GNB susceptible to colistin(22). Colistin is administered as a pro-drug, colistin methansulphonate(23), which is then converted in the body into the active colistin. Colistin possesses a narrow antibacterial spectrum and is effective against PA, AB and KP(23,24).

Commercially, colistimethate sodium (CMS) is available in 2 forms, namely Colomycin ® (Europe) and Coly-Mycin M ® (USA). Colistin 1mg base is equivalent to approximately 2.4 mg of colistimethate sodium. CMS has a potency of 12,500 IU/mg(22).

Intravenous colistin as Colomycin ® (colistimethate sodium) contains 1 million international units (MIU) powder/vial equivalent to 30,000IU/mg(3). Coly-Mycin M® contains 4.5 million international units (MIU) equivalent to 150 mg colistin base(25). The recommended dose for both these preparations vary greatly; Colomycin® 1.5-2.5 mg /kg/d and for Coly-Mycin M® 2.5-5 mg/kg/day(21).

With concerns surrounding the development of resistance to one of the last resorts against MDR-GNB, there is a huge debate mostly in favor of high dose colistin(21). Recently, doses as high as 10 mg/kg/day have been used(4). However, significant literature exists regarding low dose colistin with comparable effectiveness(4,5). Still, there are however, no definite dosing recommendations and limited information is available about the comparative effectiveness of low versus high dose colistin.

Nephrotoxicity is one of the most commonly cited adverse effects of colistin treatment(18,26–28). A number of factors have been associated with colistin induced nephrotoxicity, such as concomitant nephrotoxic medications(26),(29), body weight(28), hypoalbuminemia(29), advanced aged(29), colistin dose(4) and duration of treatment(27). For this study, the following definition for nephrotoxicity due to colistin was used; increase in serum creatinine by 0.3mg/dL (26.52 µmol/L) or more within 48 hours or increase in serum creatinine to 1.5 times baseline or more within the last 7 days(30).

Given the reported efficacy of low dose colistin in the treatment of MDR GNB(3–5) and the financial burden that NP places on healthcare systems worldwide, it is logical to construct an economic model that will allow the comparison of low and high dose colistin in the treatment of pneumonia caused by colistin-only sensitive MDR GNB. Such a model would be able to capture all clinical outcomes using a probability based decision tree to gauge the benefit and/or harms associated with low dose versus high dose colistin.

1.2.2 Medical expenditure

Medicine expenditure is growing globally. This is well reflected by the fact that prescription medicine expenditures in United States have more than doubled over the last decade; US spent $120 billion on prescription medicines in the year 2000 compared to $263 billion in 2011(31). Similar increasing trends

have been observed across the world where pharmaceutical expenditures per capita in Organization for Economic Co-operation and Development countries have consistently increased over the period of 2008-2013(32). Given the growing pressures of cost containment initiatives arising from global financial crisis, funding decisions are increasingly based on objective analysis of pharmacoeconomic data. Funding bodies in United Kingdom(33) and Australia(34) require pharmacoeconomic and budget impact analysis data at the time of submission for new Health Technology Applications.

The most recent (2007) inflation adjusted US estimates of the cost of health care associated infections derived from 1992 data are in the region of US$6.65 billion(15). The economic impact of NP on hospital costs is significant and even greater in patients who develop VAP(6,35). According to the WHO, estimates of the overall extra costs in ICU for Nosocomial pneumonia is US$2255 per case in some developing countries(35). Studies have also reported on the significant increase in hospital costs as a result of drug-resistant pathogens(36,37).

Given the impact of NP in terms of mortality, length of ICU and hospital stay, added costs and the paucity of information on cost effectiveness of colistin in the treatment of NP caused by colistin only sensitive GNB, such information will add significantly to the medical literature. Studies on the safety and efficacy of colistin abound both with high(24,38) and low doses(3–5). Studies have shown efficacy with both these doses with variable level of adverse effects. The absence of a definite dosing strategy makes a model to compare low and high dose Colistin in the treatment of pneumonia caused by colistin-only sensitive MDR-GNB invaluable in assisting clinicians, hospitals and insurance agencies in making decisions regarding the appropriate use of colistin in critically ill patients.

1.2.3 Principles of Pharmacoeconomics

Pharmacoeconomics (PE) is an established discipline of Health Economics. Several definitions exist for PE but in simple terms, it is a scientific discipline that compares the value of one pharmaceutical agent, service or programme to another to make a conclusion about the preferred choice from a payer, societal or an individual perspective.

There are four economic evaluations that are used, namely, Cost Minimization Analysis (CMA), Cost Benefit Analysis (CBA), Cost effectiveness analysis (CEA) and Cost Utility Analysis (CUA). CMA compares two therapeutically equivalent treatment alternatives to determine the least costly. CBA

compares the benefits and costs of treatment alternatives. The benefits and costs are measured and converted to equivalent dollars and expressed as a benefit to cost ratio.
CEA compares two treatment options for which there is no evidence to support equivalence in safety and efficacy. Costs are measured in dollars and outcomes are measured in nonmonetary terms e.g. lives saved or cases cured. The results of a CEA are expressed as Incremental Cost Effectiveness Ratio (ICER) which is the ratio of health care costs divided by the clinical outcome. CEA therefore deals with cost optimization as compared to cost reduction for CMA.

CUA compares treatment alternatives that include patient preference and health related quality of life (HRQOL). Results of CUA are expressed as a ratio of cost versus utility. Cost-effectiveness analysis is one type of PE analysis that identifies the most economical option when efficacy and safety of comparisons is not similar. Outcomes are measured as increase in effectiveness delivered for each dollar invested.

This study, using the ICER, is intended to assist in containing healthcare costs without adverse health consequences. Conducting an ICER requires that the two interventions have different efficacy and safety profile. This was tested in this study prior to an assessment of costs. In PE, an assessment of costs depends on the perspective of the study and these may include the patients, providers, payer and society. The patient perspective considers all costs incurred by the patient for the healthcare services received and the consequences are more subjective and may include cure or Quality of Life (QoL). The societal perspective considers all costs (direct and indirect) and considers all consequences including QoL. The payer perspective considers cost of delivering the healthcare service and includes personnel and supply costs and considers consequences such as LoS and mortality. This study considered the perspective of the payer with regards to cost and consequences.

The costs include only direct medical costs which relate to administration costs, healthcare provider costs, hospitalization costs, laboratory tests and the cost of medication. In this analysis from a payer's perspective, indirect medical costs such as transportation; indirect non-medical cost such as lost income; and intangible costs such as pain are not considered. Figure 1 provides an outline of PE analysis conducted.

Due to various uncertainties that may arise when performing PE analyses, sensitivity analyses may be used to test the conclusions of the study when these depend on certain assumptions(39). One-way sensitivity analyses allow for the evaluation of the impact of one parameter on the conclusion of the

study. This is done by allowing one variable to be adjusted while keeping the others at the baseline. This allowed for an assessment of which parameters will likely have the greatest impact on the conclusions.

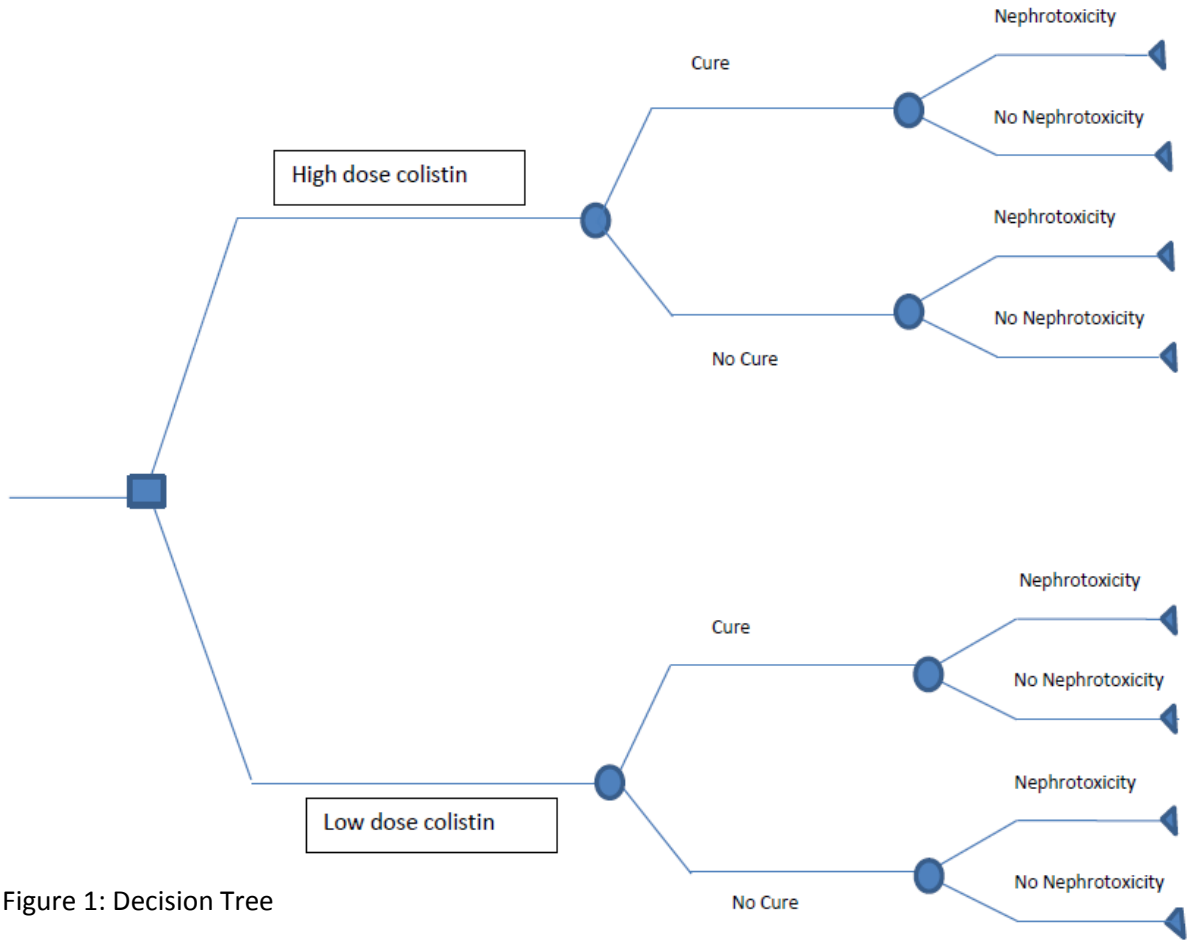

Figure 1: Decision Tree

1.3 Research questions

This study focused on the following research question:

Is low dose Colistin more cost effective than high dose Colistin in the treatment of Pneumonia caused by Colistin-only sensitive gram Negative Bacteria

1.4 Aims and objectives

This study aims to determine the cost effectiveness of low dose versus high dose Colistin in the treatment of Pneumonia caused by Colistin-only sensitive MDR-GNB at a tertiary care hospital in Saudi Arabia.

By the end of the study period, the objectives were to:

1. Calculate and compare the clinical cure rates of low dose Colistin (LDC) and high dose Colistin (HDC) for the treatment of nosocomial pneumonia (NP) due to colistin-only sensitive multi-drug resistant gram –negative bacteria (MDR-GNB).

2. Calculate and compare the incidence of nephrotoxicity in patients receiving LDC and HDC for NP caused by colistin-only sensitive MDR-GNB.

3. Propose an outcome-based economic model to compare LDC and HDC for NP caused by colistin-only sensitive MDR-GNB.

1.5 Significance of the study

HAP due to MDR-GNB has escalated in recent years and is a major concern(2). The increasing incidence of pneumonia in critically ill patients caused by MDR-GNB resistant to Carbapenems limits available treatment options (2,18,19).

In the Kingdom of Saudi Arabia (KSA) there are some studies on incidence of VAP. Memish ZA, et al described the incidence of VAP in a tertiary hospital in Riyadh Saudi Arabia and found the incidence to be 16.8/1000 ventilation days. The most common GNB responsible were *Pseudomonas* then *Acinetobacter species*(40,41). A more recent study by El-Saed et al found that the combined incidence of VAP in three Middle Eastern countries was 4.8/1000 ventilator days(14). This study did not report on the pathogens that were responsible.

To the best of our knowledge, there are no studies reporting on models for the cost effectiveness of low and high dose of intravenous colistin in the treatment of colistin-only sensitive MDR-GNB. This study is intended to clarify the appropriate safe and effective dosing of colistin in the treatment of colistin-only sensitive MDR GNB and assist healthcare professionals in making decisions related to colistin prescribing in critically ill patients.

Such an analysis would be able to capture all clinical outcomes using a probability based decision tree to gauge the benefit and/or harms associated with low dose and high dose colistin. Furthermore, such an

economic model will add significantly to the medical literature and assist healthcare professionals in making decisions related to colistin prescribing in critically ill patients. This will also be beneficial to antimicrobial stewardship programs in their efforts to contain healthcare costs and minimize adverse health consequences.

1.6 Research Methodology

1.6.1 Study design

This study is a retrospective, single-centre cohort design, using cost effectiveness analysis. A pharmacoeconomic model was developed to compare the cost-effectiveness of low versus high dose colistin in the treatment of nosocomial pneumonia caused by MDR-GNB at King Abdulaziz Hospital, AlHasa, Saudi Arabia. All patients receiving colistin for the treatment of nosocomial pneumonia from July 2011 to December 2014 were included in the study. The economic evaluation was conducted from the perspective of King Abdulaziz Hospital and only direct costs, obtained from the hospital business centre 2016 price list, were included in the study.

1.6.2 Data Collection

A standardized case form was used to record patient characteristics, including age, gender, weight, ICU or non- ICU location, renal function, underlying comorbidities using the Charlson comorbidity index, concomitant medications that may be potentially nephrotoxic, causative organism, daily dose of colistin, frequency and duration of colistin therapy, cumulative dose of colistin, clinical response to therapy (defined as resolution of signs and symptoms of infection including absence of fever for a minimum of 72 hours and a white blood cell count below 12 000 cells/ $mm^{3)}$), duration of hospitalization and incidence of acute kidney injury.

1.6.3 Data source

Data was extracted from the electronic records of the Health Information Managements system as well as paper medical records maintained by the Health Information Management department. Records were searched from July 2011 to December 2014 and included all patients treated with colistin. This was then cross referenced with all patients treated for nosocomial pneumonia during the same period. Patients were matched as per inclusion and exclusion criteria. Data was initially collected on the case form and subsequently imported into Microsoft® Excel. Data abstractors that have previous experience with the management of data were oriented to the requirements of the study data but remained blind to the study aims and objectives.

1.6.4 Data Analysis

The primary objectives were to calculate and compare the clinical cure rates (efficacy) and incidence of colistin induced nephrotoxicity (safety). The data was modelled using a decision analysis and each outcome on this model was assigned a cost with the help of hospital business center. Incremental cost effectiveness ratio was calculated for each option considering clinical cure and colistin induced nephrotoxicity.

For all statistical analyses, two-sided significance was used. All p values of 0.05 or less were considered statistically significant providing a 95% confidence interval. Dichotomous data were compared using the Chi-Square test. Normally distributed continuous data were expressed as mean and standard deviation and compared using the Student's t-test. Otherwise, values were presented as medians with ranges and were compared using the Mann – Whitney test. Quantitative variables were analyzed with the chi square test or Fischer's exact test (two-tailed) when necessary. All data was entered in a database and IBM® SPSS® 20.0 software was used to analyze the data.

1.6.5 Data Management

Raw data was imported into Microsoft® Excel. All computers are password protected. Only the primary investigator and data abstractors had access to the data stored on the computer. Data was shared with supervisors via a Dropbox folder that is password protected and the password was only shared with the supervisors. Data will be stored for a period of 5 years on hard copy and Microsoft Excel and then shredded/deleted.

1.6.6 Ethics Approval

The study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments and in compliance with International Conference on Harmonization, Good Clinical Practices, and all applicable regulatory guidelines.

Full ethical approval for the study was obtained from King Abdullah International Medical Research Centre (HAS-16-437780-10741) on 19 January 2016 (Annexure 1) and from the Humanities and Social Sciences Research Ethics Committee of the University of KwaZulu-Natal (HSS/0975/015M) on 29 January 2016 – (Annexure 2). Patient confidentiality was maintained at all times and no patient information was reported in the data sets.

1.7 Chapter summary

This chapter provided a background and rationale to the study.

The dissertation consists of four chapters as follows:

- Chapter 1: Provides an introduction to the study as well as aims, objectives and a brief overview of the methodology.
- Chapter 2: consists of the literature review
- Chapter 3: Provides the results, discussion and conclusion written in manuscript format.
- Chapter 4: provides the general conclusions, strengths, limitations of the study and recommendations.

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CHAPTER 2
LITERATURE REVIEW

2.1 INTRODUCTION

In order to conduct a cost effectiveness analysis (CEA), the efficacy and safety of the alternative medications must be considered. A literature review was conducted to justify the assumption that low dose and high dose colistin are not equivalent. Given the impact of NP in terms of mortality, length of ICU and hospital stay, added costs and the paucity of information on cost effectiveness of colistin in the treatment of NP caused by colistin-only sensitive GNB, such information will add significantly to the medical literature.

2.2 LITERATURE SEARCH

The following databases were searched: PubMed, Google Scholar, Science Direct and CINAHL (Ebscohost) using the following search terms: "cost effectiveness", "efficacy", "colistin", "pneumonia", "gram negative" and "multi drug resistant". Searches conducted in Pubmed retrieved 118 articles, 25 with the search terms "colistin AND pneumonia AND gram negative AND efficacy"; 2 with the search terms "colistin AND pneumonia AND cost effectiveness"; 12 with the search terms "colistin AND efficacy AND multi drug resistant" and 79 with the search terms "colistin AND gram negative AND efficacy". Searches in Google Scholar retrieved 167 studies, Science Direct 862 studies and CINAHL (Ebscohost) 196 studies. The titles were reviewed and irrelevant topics and duplicates were eliminated. The abstracts were then reviewed and those meeting the inclusion criteria were retrieved. A total of 38 studies matching our inclusion criteria were retrieved. All studies were in English language.

2.3. LITERATURE REVIEW OF COLISTIN

2.3.1 Effectiveness of high dose colistin

In a retrospective study by Kalin et al(4) on 45 patients comparing doses less than 5mg/kg/day (low), 5mg/kg/day (normal dose) and 10 mg/kg/day (high dose) colistin in the treatment of VAP caused by *Acinetobacter Baumannii* (AB), the clinical response at the end of therapy was 30% in the low and normal dose groups and 7% in the high dose group. Mortality was higher in the high dose group at 67% compared to 40% in the low dose group and the authors concluded that high dose colistin has no benefit in the treatment of VAP caused by AB. This was a small sample that was further confounded by the severity of the disease of the included cohort. The clinical response obtained by Kalin et al. are in contrast to another study (24) using doses between 2 and 10mg/kg/day in the treatment of infections due to MDR-GNB where out of 60 patients, 71.7% had a favorable response. Subgroup analysis revealed that 69.4% of the patients with pneumonia had a favorable response. It must be noted that in this study colistin was used in combination with other antimicrobials and this was a heterogeneous sample with various infection types so it is rather difficult to assign the positive outcomes achieved solely to colistin.

A small prospective, observational, cohort study(42) using 720mg/day (approximately 10mg/kg/day) colistin found that the higher doses achieved higher clinical cure i.e. 82.1% in all patients treated for sepsis due to GNB susceptible only to colistin. Clinical cure in VAP patients was 100% however the bacteriologic cure was attained in only 40% of these patients. Colistin was used as monotherapy in 50% of the cases. A major limitation of this study was the small sample size. A prospective study with a much larger sample (43) found that mortality was much higher amongst patient who received colistin (39%) compared to other antibiotics (28.8%). Notably the patients receiving colistin were very different from those receiving other antibiotics (age, MDR *Klebsiella Pneumonia*) and the doses used were much lower at approximately 2.5mg/kg/day.

In a retrospective study of 121 patients (38) using daily doses ranging between 120-480 mg against MDR *Pseudomonas Aeruginosa*, a favorable clinical outcome was found in 65% of patients with pneumonia. In patients receiving more than 240mg/day, 85% achieved a favorable clinical response compared to 69.3% in patients receiving doses lower than 240mg/day however this was not statistically significant. Furthermore, mortality related to MDR pseudomonas in this study was 16.5%. The major difference between this and other studies is the inclusion of the majority of patients from non-ICU setting. The findings of this study concur with those of Dalfino et al (42) in that a better clinical response (73%) was observed when higher doses were utilized.

Falagas et al (44) have also used doses up to 720mg/day and achieved higher rates of clinical response in the treatment of MDR-GNB. Furthermore this study found colistin to be more effective in the treatment

of pneumonia. Regimens of colistin alone or in combination with Meropenem also favored a better response compared to regimens containing colistin with other agents. Older patients and those with greater changes in renal function fared worse. Mortality among patients who received an average daily colistin dose of 240mg/day (3.4mg/kg/day) (38.6%) was higher than mortality among patients who received 480mg/day (27.8%) as well as those who received 720mg/day (21.7%). The mortality in the low dose group was similar to that reported by Paul et al (43) when doses of 2.5mg/kg/day were used. The mortality rates reported are however very different to those reported by Kalin et al (5) where mortality was much higher in the high dose group. Whereas Kalin et al studied VAP caused by *Acinetobacter*; the study by Falagas et al included various MDR-GNB at different sites.

2.3.2 Effectiveness of low dose colistin

As mentioned earlier, the study by Kalin et al (4) showed a higher clinical response (30%) in patients using doses less than 5mg/kg/day (low) compared to patients using the higher 10mg/kg/day in the treatment of VAP caused by *Acinetobacter Baumannii* (AB). The clinical response in the low dose group, although higher than that of the high dose group, was relatively low (30%) compared to some other studies and this can be attributed to the severity of illness of the study patients.

Yilmaz et al (3) studied patients receiving colistin in doses ranging from 1.25 to 2.5 mg/kg/day for nosocomial infection due to colistin only sensitive pathogens and reported a clinical response rate of 69.2%, a rate similar to that reported in some previous studies(45). Clinical and microbiological cure rates were similar as well. Another study (5) aiming to determine the bacterial cure rate of low dose colistin in MDR GNB, concluded that the low dose is effective. A bacterial cure rate of 75.2% was achieved and there was no statistical difference between the group that achieved and did not achieve cure in relation to dose or duration of colistin. A limitation of this study was that the possibility of colonization could not be excluded and so patients classified as infection may have been colonized. Both studies included patients that were not homogeneous in the site of infection.

In a study investigating the clinical response of colistin in VAP caused by Carbapenem resistant *Acinetobacter Baumannii* response rates were similar between groups that were treated with monotherapy (72.7%) and combination therapy (78.8%)(45). Response for regimens containing colistin was 66.7%. Whether combinations would provide any additional benefit was unclear due to the small sample size however another study(38) failed to demonstrate any additional benefit when combining colistin with

other antimicrobials. This study was confounded by polymicrobial VAP and the use of concomitant antimicrobials. Furthermore, VAP was confirmed by different techniques for different patients and this could have affected the results.

2.3.3 Nephrotoxicity associated with the use of colistin

Nephrotoxicity is a most commonly cited adverse effects of colistin treatment (18,26–28) and numerous studies have reported on the factors associated with colistin induced nephrotoxicity (4,26,28,29). In a study by Montero et al (38), nephrotoxicity was reported as 8.3%. Colistin dose was not identified as an independent risk factor of nephrotoxicity however previous chronic renal impairment, diabetes mellitus, and the use of aminoglycosides were risk factors. On the other hand, an earlier study (27) reported a rate of nephrotoxicity of 14.3 % but noted a dose dependent relationship (higher doser, higher nephrotoxicity) that was statistically significant. The authors also noted a correlation between development of nephrotoxicity and duration of treatment. This study was confounded, however, by the administration of other potentially nephrotoxic medications which may have led to an overestimation of nephrotoxicity. It must be noted further that both these studies used slightly different definitions of nephrotoxicity.

In another cohort (46), nephrotoxicity was reported as 43%. The authors identified doses greater than 5mg/kg/day as an independent risk factor for nephrotoxicity (using RIFLE criteria). Furthermore, a trend towards greater nephrotoxicity was identified when colistin was dosed between 3mg/kg/day and 4.9mg/kg/day. Aminoglycoside use was however not associated with an increase risk. In a later study(4) colistin in various doses was investigated in the treatment of VAP caused by *Acinetobacter Baumannii*. A dose response relationship was noted with higher doses up to 10mg/kg/day contributing to greater rate (40%) of nephrotoxicity. The severity of illness of this cohort may have contributed to the higher rates since the majority exhibited sepsis or septic shock (4).

Another study(45) reported a much higher rate of colistin associated nephrotoxicity using doses between 2.5 and 5mg/kg/day. The rate of nephrotoxicity was 18% however once other potentially nephrotoxic medication were excluded the rate in the colistin based group was 57.1%. This study was confounded by the presence of polymicrobial VAP treated with concomitant antibiotics as well as the use of polymixin B and colistin. Furthermore, the majority of patients were trauma victims and hence more critically ill.

Dalfino et al (42) did not observe any deterioration of renal function in 82.1% of the cohort using a high dose strategy that was administered over extended intervals. In the patients whose renal function was

affected, they did not find any correlation between renal function and cumulative colistin dose or duration of treatment. Similar results were obtained in another prospective study using the same dosing strategy for colistin in the treatment of colistin-only susceptible GNB (47).

Renal function was not affected in 83.87% of patients. In the patients that did develop nephrotoxicity, almost half had some pre-existing renal impairment. Both these studies were limited by the small samples and lack of control group. In a retrospective study (3) nephrotoxicity was reported as 7.7 % for patients that received low dose (approx. 1.25mg/kg/day) and 18.2 % for those that received high (2.5mg/kg/day) dose colistin. Although the rate of nephrotoxicity was greater with high dose colistin group, this was not statistically significant. It is plausible that due to the low sample size, this study was not powered to detect any significant difference. These results are in contrast to an earlier mentioned study(27) that reported a dose response relationship that was significant as well as a correlation with cumulative dose of colistin. Zaidi et al (5) in their investigation of the safety of low-dose (approximately 2mg/kg/day) colistin in the treatment for MDR-GNB infections reported a rate of nephrotoxicity of 12.8%. The rate of nephrotoxicity was independent of location in hospital (ICU or not) and similarly with the use of other potentially nephrotoxic medications, i.e. gentamycin, vancomycin, NSAIDs or ACE inhibitors.

2.3.4 Cost-effectiveness studies in Nosocomial Pneumonia

Models for cost effectiveness analysis are available for nosocomial pneumonia in general(48) and for methicillin-resistant Staphylococcus aureus(49,50), however there are significant differences with MDR NP. Currently no studies of colistin cost effectiveness could be found and thus there is an urgent need to study this aspect of NP.

2.3.5 The role of Colistin use in Antimicrobial Stewardship

Antimicrobial stewardship programs (ASP) are hospital based programs aimed at improving antibiotic use. ASP can optimize treatment of infections and minimize antibiotic related adverse effects (51,52). ASP assists in improving quality of patient care(53) and improve patient safety by providing better cure rates(54,55).

The introduction of ASP stemmed from the unavailability of newer drugs to treat GNB and the increase in MDR organisms. Inappropriate colistin dosing may lead to the emergence of resistance. (56)

The CDC in their 2006 guideline on "Management of Multi-Drug Resistant Organisms in Healthcare Settings" stated that control of multi-drug resistant organisms "must include attention to judicious antimicrobial use" (57) and in 2014 recommended the implementation of ASP in all acute care hospitals (58).

The growing problem of the misuse of antibiotics has contributed to antibiotic resistance which is now a serious public health threat (59) and one of the great aims of ASP is to reduce the emergence of antibiotic resistant strains.

An important strategy for the role of colistin in ASP is the use of patient characteristics and optimizing doses based on pharmacokinetic and pharmacodynamics(56).

Intravenous polymixins (e.g. colistin) are recommended against carbapenem-resistant bacteria that are sensitive only to polymixins in patients with HAP/VAP. A seven-day course is recommended; however, a shorter or longer duration may be required based on the clinical picture.(60)

2.4 Summary of Literature Review

The studies reviewed have shown efficacy with both low and high dose colistin with variable level of adverse effects. The gap in research is that there is no direct comparison of low and high dose colistin in the treatment of NP caused by colistin-only sensitive GNB.

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CHAPTER 3

MANUSCRIPT FOR SUBMISSION AND PUBLICATION

3.1 Introduction

This chapter describes the general findings and discussion of the results of the study and is represented in the form of a manuscript titled "Pharmacoeconomic model to compare the cost-effectiveness of low vs high dose colistin in the treatment of nosocomial pneumonia caused by Multi-Drug Resistant (MDR) gram negative Bacteria in Saudi Arabia". This manuscript was submitted to the *"International Journal of Clinical Pharmacy"* for publication.

The journal instructions to the author can be found at the following link:

http://www.springer.com/medicine/internal/journal/11096?detailsPage=pltci_3137197

The reference list is cited according to the instructions for authors as required by the IJCP. A complete reference list is included at the end of every chapter and according to the reference style of the University of KwaZulu Natal.

3.2 Manuscript

Pharmacoeconomic model to compare the cost-effectiveness of low vs high dose colistin in the treatment of pneumonia caused by Multi-Drug Resistant (MDR) gram negative Bacteria in Saudi Arabia

Abdul Karim Suleman Cara[a*], Syed Tabish Razi Zaidi[b], Fatima Suleman[a]

[a]School of Health Sciences, University of KwaZulu-Natal, Westville Campus, Private Bag X54001, Durban 4000, South Africa.

[b]Division of Pharmacy, School of Medicine, Faculty of Health, University of Tasmania, Private Bag 25, Hobart, TAS, 7001

*Corresponding author email: akcaraza@yahoo.com

Contact number: +966 54 786 1134

ABSTRACT

Background

Gram negative pathogens are increasingly resistant to common first line antibiotics and colistin is often the only medicine available. Limited information is available comparing the effectiveness and costs of low dose colistin(LDC) versus high dose colistin(HDC). Studies show efficacy with both and with variable levels of adverse effects. The absence of a definite dosing strategy makes a model comparing LDC and HDC invaluable in making decisions regarding the appropriate use of colistin.

Objective

This study was designed to evaluate the cost effectiveness of LDC versus HDC in the treatment of Pneumonia caused by colistin-only sensitive gram negative bacteria from the perspective of tertiary care hospital in Saudi Arabia.

Setting

300-bed tertiary care hospital in Saudi Arabia.

Method

A decision–analytic model using data from a retrospective review was developed comparing the costs and outcomes of treatment of pneumonia with LDC versus HDC. The model followed an average patient from initiation of treatment until clinical cure or failure.

Main outcome measures

The main outcomes were cure, nephrotoxicity, total direct costs per episode, cost per additional cure and cost per nephrotoxicity avoided.

Results

There was no significant difference between HDC and LDC with regards to clinical cure (30% vs. 21%; p=0.292). More patients experienced nephrotoxicity with HDC vs. LDC (30% vs. 8%; p= 0.004)

With LDC the incremental costs per nephrotoxicity avoided was SAR -3056.28/nephrotoxic case prevented and the incremental cost effectiveness ratio was SAR -13894.66/nephrotoxic case prevented.

Conclusion

LDC was not inferior to HDC in terms of clinical cure and had a lower incidence of nephrotoxicity resulting in significant cost avoidance.

Keywords:
"cost effectiveness", "efficacy", "colistin", "pneumonia", "gram negative" and "multi drug resistant".

Introduction

Nosocomial Pneumonia (NP) is defined as pneumonia that occurs after healthcare contact. NP encompasses hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) (1,6). Rates of HAP due to multidrug-resistant gram-negative bacteria (MDR-GNB) have escalated in recent years and are a major concern(2). Gram negative pathogens are increasingly resistant to commonly used first line antibiotics and often colistin is the only medicine available against MDR-GNB. The incidence of VAP in developing countries ranges from 16.7 to 73.4 per 1,000 ventilator-days in adult ICUs (9,10). The effect of MDR bacterial infections have been studied and demonstrate an increase in overall costs (17).

Various studies have reported on the effectiveness of high dose colistin (HDC) (21) and low dose colistin (LDC) (4,5). There are still no definite dosing recommendations and limited information is available about the comparative effectiveness of LDC versus HDC. Studies on the safety and efficacy of colistin abound both with HDC(24,38) and LDC (3–5). Studies have shown efficacy with both these doses with variable level of adverse effects, mainly nephrotoxicity which is one of the most commonly cited adverse effects of colistin treatment (18,26–28).

There is convincing evidence of greater incidence of nephrotoxicity using higher doses of colistin.
Falagas et al (27) reported nephrotoxicity that had a statistically significant dose dependent relationship. Nephrotoxicity was reported as 43% by Pogue et al (46), with greater nephrotoxicity with doses between 3mg/kg/day and 4.9mg/kg/day. Chan et al (45) reported a much higher rate of colistin associated nephrotoxicity using doses between 2.5 and 5mg/kg/day.

A model to compare LDC and HDC in the treatment of pneumonia caused by colistin-only sensitive MDR-GNB will assist clinicians in decision making. Given the reported efficacy of low dose colistin in the treatment of MDR GNB (3–5), greater nephrotoxicity with higher doses and the financial burden that NP places on the healthcare systems worldwide, the purpose of this study was to construct an economic model that will allow the comparison of LDC and HDC in the treatment of pneumonia caused by colistin-only sensitive MDR GNB.

Aim of the study

The aim of this study was to determine cost effectiveness of low dose colistin (less than 2.5mg/kg) versus high dose colistin (greater than 2.5mg/kg) dosed every 12 hours in the treatment of NP due to MDR-GNB using a decision analytic (DA) model.

Ethical Approval

The study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments and in compliance with International Conference on Harmonization, Good Clinical Practices, and all applicable regulatory guidelines.

Full ethical approval for the study was obtained from King Abdullah International Medical Research Centre (HAS-16-437780-10741) on 19 January 2016 (Annexure 1) and from the Humanities and Social Sciences Research Ethics Committee of the University of KwaZulu-Natal (HSS/0975/015M) on 29 January 2016 (Annexure 2).

Patient confidentiality was maintained always and no patient hospital numbers, names or date of birth/identification numbers were reported in the data sets.

METHODS:

Study design

The design of this study was a retrospective analysis conducted at a 300-bed hospital in Saudi Arabia comparing the treatment of NP with low dose colistin versus high dose colistin. The study population consisted of all patients treated with colistin for Nosocomial Pneumonia caused by MDR-GNB at King Abdulaziz Hospital, AlHasa, Saudi Arabia. Patients in the low dose colistin group received less than 2.5mg/kg and the high dose colistin group received greater than 2.5mg/kg administered every 12 hours. The commercial product used was Colomycin® containing 33mg colistin base per vial (30,000 international units per mg)

Definitions

Multidrug–resistant gram negative bacteria for the purposes of this study are defined as bacteria resistant to aminoglycosides, anti-pseudomonas penicillins, carbapenems, cephalosporins and fluoroquinolones (61).

Clinical cure was defined as resolution of signs and symptoms of infection including absence of fever for a minimum of 72 hours and a white blood cell count below 12 000 cells/ mm^3

Nephrotoxicity was defined as an increase in serum creatinine by 26.52µmol/L or more within 48 hours or increase in serum creatinine to 1.5 times baseline or more within the last 7 days (30).

Participants

There was a total of 171 patients that received colistin during the study period. After applying the inclusion and exclusion criteria 96 were evaluated. This included 63 and 33 in the LDC and HDC groups, respectively.

Inclusion criteria

The following patients were included in the study:

1. Patient over 12 years old and receiving colistin for documented nosocomial pneumonia in ICU and Non-ICU wards
2. Patients must have received colistin for colistin-only sensitive MDR-GNB infection
3. Patients must have received colistin for at least 72 hours
4. If a patient received more than one course of colistin within a single admission, only the first course was included

Exclusion criteria

The following patients were excluded from the study:

1. age less than 12 years old
2. patients treated only with inhaled colistin
3. patients who did not receive colistin for at least 72 hours
4. patients with moderate to severe renal impairment or received renal replacement therapy or dialysis

Statistical Analyses

In this study, two-sided significance was used for statistical analyses. All p values of 0.05 or less were considered statistically significant providing a 95% confidence interval. Dichotomous data were

compared using the Chi-Square test. Normally distributed continuous data are expressed as mean and standard deviation and compared using the Student's t-test. Otherwise, values are presented as medians with ranges and compared using the Mann – Whitney U test. Quantitative variables were analyzed with the chi square test or Fischer's exact test (two-tailed) when necessary. All data was entered in a database and SPSS 20.0 software package was used to analyze the data.

Model Outcomes and Pharmacoeconomic Analyses

The data was modelled using a decision analysis, considering the occurrence of NP with MDR-GNB, the two treatment alternatives (LDC versus HDC) and two outcomes (cure and no cure) as well as nephrotoxicity in each. Figure 1 shows the decision tree. Clinical outcomes (cure rate and nephrotoxicity rate) and the cost outcomes (total cost per patient) were calculated. Effectiveness was measured as rate of clinical cure and nephrotoxicity avoided. Probabilities of the different outcome parameters came from analysis of our retrospective study.

Incremental cost (IC) was calculated as Cost of HDC - Cost of LDC. Average cost effectiveness ratio (CER) was calculated as C LDC⁄E LDC for the LDC strategy and C HDC⁄E HDC for the HDC strategy; where C = cost (SAR) and E= efficacy (cure or nephrotoxicity avoided)(62). Efficacy was defined as the probability of patients who experienced NP responded to the study medicine (defined as 'cure') and probability that nephrotoxicity would be avoided in patient treated with the study medicine. Cost effectiveness was measured in terms of Incremental Cost Effectiveness Ratio (ICER).

ICER was calculated using the following equation:

(Cost of LDC) – (Cost of HDC)⁄(Efficacy of LDC) – (Efficacy of HDC)(62)

A dominant strategy was defined as being less costly with increased efficacy (clinical cure) or with least toxicity (nephrotoxicity).

Costing

Direct costs for each treatment option were calculated considering the cost of medicines, ward costs, physician and consultant costs, nurse costs, laboratory costs and cost of colistin therapy. Direct non-medical costs such as transportation; indirect non-medical costs such as lost income; and intangible costs such as pain are not considered since they are beyond the scope of the study. Cost of consumables and administration sets as well as costs for pharmacy staff were not included as they were assumed to be identical for the two arms (prepared and administered in the same manner).

Perspective and Timescale

This economic analysis was conducted from the perspective of the payer King Abdulaziz Hospital. The study period was that of the treatment period being from initiation of colistin to treatment cure or failure.

Discounting and currency

Future costs were not included since the costs and benefits pertained to the time horizon of colistin treatment. Discounting was therefore not performed because the time-period was too short to show any significant contribution. The currency used was Saudi Arabian Riyal (SAR) (USD 1= SAR 3.77 as at 16 November 2016, www.xe.com).

Assumptions:

Being a cost-effectiveness analysis, there were some assumptions made that could limit the generalizability of these results.

Parameters for adverse reactions (ADRs) other than nephrotoxicity were not included because it was assumed to have non-significant contributions to the overall cost-effectiveness and because nephrotoxicity is the main adverse drug reaction affecting outcomes. Antibiotics used to treat other gram-negative and gram-positive organisms were assumed to be equivalent between both groups and thus not included into the model. The costs of infection focused on NP due to *Acinetobacter Baumannii* (AB), *Pseudomonas Aeruginosa* (PA) and *Klebsiella Pneumonia* (KP) and any treatment costs associated with other infections were not accounted for in the model.

RESULTS:

Baseline characteristics:

The baseline characteristics of the samples are summarized in Table 1. The two groups did not differ significantly with regards to age (68.76 years and 67.08 years; p=0.7070), however, there was a significant difference with regards to weight (56.52 kg and 76.87 kg; p=<0.001) and gender (79 % and 56% male; p=0.025) between the HDC and LDC groups, respectively.

Comorbidities between the two groups were not significantly different in all respects except for malignancy (2 vs 0; p=0.048) for the HDC and LDC groups, respectively. The Charlson comorbidity index between the two groups (3.88 and 3.67; p=0.585) was not significantly different for the HDC and LDC groups, respectively.

There was no significant difference with respect to concomitant nephrotoxic medications (vancomycin, aminoglycosides, NSAIDs, ACEI/ARBS and furosemide) used in the two groups. The average duration of colistin treatment, average length of stay and location of patients within the hospital between the two groups was not significantly different.

The two groups were significantly different in terms of the causative organism; AB (76% and 53%; p=0.037), PA (24% and 49%; p=0.018), for HDC and LDC, respectively. However, KP (6% and 9%; p=0.56) was not significantly different, for HDC and LDC, respectively. The average dose (mg) of colistin was 2.83±-0.50 and 1.52 ±0.43 (p= 0.001) and the average duration of colistin treatment (days) was 12.76 ±13.38 and 12.67 ±12.51 (p= 0.974) in the HDC and LDC groups, respectively.

Table 1 Characteristics of patients based on colistin dose group

	High Dose Colistin (n=33) n (%)	Low Dose Colistin (n=63) n (%)	p-value
Demographics			
Age in years (mean ± SD)	68.76±20.61	67.08±20.77	0.707
Weight in kg (mean ± SD)	56.52 ±17.42	76.870 ±24.87	0.000
Gender (Male)	26 (79)	35 (56)	0.025
Gender (female)	7 (21)	28(44)	0.025
Comorbidities			
Charleston Comorbidity Score (SD)	3.88±1.71	3.67±1.85	0.585
COPD	4	4	0.331
CHF	2	9	0.220
malignancy	2	0	0.048
Endocrine	8	17	0.771
Sepsis	16(48)	23(36)	0.256
UTI	4(12)	6(9)	0.692
Location of patient			
Patients admitted to ICU	9 (27)	20 (32)	0.650
Patients admitted to general wards	24(73)	43(68)	0.650

Table 1 (continued)

	High Dose Colistin (n=33) n (%)	Low Dose Colistin (n=63) n (%)	p-value
Colistin treatment			
Average Colistin dose (mg/kg)	2.83±0.50	1.52 ±0.43	0.001
Average duration of colistin treatment (days)	12.76 ±13.38	12.67 ±12.51	0.974
Average length of stay (days)	124.40 ±202.70	113.10±340.80	0.861
Concomitant nephrotoxic meds			
Vancomycin	18(55)	46 (73)	0.068
Aminoglycosides	5(15)	4(6)	0.160
NSAID	11(33)	29 (46)	0.231
ACEI/ARBS	4(12)	10 (16)	0.621
Furosemide	15(45)	36(57)	0.276
Causative organisms			
AB **(**n=59)	25 (76)	34 (53)	0.037
PA (n=39)	8 (24)	31 (49)	0.018
KP (n=8)	2 (6)	6 (9)	0.56

Abbreviation: COPD = Chronic Obstructive Pulmonary Disease; CHF = Congestive Failure; UTI= Urinary Tract Infection; ICU = Intensive Care Unit; NSAID = Non-Steroidal anti- inflammatory Drugs; ACEI = Angiotensin Converting Enzyme Inhibitor; ARBS = Angiotensin II receptor blockers; AB = Acinetobacter Baumannii; PA = Pseudomonas Aeruginosa; KP = Klebsiella Pneumoniae.

[a]Mean values (+ SD) and the number of cases with their relevant percentage in brackets.

Efficacy and safety outcomes (Table 2)

Table 2: Outcomes

	High Dose Colistin (n=33) n (%)	Low Dose Colistin (n=63) n (%)	p-value
Clinical Cure	10(30)	13(21)	0.292
Nephrotoxicity	10(30)	5(8)	0.004

Clinical cure analysis

HDC was associated with a greater probability of clinical cure (30%) compared to LDC (21%), however the difference was not found to be significant (p=0.292).

Nephrotoxicity analysis

Safety was measured as number of incidents of nephrotoxicity avoided by comparing treatment with HDC and LDC. There was a significant difference in the incidence of nephrotoxicity, 30% and 8% (p= 0.004) between the HDC and LDC groups, respectively. Using this data, we calculated the percentage of patients in which nephrotoxicity was avoided with HDC (100-30=70%) and with LDC (100-8=92%).

Multivariate Analysis of outcomes (Table 3)

Multivariate analysis revealed significant nephrotoxicity within high dose colistin arm (p- value 0.011). Multivariate analysis further revealed that high dose colistin did not achieve better cure compared to low dose colistin (OR 1.74, 95% CI 0.63 – 4.80; P= 0.283). However, they have a greater chance of developing nephrotoxicity (OR 4.71, 95% CI 1.42 – 15.67; p=0.011).

Table 3: Multivariate Analysis of Outcomes

	OR	95% CI	p-value
Clinical Cure	1.74	0.63 – 4.80	0.283
Nephrotoxicity	4.71	1.42 – 15.67	0.011

Costs

Average total direct costs per episode of colistin treatment in the LDC and HDC groups were SAR 24718.42 and SAR 27775.25, respectively. The main components of costs were days of ICU stay (18.8% and 24.37%) and physician visits (20.5% and 18.37%) for patients in LDC and HDC groups, respectively. Costs were obtained using data from hospital resources utilized (Table 4) and costs from the hospitals business center December 2016 price list (Table 5). Direct costs for the treatment duration in both arms listed in Table 6.

Table 4: Hospital Resources utilized

	High Dose Colistin (n=33) (SD)	Low Dose Colistin (n=63) (SD)	p-value
Number of ICU consultant visits (mean)	12.42± 12.61	4.81 ± 6.61	0.006
Number of GW consultant visits (mean)	11.33± 13.86	14.29 ± 14.65	0.425
Number of physician visits (mean)	25.52 ± 26.77	25.33 ± 25.03	0.974
Number of ICU Nurse visits	4.52 ± 9.56	3.11 ± 5.96	0.379
Number of GW nurse visits	8.5 ± 12.94	9.21 ± 13.53	0.808
Number of ICU days	4.52 ± 9.56	3.11 ± 5.96	0.379
Number of GW days	12.76 ± 13.39	12.44 ± 12.62	0.910
Number of CBC tests	12.76 ± 13.39	12.67 ± 12.51	0.974
Number of basic screens	3.19 ± 3.35	3.17 ± 3.13	0.978
Number of renal panels	4.25 ± 4.46	4.22 ± 4.17	0.975
Number of lab cultures	1.56± 1.24	2.44± 1.85	0.019

Key: ICU=Intensive Care Unit; GW=General ward; CBC=Complete Blood Count.

Results are expressed as mean ± standard deviation

Table 5: Costs

Business Center Pricing (December 2016)	Cost (SAR)
Cost of ICU stay/day	1,500
Cost of general ward stay/day	500
Cost of consumables in ICU/day	250
Cost of consumables in General Ward /day	50
Cost of ICU physician consultation	1,000
Cost of General Ward physician consultation	200
Cost of ICU nurse/day	300
Cost of General ward nurse/day	100
Cost of CBC	80
Cost of Basic Screen	200
Cost of Renal Panel	240
cost of tracheal culture	150
cost of throat culture	150
cost of sputum culture	150
cost of respiratory culture	190
cost of tracheal culture	150

Key: ICU=Intensive Care Unit; CBC=Complete Blood Count

Table 6: Mean Direct Cost of treatment per patient

	High dose colistin (n=33) mean ±SD	Low dose colistin (n=63) mean ±SD	p-value
GW consultant visits	2069.54± 1972.18	1821.38± 1788.57	0.535
ICU consultant visits	3733.64± 7804.30	2421.05± 4252.24	0.288
GW days	4121.21± 6412.91	4738.10± 6759.02	0.667
Staff physician visits	5103.03± 5354.47	5066.67± 5007.35	0.974
ICU days	6772.73± 14344.04	4666.67± 8939.76	0.379
Renal panel	1020.61± 1070.89	1013.33± 1001.47	0.974
GW nurse visits	1275.76± 1338.62	1266.67± 1251.84	0.974
ICU nurse visits	1354.55± 2868.81	933.33± 1797.95	0.379
Basic screen	318.94± 334.65	317.02± 312.69	0.978
CBC tests	1020.61± 1070.89	1013.33± 1001.47	0.974
Cost of colistin	756.16± 495.83	1129.91± 847.51	0.022
Laboratory cultures	228.48± 189.56	340.48± 286.65	0.046
Mean Total costs	**27775.24± 31893.63**	**24718.42± 21166.64**	**0.576**

Key: ICU=Intensive Care Unit; GW= General Ward; CBC=Complete Blood Count

Cost effectiveness

Based on the efficacy and safety outcomes and the costs attached to each outcome, it was possible to calculate the IC, CER and ICER (Tables 7). When LDC and HDC were compared using ICER, LDC was the dominant strategy compared to HDC in terms of number of incidents of nephrotoxicity avoided (ICER = -SAR 13, 894.66 per nephrotoxicity avoided).

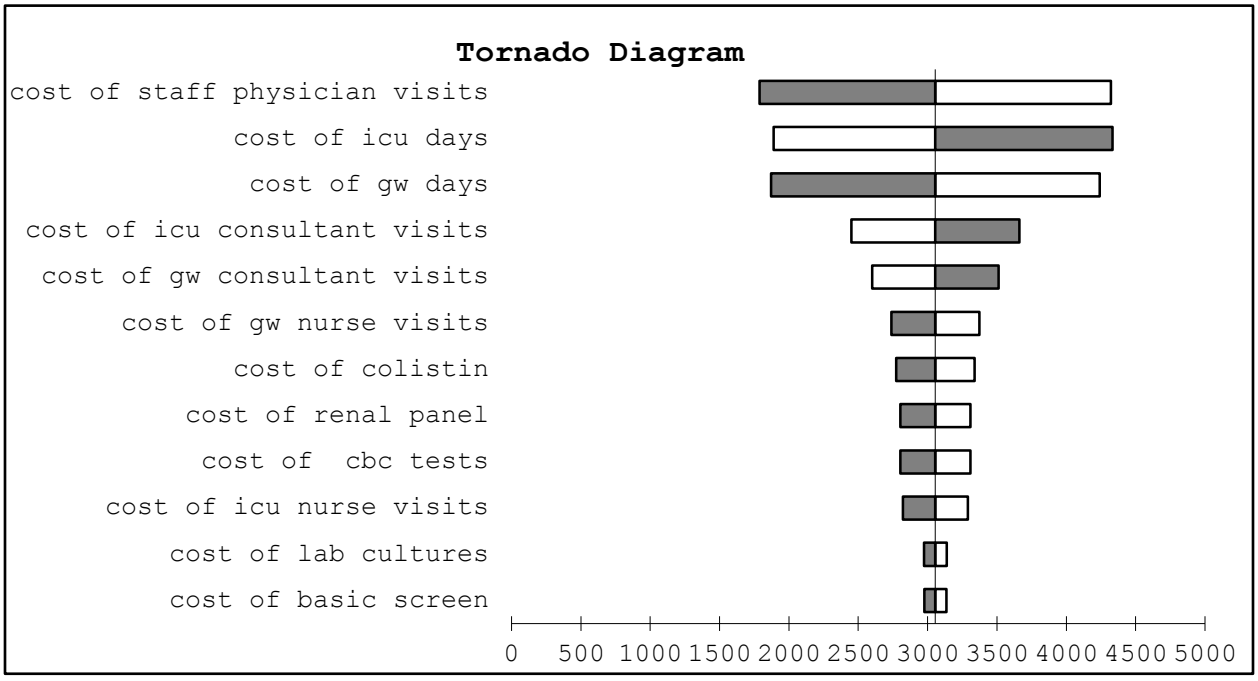
Table 7: Cost effectiveness analysis- Nephrotoxicity avoided

Strategy	Cost	Incremental cost	effect	CER	ICER
High dose colistin	27775.24		0.70	39678.92	
Low dose colistin	24718.42	-3056.82	0.92	26867.84	-13894.66

Sensitivity Analysis

To reflect the uncertainty inherent in the analysis, a series of univariate (one-way) sensitivity analyses was performed for all parameters in the model to assess the effect of varying certain parameters by 25%. Changes in the incremental costs are depicted in a tornado diagram (Figure 2). Analyses were performed using Microsoft Excel (2003; Microsoft Corp, Redmond, WA, USA). The incremental costs per nephrotoxicity avoided was most sensitive to the cost of staff physician visits, ICU days and general ward days. However, varying these parameters by 25% did not change the conclusions.

Figure 2 – Sensitivity analysis- Tornado Diagram



Key: icu= intensive care unit; gw= general ward; cbc= complete blood count

Table 8: One way sensitivity analysis for low dose colistin (Incremental cost=SAR3056)

Parameter	25% decrease	25% increase	% change
Cost of staff physician visits	1789.33	4322,67	41.48%
Cost of general ward days	1871.48	4240.52	38.79%
Cost of ICU days	1889.33	4223.49	38.20%
Cost of ICU consultant visits	2450.74	3661.26	19.83%
Cost of general ward consultant visits	2600.65	3511.35	14.93%
Cost of general ward nurse visits	2739.33	3372.67	10.39%
Cost of colistin	2773.52	3338.48	9.27%
Coat of renal panel	2802.67	3309.33	8.32%
Cost of CBC tests	2802.67	3309.33	8.32%
Cost of ICU nurse visits	2822.67	3289.33	7.66%
Cost of lab cultures	2973.26	3138.74	2.73%
Cost of basic screen	2976.74	3135.26	2.62%

DISCUSSION:

Several studies have reported on the efficacy of LDC in the treatment of MDR GNB(3–5) and because the financial burden that NP places on healthcare systems worldwide, we constructed an economic model to compare LDC and HDC.

Our study design was similar to that used by Bounthavong M, et al.(49) in their cost effectiveness analysis of linezolid versus vancomycin in MRSA complicated skin and soft tissue infection. Whereas the authors of that study used past clinical trials to obtain the different probability parameters, our

study utilized the probabilities from the retrospective analysis of patients treated at our institution during the study period. The outcomes of our study were also calculated in the same manner as that utilized by Bounthavong M, et al.

A German cost effectiveness analysis of linezolid vs vancomycin in NP conducted by De Cock E, et al. (50) used a similar methodology to Bounthavong M, et al. The German authors, however, used a Delphi panel to supplement the clinical trial data as well as economic data when these were no available from the trials. Conditions of clinical trials are likely to be different from real life practice and our study used real life data.

The findings of this study show that there is no significant difference in clinical cure between HDC and LDC (30% vs 21%; p=0.292). The low clinical cure rates are similar to those of Kalin et al (4) but much lower than those obtained by Yilmaz et al. (3)

Our findings also show that LDC produced significantly less nephrotoxicity than HDC (8% vs 30%; p=0.004). The low incidence of nephrotoxicity with LDC is similar to that of Yilmaz et al (3) who reported an incidence of 7.7% as well as those of Zaidi et al (5) who reported a rate of 12.8% in patients receiving LDC.

Interpretation of the ICER per nephrotoxicity avoided is appropriate considering that the costs and benefits relate to the model time horizon of colistin treatment.

The use of LDC would provide the same efficacy as HDC and realize a saving of SAR 13, 894.66 due to nephrotoxicity avoided.

Limitations

This was a retrospective single center study and this only provides insight into colistin use for NP at King Abdulaziz Hospital. A randomized controlled study would be preferred however limitations of resources did not warrant same. Due to the limited number of evaluable patients, the small sample size included in this study did not provide the required power. A larger sample would allow for more robust results.

Resistance to colistin is a major concern since this is frequently the only available medicine against MDR-GNB. Colistin resistance has been reported to be due to inadequate colistin dosing(63). Higher doses seem to be more beneficial but no optimal dose has yet been defined. The effect of resistance was

not investigated in our model and future studies should investigate whether resistance patterns would change the outcomes.

There is a possibility of selection bias since patients in the low dose group were of higher weight compared to the low dose group and it is possible that the physician prescribed lower doses of colistin for these patients and higher doses for patients in the high dose group.

This study defined nephrotoxicity using change in serum creatinine, as this was the most readily available in patient's charts. The use of RIFLE criteria would have been ideal as this is now recognized as the standard diagnostic criteria(30). The RIFLE criteria used three severity categories, namely risk, injury and failure; and two outcome categories, complete loss of kidney function and end-stage kidney disease.

Parameters for adverse reactions (ADRs) other than nephrotoxicity were not included because it was assumed to have non-significant contributions to the overall cost-effectiveness and because nephrotoxicity is the main adverse drug reaction affecting outcomes.

Antibiotics used to treat other gram-negative and gram-positive organisms were assumed to be equivalent between both groups and thus not included into the model. Inclusion of other treatment costs could affect the results.

CONCLUSION:

To the best of the authors' knowledge, this is the first study undertaken in exploring the cost effectiveness of LDC versus HDC in the treatment of NP. Despite the assumptions and limitations mentioned, this study provides a deeper insight into the use of colistin in NP. Based on the results of this study, KAH should adopt the LDC strategy for treatment of NP caused by MDR-GNB while taking cognizance of local resistance patterns. Further studies are needed to investigate the true impact of using low dose colistin on healthcare costs.

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CHAPTER 4

CONCLUSION

4.1 INTRODUCTION

This study was conducted to evaluate the safety and efficacy of low dose colistin versus high dose colistin and construct a cost effectiveness analysis comparing the two strategies.

4.2 Conclusions drawn from the study findings

There was no significant difference in efficacy between LDC and HDC in the treatment of NP due to MDR-GNB (21% vs 30%, respectively; p=0.292). Although the researchers could not find any studies comparing low dose and high dose colistin directly, many studies have reported on the efficacy of both doses in the treatment of various infections(3,4).

The incidence of nephrotoxicity in this study is much less with LDC than with HDC (8% vs 30%, p=0.004). These finding are similar to other studies reporting on incidence of colistin induced nephrotoxicity(3–5,43,45). Thus, LDC is more cost effective than HDC for the treatment of NP due to MDR-GNB. This study also showed that the factors that contribute most to the overall cost of treatment are ICU days and cost of physician visits. The incremental costs per patient cured and incremental costs per nephrotoxicity avoided were most sensitive to the cost of ICU days, physician visits and consultant visits. Sensitivity analyses did not change the outcomes though. Results of this study further showed that although LDC and HDC acquisition costs vary significantly, the mean total costs of treatment do not differ significantly, indicating that medicine costs are a small component of the overall cost of treating NP.

4.3 Significance of the study

Pneumonia due to MDR-GNB places a great drain on hospital resources. There is also a lack of an optimal dosing strategy for colistin. Furthermore, high dose colistin has been associated with a higher incidence of nephrotoxicity. To the best of the authors knowledge there are no other studies investigating the cost effectiveness of LDC versus HDC. This study intended to fill that gap.

4.4 Recommendations

LDC is as effective as HDC in the treatment of NP due to MDR-GNB and has a lower incidence of nephrotoxicity. LDC is more cost effective and should therefore be the considered for the treatment of NP due to MDR-GNB.

KAH should adopt the LDC strategy for treatment of NP caused by MDR-GNB while taking cognizance of local resistance patterns using the hospital antibiogram.

Given the limitations of this study, clinical studies with larger numbers are required to confirm these results and investigate the true impact of using LDC in order for these results to be generalizable.

4.5 Chapter summary

This chapter highlighted the conclusions of the study while describing the strengths and weaknesses and providing recommendations for change of treatment guidelines and future research.

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APPENDICES

Appendix 1 - King Abdullah International Medical Research Centre approval

Kingdom of Saudi Arabia
Ministry of National Guard
Health Affairs

المملكة العربية السعودية
وزارة الحرس الوطني
الشؤون الصحية

MEMORANDUM

Sys Reg Num	HAS-16-437780-10741
Memo Date	19-Jan-2016 / 09-04-1437
To	Abdul Karim Cara - Supervisor Pharmacy Services - Pharmaceutical Care
Thru	Yusri Taha - Consultant Infectious Diseases - Ma - Medicine - Al Ahsa - (Approved)
From	Kaimrc Research Office - King Abdullah International Medical Research Center
Subject	RA15/003/A - "Development of a Pharmacoeconomic model to compare the cost-effectiveness of low vs high dose collistin in the treatment of Nosocomial Pneumonia caused by multi-drug resistant (MDR) gram-negative bacteria in Saudi Arabia"

After careful scientific re-evaluation of the above-mentioned proposal, as per comments and suggestions of the respective reviewer and in behalf of the committee, I am grateful to inform you that your Research Proposal has been finally **approved** and you may begin your data collection upon receipt hereof.

According to policies and procedures since your proposal does not include Ethical/Budget consideration, the Committee would like you to submit the progress of your report in three months time. You are further requested to submit a report upon completion of the project and final manuscript.

Indeed, I would like to acknowledge your participation chained with efforts and hard works to the research center.

Thank you and best regards.

CC : King Abdullah International Research Center Department - King Abdullah International Medical Research Center

Appendix 2 – Full Approval - University of Kwazulu-Natal

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

29 January 2016

Mr AK Suleman Cara 214515660
School of Health Sciences – Pharmaceutical Sciences
Westville Campus

Dear Mr Cara

Protocol reference number: HSS/0975/015M
Project title: Development of a Pharmaeconomic model to compare the cost-effectiveness of low vs. high dose colistin in the treatment of Nosocomial Pneumonia caused by multi-drug resistant (MDR) gram-negative bacteria in Saudi Arabia

Full Approval – Expedited Application

In response to your application received 24 July 2015, the Humanities & Social Sciences Research Ethics Committee has considered the abovementioned application and the protocol has been granted **FULL APPROVAL.**

Any alteration/s to the approved research protocol i.e. Questionnaire/Interview Schedule, Informed Consent Form, Title of the Project, Location of the Study, Research Approach and Methods must be reviewed and approved through the amendment /modification prior to its implementation. In case you have further queries, please quote the above reference number.

PLEASE NOTE: Research data should be securely stored in the discipline/department for a period of 5 years.

The ethical clearance certificate is only valid for a period of 3 years from the date of issue. Thereafter Recertification must be applied for on an annual basis.

I take this opportunity of wishing you everything of the best with your study.

Yours faithfully

.....
Dr Shenuka Singh (Chair)
Humanitities & Social Scinces Research Ethics Committee

/pm

Cc Supervisor: Professor Fatima Suleman
Cc Academic Leader Research: Professor Mershen Pillay
Cc School Administrator: Ms P Nene

Humanities & Social Sciences Research Ethics Committee
Dr Shenuka Singh (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 3587/8350/4557 **Facsimile:** +27 (0) 31 260 4609 **Email:** ximbap@ukzn.ac.za / snymanm@ukzn.ac.za / mohunp@ukzn.ac.za
Website: www.ukzn.ac.za

Appendix 3 – Case Report Form

Study Code:	Subject no:		Subject initials:	

SCREENING

Date: _____
DD MMM YYYY

DEMOGRAPHIC DATA

Age (yrs): | Sex: Female | Male

Height (m): •

Weight (Kg): •

Body Mass Index (BMI = Wt (kg)/H^2 (m)): •

LOCATION IN HOSPITAL (Indicate with X)

ICU

NON - ICU

CONCOMITANT NEPHROTOXIC MEDICATIONS		YES	NO
1	AMINOGLYCOSIDES(GENTAMYCIN, AMICACIN)		
2	VANCOMYCIN		
4	NSAIDS		
5	ACEI/ARBS		
2	FUROSEMIDE		
4	INOTROPES		
5	CONTRAST AGENTS		

ALL MEDICATIONS TAKEN

Is the subject currently or previously taking any medication including OTC, vitamins and/or supplements? Yes | No

*Record <u>all</u> medications on Concomitant Medications page

Study Code:	Subject no:		Subject initials:	

SCREENING

PREVIOUS MEDICAL HISTORY

Is there any relevant medical history in the following systems?

Acute Kidney Injury(Code 5)	YES		No	
Chronic Renal Insufficiency(Code 5)	YES		No	
Hypertension(Code 1)	YES		No	
Diabetes Mellitus(Code 6)	YES		No	
COPD (Code 2)	YES		No	

Code	System	*Yes	No
1	Cardiovascular		
2	Respiratory		
3	Hepato-biliary		
4	Gastro-intestinal		
5	Genito-urinary		
6	Endocrine		
7	Haematological		
8	Musculo-skeletal		

Code	System	*Yes	No
9	Neoplasia		
10	Neurological		
11	Psychological		
12	Immunological		
13	Dermatological		
14	Allergies		
15	Eyes, ear, nose, throat		
00	Other		

*If ***YES*** for any of the above, enter the code for each condition in the boxes below, give further details (including dates) and state if the condition is currently or potentially active. If giving details of surgery please specify the underlying cause. Use a separate line for each condition.

		Currently Active?	
Code	**Details (including dates)**	**Yes**	**No**

Study Code:	Subject no:		Subject initials:	

DAY 0 (BASELINE)

VITAL SIGNS

Pulse rate ☐☐☐ bpm

BP ☐☐☐ / ☐☐☐ mmHg

Body temp ☐☐ Degree Celcius

Respiratory Rate ☐☐ /min

RENAL FUNCTION

Serum Creatinine ☐☐☐ uMol/L

Serum Albumin ☐☐☐ g/dL

HEPATIC FUNCTION

AST ☐☐☐

ALT ☐☐☐

LABORATORY VALUES

ANC ☐☐☐ X 10 9/L

Platelets ☐☐☐ x 10 3 /L

..... ☐☐☐

..... ☐☐☐

MICROBIOLOGY

Responsible Colistin –only sensitive MDR GN pathogen

Acinobacter Baumannii ☐

Pseudomonsa aeruginosa ☐

Klebsiella pneumonia ☐

Signature: ..... Date: ☐☐☐☐☐☐☐☐

d d m m m y y y y

Study Code:	Randomisation no:		Subject initials:	

CONCOMITANT MEDICATIONS

Medication	Total Daily Dose	Units	Reason	Start Date *(MM/DD/YYYY)*	Stop Date *(MM/DD/YYYY)*	Continuing
				__/__/____	__/__/____	☐
				__/__/____	__/__/____	☐
				__/__/____	__/__/____	☐
				__/__/____	__/__/____	☐
				__/__/____	__/__/____	☐
				__/__/____	__/__/____	☐
				__/__/____	__/__/____	☐
				__/__/____	__/__/____	☐
				__/__/____	__/__/____	☐