Cost-Minimization Analysis of Imipenem/Cilastatin versus Meropenem in Moderate to Severe Infections at a tertiary care hospital in Saudi Arabia.

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Discipline of Pharmaceutical Sciences

University of KwaZulu-Natal, South Africa

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ACKNOWLEDGEMENTS

ACRONYMS AND ABBREVIATIONS

ADE   Adverse Drug Events

CAP   Community-acquired pneumonia

CBC   Complete blood count

CBA   Cost-benefit analysis

CEA   Cost-effectiveness analysis

CMA   Cost-minimization analysis

COPD   Chronic obstructive pulmonary disease

CUA   Cost-utility analysis

DM   Diabetes mellitus

ESBL   Extended-spectrum beta-lactamase

FDA   (United States) Food and Drug Administration

GW   General ward

IAI   Intra-abdominal infection

IC   Imipenem/Cilastatin

IDSA   Infectious Disease Society of America

ITT   Intention to treat

LFT   Liver function test

LOAS   Length of antibiotic stay

LRTI   Lower respiratory tract infection

KAH   King Abdulaziz Hospital

MIC	Minimum inhibitory concentration
MEM	Meropenem
MONG	Ministry of National Guard
MRSA	Methicillin-resistant *Staphylococcus aureus*
NHS	National Institute for Health Research
NNIS	National Nosocomial Infection Surveillance
PI	Principal investigator
PT	Prothrombin time
PTC	Pharmacy and Therapeutics Committee
PTT	Partial thromboplastin time
RCT	Randomised controlled trials
SFDA	Saudi Food and Drug Authority
SSI	Skin and skin structure infection
UTI	Urinary tract infection
q8h	Every 8 hours
q6h	Every 6 hours
q12h	Every 12 hours
QALY	Quality-adjusted life years
SAR	Saudi Arabian Riyal
WBC	White blood cell count

ABSTRACT

Introduction: The aim of this study was to compare the costs of management of moderate to severe infections in patients treated with imipenem/ cilastatin (IC) and meropenem (MEM). Pharmacoeconomic studies in Saudi Arabia are scarce. Available hospital data illustrate that carbapenem antibiotics are among the most expensive medicines being procured. The current hospital formulary at the King Abdulaziz National Guard Hospital, Al-Ahsa, Saudi Arabia, contains 2 carbapenems: IC and MEM. These antibiotics share a similar spectrum of activity, with the unit cost of IC (500mg/ 500mg) being less than that for MEM (1 gram). There are conflicting reviews with regard to the relative cost-effectiveness of these 2 agents. An unpublished pharmacoeconomic review at our institute has shown that an interchange programme substituting MEM with IC would lead to a cost saving of SAR2 306 257 per year.

Methods: A retrospective, single-centre cohort study of 88 patients, applying cost-minimization analysis, of IC versus MEM in moderate to severe infections was conducted at the King Abdulaziz National Guard Hospital, Al-Ahsa. In accordance with cost-minimization analysis methods, the assumption of equivalent efficacy was demonstrated by literature retrieved and cited. Direct costs related to the management of the infections were included in the study. Adult patients ($\geq$ 18 years old) diagnosed with moderate to severe infection, including skin and skin structure infections (SSIs), sepsis, intra-abdominal infections (IAIs), respiratory tract infections, urinary tract infections (UTIs) and hospital-acquired infections (HAIs), who were prescribed IC 500mg every six hours intravenously (2 gram per day) or MEM 1 gram every eight hours (3 gram per day), were included in the study.

Results: Overall there was no difference in the mean total daily costs between IC (SAR 4 784.46, 95% CI 4 140.68, 5 428.24) and MEM (4 390.14, 95% CI 3 785.82, 4 994.45;, p = 0.37). The study showed no significant difference in terms of mean daily critical care hospital stay costs. Mean general ward costs were significantly lower in the IC group. Significantly lower medicine acquisition vial cost of IC was observed when compared to MEM, however there was a significantly higher cost attached to administration sets used in the IC group than the MEM group. Consultation, nursing and physician costs were not significantly different between the groups. No differences were observed in costs associated with adverse drug events (ADEs).

Conclusion: This study has shown that while acquisition costs of IC at a dose of 500mg q6h may be lower than for MEM 1 gram q8h, mean total costs per day were not significantly different between IC and MEM, indicating that medicine costs are only a small element of the overall costs of managing moderate to severe infections. Enforcing the Pharmacy and Therapeutic Committee (PTC) recommendations will assist in selecting the most appropriate carbapenem, while at the same time minimize drug costs. Further pharmacoeconomic research within the Kingdom of Saudi Arabia is essential in selecting cost-effective medicines.

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CHAPTER 1: INTRODUCTION

1.1.   Introduction

As in almost every health system, medication costs at the King Abdulaziz Hospital (KAH) have increased noticeably over time. High prices of essential medicines are a heavy burden on the government budget. Policymakers are in search of the most cost-effective options for the government and society as a whole.

Available hospital data show that the carbapenem antibiotics were the third most expensive pharmacological class procured during the 2009. The current hospital formulary lists two carbapenems: the fixed-dose combination of imipenem/cilastatin (IC) and meropenem (MEM). MEM is restricted to infection control physicians, while IC is restricted to infection control, intensivists and haematology/oncology practitioners. These antibiotics share a similar spectrum of activity, but the unit cost of IC (500mg/500mg) is less than that for the equipotent dose of MEM (1g). There are conflicting reviews with regard to the relative cost-effectiveness of these two medicines (1, 2).

There have been considerable differences in prescribing patterns among local physicians at KAH. Hospital usage data indicate that MEM is prescribed much more frequently than IC. Partly, this may be related to the concern about seizures associated with the use of IC (3). IC has been used for more than 20 years, and has an extensive range of approved indications. IC may therefore be an attractive choice in terms of acquisition cost.

An unpublished pharmacoeconomic review at KAH has shown that an interchange programme, substituting MEM with IC, would lead to a cost saving of Saud Arabian Riyals (SARs) 2 306 257 per year. Hospital antimicrobial usage data since 2004 shows that IC usage is

significantly lower than MEM. This has had a considerable impact on the hospital budget. There have been limited applications of pharmacoeconomic evaluations in Saudi Arabia (4). It would be most appropriate to test the economic impact of the proposed substitution as well as the main factors influencing hospital costs, in this setting, based on pharmacoeconomic principles. In this regard, a cost-minimization analysis could provide an estimate of the economic impact of these therapeutically equivalent medicines, focusing on local Saudi Arabian data.

1.1.1. Aim:

To contribute to the rational selection of medicines, in order to achieve efficiencies and better patient outcomes, by focusing on high-cost medicines used in the Saudi Arabian health system.

1.1.2. Objectives:

1. To conduct a cost-minimization analysis of the cost of management of moderate to severe infections in adult patients treated with either imipemen-cilastatin or meropenem in a Saudi Arabian tertiary hospital.

2. To determine whether the existing antimicrobial interchange protocol was appropriate, in the light of the direct costs incurred for patient care.

3. To make recommendations on strengthening the selection of medicines in this setting.

1.2. Background

In Saudi Arabia, the population of 27 million has access to over 400 hospitals, 2075 health care centres and 850 private clinics. Medicine costs have been increasing substantially over time, with an estimated total national expenditure of SAR 13.9 billion ($3.7 billion) in 2013 (5). Health care in Saudi Arabia is predominantly provided by the government (public) sector. This includes the Ministry of National Guard, Ministry of Health, Ministry of Defence and Ministry of Higher Education (through the University-associated hospitals) (6).

The Ministry of National Guard (MONG) provides free health care to members of the National Guard and their dependents. MONG operates 5 hospitals with almost 3000 beds in total. Unofficial reports estimate the total medicine expenditure at these MONG facilities to be approximately SAR 1 billion per annum.

In 2012, total annual expenditure on MEM at KAH placed it in the top 10 medicines at the institution in value terms. Data on carbapenem utilisation in the KAH intensive care unit (ICU) for 2009 was compared to similar figures reported in the United States National Nosocomial Infection Surveillance (NNIS) report for 2004 (7). Usage was measured in defined daily doses (DDDs) per 1000 patient days (7). The NNIS report interprets any result above the 90th percentile as a higher outlier, which indicates a problem in terms of usage. Usage at KAH in 2009 extended into the 90th percentile of US usage, as measured in 2004, as shown in Figure 1. This can be interpreted as indicative of excessive use of the carbapenem group as a whole, in comparison to the US norm.

Figure 1 - Carbapenem usage at King Abdulaziz Hospital (KAH)
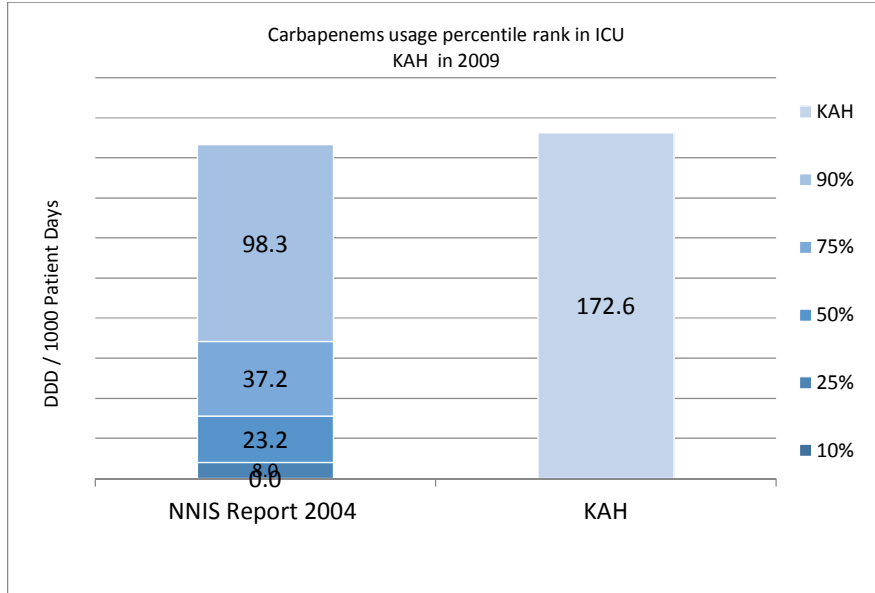
The Department of Infection Control, Department of Microbiology and Pharmacy attempted to minimise usage of MEM by suppressing mention of this agent in sensitivity reports appearing in the hospital's electronic health information system. If MEM was sensitive to the causative organism, the health information system would not suggest MEM as a treatment option to prescribers; however it would report other alternative antibiotics that are sensitive to the organism. In the case where there are no alternatives, then only would the sensitivity reports disclose MEM as the drug of choice. This was implemented in an attempt to encourage usage of alternative antibiotics, including IC. The Pharmacy and Therapeutics Committee (PTC) also restricted the use of MEM to infection control practitioners only. IC was restricted to infection control, intensivists and haematology/oncology practitioners. The Infection Control Department developed usage guidelines for IC and MEM. It was projected that the institute could save more than SAR 2 million, if these guidelines were followed. The hospital's clinical pharmacist

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subsequently reviewed the usage of IC in the intensive care unit, using the approved guidelines. These interventions have assisted in the rational use of some of the most expensive antibiotics, especially in the intensive care unit. The unpublished pharmacoeconomic review examined the acquisition costs of the study drugs and did not include resource costs associated with the primary infection. A cost-minimization analysis is therefore proposed in an attempt to investigate overall costs between these two clinically equivalent drugs.

1.2.1. Pharmaceutical Expenditure in Saudi Arabia

Saudi Arabia is the largest oil producer in the world, and is considered affluent enough to meet its health expenditure bill comfortably. However, an increase in health care demand in any country places stress on the ability of that government to cover the financial costs. In a country where citizens do not pay taxes and rely on the government to pay the totality of all health care costs, considerations of cost-effectiveness and value-for-money need to be prioritised, Pharmacoeconomics could play an important role in guiding hospital formularies in selecting cost-effective therapies. It may seem that there are limited restrictions to health care budgets in Saudi Arabia; however it seems inevitable that the country will increasingly look for strategies to minimise expenses as demands on the fiscus increase.

In 2010, the population in Saudi Arabia was reported to be 27 136 977, with an annual population growth rate of 3.2% (6). The Gross Domestic Product (GDP) growth rate was 4.15% in 2010. Life expectancy at birth is 72.6 years for males and 74.9 years for females. Infectious and parasitic diseases are the sixth most important cause of death (6), after:-

1. accident, injury, poison, and external reason;
2. circulatory system disease;

3. certain cases arising in the perinatal period;

4. respiratory disease; and

5. tumours.

Approximately 69% of the population receives free medical care from the government sector (6). The total annual health expenditure in 2009 was SAR 72.3 billion. In 2010, pharmaceutical expenditures were reported to be SAR 13.5 billion. Pharmaceutical expenditure makes up 18% of the total health expenditure (6).

Saudi Arabia is a member of the World Trade Organization and is therefore a signatory of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). Patents on pharmaceutical products are therefore routinely exercised in Saudi Arabia, limiting early access to generic medicines except in the case of deliberate licensing by the patent-holder. There are approximately 19 licensed pharmaceutical manufacturers in Saudi Arabia. However both IC and MEM are imported into the country as finished pharmaceutical products. IC is imported from the Netherlands and MEM from Italy. The local supplier (Al-Naghi) bears the responsibility for importation of both of these products. Under Saudi law, the medicines regulatory authority, the Saudi Food and Drug Authority (SFDA), also controls medicine pricing. Control of pricing includes pharmaceutical companies' factory costs at the country of origin, plus insurance and freight charges (8). IC was priced at SAR 70.40 (for imipenem 500mg/cilastatin 500mg) on the SFDA human price list for October 2013, while MEM was priced at SAR 151.26 (for meropenem 1g) (8).

1.2.2 Pharmacoeconomic principles

Health care has become a challenging environment for professionals, in trying to achieve the highest quality of care based on sound evidence-based principals. However, rising health care costs may hinder best practices. In a cost-sensitive culture, pharmacoeconomics may shed light on the value achieved for a set investment. Applications of pharmacoeconomics must be based on a clear understanding so as to ensure that the findings enable effective interventions, such as in the field of medicines selection.

The field of pharmacoeconomics identifies the costs and consequences of alternative medicines therapy in order to make the best possible decision, while ensuring the maximum benefit and efficiency of budgets or resources (9). Pharmacoeconomics utilises sound evidence-based principles by comparing benefits in terms of the resources available. It attempts to quantify the value of pharmaceutical care and services. As two or more agents are being compared, it is essential to consider the relative efficacy and safety of these options. The four main forms of pharmacoeconomic analyses are cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA) and cost-minimization analysis (CMA).

In a CEA, the relative costs and effects of two or more courses of action are measured. The effects are measured in natural units, such as years of life gained or symptom free days (9). Generally speaking, CEA could be used to determine if an additional budget is worth the additional benefit of the competing option (be that a medicine or other health care intervention) (10). However such studies have received criticism due to the interpretation of these 'effects' (9). Critically, one of the agents must be therapeutically superior to the other and more expensive. The incremental cost of achieving the additional benefits associated with the more expensive option are determined, and compared with a pre-determined cost-effectiveness threshold. In a

CUA the consequences are combined in a single generic measure such as quality adjusted life years (QALY) gained, cost per healthy year equivalent or cost per disability adjusted life year (DALY) (11). The term 'utility' has not been precisely defined. However in practice it may be thought of as an interval scale measuring the strength of preference for a given health state (11). A utility may be represented by a number measuring the intensity of preference, where full health is given the utility 1 and death 0. The methods used in estimating utilities have been much debated (11). In a CBA, the consequences are measured in terms of money (9). With CBA, studies apply a monetary value to outcomes, facilitating comparisons between health and non-health programmes (11). In all pharmacoeconomic analyses, generalisability may be limited by the reliance on local data.

In this study, a CMA approach was selected, which assumes that the consequences are clinically equivalent and then determines the least costly alternative (12). The assumption that both IC and MEM are clinically equivalent in terms of safety and efficacy will be tested in the literature review section. A CMA can only be performed if two interventions produce the same clinical effect (12). The prospective, randomized, controlled trial (RCT) is considered the 'gold standard' when comparing two interventions (12). The assumption of clinical efficacy and safety equivalency between IC and MEM was tested in the literature review section. Studies on the local population may be more applicable to the context of Saudi Arabia and hence a study of this nature was considered.

Assessing the costs and consequences depends on the perspective of the study. The patient perspective includes the costs that the patient pays for a product or service. The consequence includes the clinical effects. The societal perspective considers the benefits to society and thus measures both direct and indirect costs associated with the treatment. In the payer perspective,

often relied upon by government institutions, the costs are represented by the costs of delivering the health services or products allowed or reimbursed. This study utilizes the perspective of the payer (government) in terms of both costs and consequences. The costs include direct medical costs only. Direct medical costs include the costs of medicines, laboratory tests, health care provider costs, hospitalization costs, supplies and administration costs. Direct non-medical costs (transportation and food), indirect medical costs (lost income) and intangible costs (pain and suffering) are not considered in a payer perspective analysis. Figure 2 outlines the basic concept of the economic evaluation conducted. Here IC and MEM are being compared in terms of success and failure. This is followed by a costing analysis. The objective is to find the least costly alternative.

Figure 2 - Economic evaluation of costs and outcomes
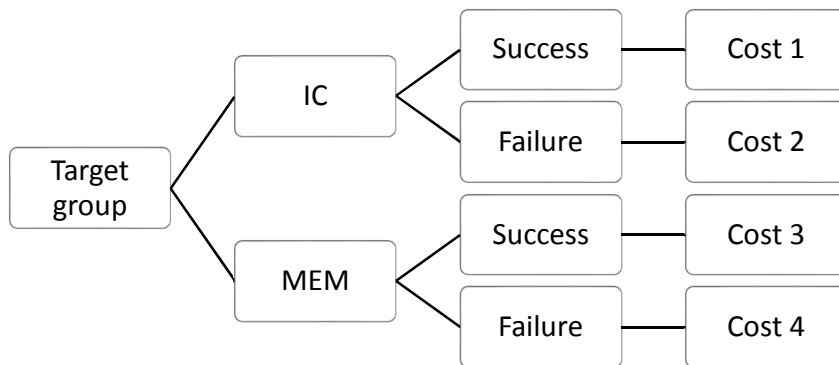
Key: IC = imipenem/cilastatin; MEM = meropenem

Although pharmacoeconomic models may provide valuable input to guide medicines selection decisions, several uncertainties may remain. In this regard a sensitivity analysis may explore if the conclusions of the study are dependent upon underlying assumptions or errors in measurement (13). A one-way sensitivity analysis allows investigators to evaluate the impact of

one parameter on the conclusions of the study. In this case one variable is varied while the others are kept at their baseline value. This can allow the researcher to assess which parameters are likely to have the greatest influence on the conclusions reached. These results can be expressed graphically in the form of a tornado diagram. A multi-way sensitivity analysis examines the relationship of 2 or more parameters on the conclusions of the study. This can be represented in a graph, plotting the input and output of the results. In this way a researcher could find the threshold at which the conclusion changes (14).

1.3. Clinical Pathology and Management

Management of a primary infection must be based on clear understanding of the pathology and the clinical course of the disease. The KAH Infection Control and Prevention Department has provided guidelines for the use of IC and MEM (15). In this study the comparative efficacy and safety of IC to MEM was assessed on the basis of the available literature. This Introductory section provides a brief explanation of the conditions for which these antibiotics are used.

1.3.1. Intra-abdominal Infection (IAI):

IAI has been described as an abscess or peritonitis affecting several areas of the gastrointestinal tract. This is generally due to infiltration of bacteria in the wall of a hollow viscus or beyond (16). Common sites include the stomach, biliary tract, duodenum, pancreas, appendix, small intestine and the colon (17). Clinical presentation includes rapid onset of abdominal pain and symptoms of gastrointestinal dysfunction. Definitions remain unclear, however. Uncomplicated IAI usually refers to inflammation or infection of the wall of an abdominal organ. If not treated appropriately, it can lead to complicated IAI (16). Most of the complicated IAIs involve peritonitis or intra-abdominal abscesses (16). The Infectious Disease Society of America (IDSA) has endorsed the use of empiric monotherapy using either IC or MEM in IAI (18).

Microbiology of IAI

The causative organisms of IAI are largely related to the resident gastrointestinal flora (16). Treatment should target Gram-negative aerobic and facultative bacilli, anaerobes as well as β-lactam-susceptible Gram-positive cocci (19). Common pathogens include *Escherichia coli, Klebsiella* species*, Pseudomonas aeruginosa, Proteus mirabilis, Enterobacter* species*, Bacteroides fragilis, Clostridium* species*, Prevotella* species*, Streptococcus* species*,* and *Enterococcus* species (18). IAI developing from perforations of the gastrointestinal tract or any of its appendages are mainly polymicrobial. Nosocomial pathogens in the health care setting make patients particularly susceptible , and such infections may further be complicated by fungal infections, especially *Candida* species (16). In obstructive disorders for distal small bowel, colon-derived infections and proximal small bowel perforations, therapy should include agents effective against obligate anaerobic bacilli (19). In the case of hospital-acquired infections, local pathogen sensitivity and resistance patterns should be considered.

Treatment of IAI

Interventions include drainage of the abscess or infected fluid collections, surgical intervention, as well as pharmacological management. Early appendectomy has been considered essential , although some experts opt for non-surgical intervention with antibiotic management (16). Treatment of diffuse peritonitis and patients with septic shock may be more complex (16).

The goal of antimicrobial therapy is to target the resident organisms as described above. Carbapenems provide a broad spectrum of coverage making them suitable for IAI. β-lactam/β-lactamase inhibitor combinations such as piperacillin/tazobactam or ampicillin/sulbactam could

be used. Cephalosporins with anaerobic cover include cefotetan and cefoxitin. Fluoroquinolones could include moxifloxacin. Other regimens have included tigecycline, cephalosporin-based regimens, monobactams and aminoglycosides. Several studies have demonstrated the efficacy of carbapenems (IC and MEM) in IAI. These studies will be discussed in the literature review section below (16).

1.3.2. Skin and Skin Structure Infections (SSI):

SSIs are responsible for about 10% of hospital admissions in the United States (20). They may be uncomplicated or complicated. Uncomplicated SSIs include impetigo, abscesses, furuncles and cellulitis (20). SSIs are considered complicated when they involve deep structures, involve patients with comorbidities like diabetes mellitus (DM), immunocompromised patients, or require surgical intervention (21). This may include major abscesses, infected burns and ulcers, infected bite wounds and diabetic foot infections (20). Clinical presentation may include pain, fever, hypothermia, tachycardia hypotension, violaceous bullae, cutaneous haemorrhage, skin anaesthesia and gas in the tissue (22). Infections may include abscess, impetigo and cellulitis, necrotizing infections, surgical site infections, immunocompromised-associated infection and animal-contact-with-human skin-associated infections (22).

Microbiology of SSI

Treatment should target *Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa,* and *Enterococcus* species*.* Recently methicillin-resistant *Staphylococcus aureus* (MRSA) has added to the complications of treatment (20).

Treatment of SSI

First-line agents include cephalosporins, such as cephalexin and cefdinir, or penicillins such as cloxacillin. Newer generation fluoroquinolones, such as moxifloxacin and gatifloxacin, may be used. In complicated SSI, aggressive treatment is necessary, making the broad spectrum carbapenems an appropriate choice (20).

1.3.3. Lower Respiratory Tract Infection (LRTI):

LRTIs are infections involving the airway and lungs that include pneumonia, bronchitis, bronchiolitis and tuberculosis. LRTIs may present as acute bronchitis, influenza, community-acquired pneumonia (CAP), acute exacerbation of chronic obstructive pulmonary disease (COPD) and acute exacerbation of bronchiectasis (23). Acute LRTI usually presents as a cough with secondary symptoms that could include sputum production, dyspnoea, wheeze or chest discomfort and pain (23). IDSA has developed a comprehensive set of guidelines to assist in hospital-based management. Severity of illness scores modified to the hospital setting may also be utilised. In community-acquired pneumonia (CAP), an example is the CURB-65 criteria (confusion, uraemia, respiratory rate, low blood pressure, and age above 65). With scores ≥ 2, intensive home health care is needed, while patients in septic shock require direct ICU admission. Diagnostic testing includes chest radiograph or other imaging demonstrating infiltrates. Blood, endotracheal fluid and sputum cultures are recommended. Consideration should be given to aspiration pneumonia, left ventricular failure, and pulmonary embolism during the differential diagnosis.

Microbiology of LRTIs

Treatment should target Gram-negative pathogens, *Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus pneumoniae, Acinetobacter* species, *Mycobacterium tuberculosis,*

Haemophilus influenzae, Legionella species, *Moraxella catarrhalis, and Chlamydia* species (23).

In recent years MRSA has been implicated in LRTIs.

Treatment of LRTIs

Early antibiotic treatment should be considered. Suitable choices include a penicillin with or without macrolides or quinolones. The newer higher penicillin dosing available (such as amoxicillin-clavulanic acid 2000mg/125mg) may prove advantageous. Quinolones with activity against *Streptococcus pneumoniae*, *Haemophilus influenzae, Staphylococcus aureus* and *Moraxella catarrhalis* are now an established treatment in LRTIs. Carbapenems provide a broad spectrum of activity and an appropriate choice for treatment in limited circumstances (23). Their usage would be limited to instances of failure of first-line penicillins, such as penicillin resistance, as they are the most active beta-lactams that counter penicillin-resistant *Streptococcus pneumonia* (23).

1.3.4. Urinary Tract Infection (UTI)

UTIs in adults are a group of disorders affecting the bladder, kidney, urethra and ureter. High-risk groups include sexually active women, the elderly, diabetics, and those undergoing a surgical procedure. Patients present with fever, pain in the lower abdomen, dysuria and increased frequency of urination. Computerised tomography (CT) scan, intravenous pyelogram, urine culture and urinalysis may be done to confirm diagnosis. UTIs have been classified as acute uncomplicated cystitis, recurrent cystitis in young women, acute cystitis in young men, acute uncomplicated pyelonephritis, complicated UTI, asymptomatic bacteriuria in pregnancy and catheter-associated UTI (24).

Microbiology of UTIs

Causative pathogens may include *Escherichia coli, Staphylococcus* species, *Proteus mirabilis, Klebsiella pneumoniae, Enterococcus* species, *and Pseudomonas aeruginosa (24).*

Treatment of UTIs

Treatment may range from simple hygiene interventions to surgical interventions or antibiotic therapy. Pharmacotherapy for acute uncomplicated UTI usually includes trimethoprim-sulfamethoxazole, fluoroquinolones, amoxicillin, cephalosporin (such as ceftriaxone), or nitrofurantoin. For recurrent cystitis, prophylactic treatment is warranted. Carbapenems offer a broad spectrum of activity which may prove effective in complicated UTIs, as they are active against organisms associated with some nosocomial UTIs (24, 25).

1.3.5. Sepsis

Sepsis is defined as an inflammatory response to infection. It could occur as a result of multiple causes and infections (26). Severe sepsis describes the occurrence of acute organ dysfunction and septic shock, when it is complemented with hypotension (26). Risk factors include chronic diseases like COPD or other pulmonary disease, and the use of immunosuppressive agents. Severe sepsis may be a result of community-acquired and healthcare-associated infections. The clinical presentation may be variable and depends on several factors like the site of infection, the causative organism, underlying health status and organ dysfunction. Cardiovascular and respiratory symptoms may accompany organ dysfunction. Other organs affected include the central nervous system and the kidneys. Criteria for diagnosis include fever (above 38 degrees Celsius), hypothermia (temperature below 36 degrees Celsius), elevated heart rate (greater than

90 beats per minute), tachypnoea, altered mental status, oedema or positive fluid balance (>

20ml/kg over 24 hour period) and hyperglycaemia. Inflammatory markers include leucocytosis,

leukopenia, elevated C-reactive protein, and elevated procalcitonin. Other variables include

arterial hypertension, acute oliguria, coagulation abnormalities, hyperbilirubinaemia, and

thrombocytopenia (26).

Microbiology of Sepsis

The most common Gram-positive bacteria implicated in sepsis include *Staphylococcus aureus*

and *Streptococcus pneumoniae.* The Gram-negatives include *Escherichia coli, Klebsiella* species

and *Pseudomonas aeruginosa* (26).

Treatment of Sepsis

Early management includes cardiovascular resuscitation and alleviating the threat of infection.

Vasopressors, oxygen, intravenous fluids and mechanical ventilation are vital during

resuscitation. Empiric pharmacotherapy depends on site of infection, hospitalized or home care

and microbial sensitivity patterns. Antibiotics should be started as early as possible. (26).

1.3.6. Hospital-Acquired Infection (HAI)

HAIs are defined as "localized or systemic conditions resulting from an adverse reaction to the

presence of infectious agents or toxins" (27). HAIs pose a huge burden to costs and hospital stay,

and are associated with a high (6%) risk of mortality (27). HAIs may occur as a result of

catheter-related blood stream infections, ventilator-associated pneumonia, surgical site infections

and catheter-associated urinary tract infections. Signs and symptoms include fever, chills and

malaise. For catheter-related blood stream infections, the catheter tip is sampled for microbial

growth. Ventilator-associated pneumonia requires examination of respiratory secretions. The presence of leucocytosis, rhonchi, and a chest radiograph showing infiltrate and compromised oxygenation and ventilation are indicative of the condition. Surgical site infections have numerous definitions that depend on patient or wound characteristics and positive culture findings. Surgical site infections mainly result from microbes invading the surgical wound at the time of surgical procedure. Patients at risk include those with compromised nutritional status, those with DM, COPD, other pulmonary disease, renal or hepatic failure, immunosuppression and MRSA carriers. Catheter-associated urinary tract infections are common in a hospital setting and usually involve organisms that infect the urinary tract. Biofilms may contaminate the catheters. Patients at risk also include females, those with renal disease, impaired nutritional status and those with infections at sites remote from the primary lesion (27).

Microbiology of HAI

For catheter-related blood stream infections, causative organisms include *Staphylococcus epidermis, Staphylococcus aureus, Enterococci,* Gram-negative bacilli as well as fungi *(Candida* species). For ventilator-associated pneumonia, the organisms may include Gram-negative bacilli such as *Pseudomonas aeruginosa, Proteus* species, *Klebsiella* species, *Acinetobacter, Escherichia coli* and *Hemophilus influenzae*. *Staphylococcus aureus* and fungi such as *Candida* may also be involved. Surgical site infections are caused by *Staphylococcus aureus* and some Gram-negative organisms. Catheter-associated urinary tract infections are associated with *Pseudomonas aeruginosa, Escherichia coli, Enterococci, Enterobacter* species, *Klebsiella* species as well as fungi such as *Candida* species (27).

Treatment of HAI

General recommendations include hand hygiene, aseptic practice and use of topical disinfectants. Catheter-related blood stream infections require removal of the catheter (except in the case of *Staphylococcus epidermis*), and then rapid clearance of bacteraemia. Infections involving *Staphylococcus epidermis,* such as haemodialysis-associated infections, may be treated with appropriate antibiotics (27). Antimicrobial therapy should be routinely given over 7 to10 days. Patients with complicated infections can receive up to 8 weeks' of therapy. Ventilator-associated pneumonia requires early antibiotic therapy based on cultures and clinical presentation, lung abscess drainage or surgical interventions. Catheter-associated urinary tract infections require removal of the catheter, and then antibiotic therapy based on culture or the clinical presentation (27).

1.4.   Pharmacology

IC and MEM are both carbapenem antibiotics. These beta-lactam antibiotics are similar to penicillins and cephalosporins, but differ in their structure, as shown in Figure 3.

Figure 3 - Chemical Structures of Imipenem and Meropenem

Imipenem

Meropenem
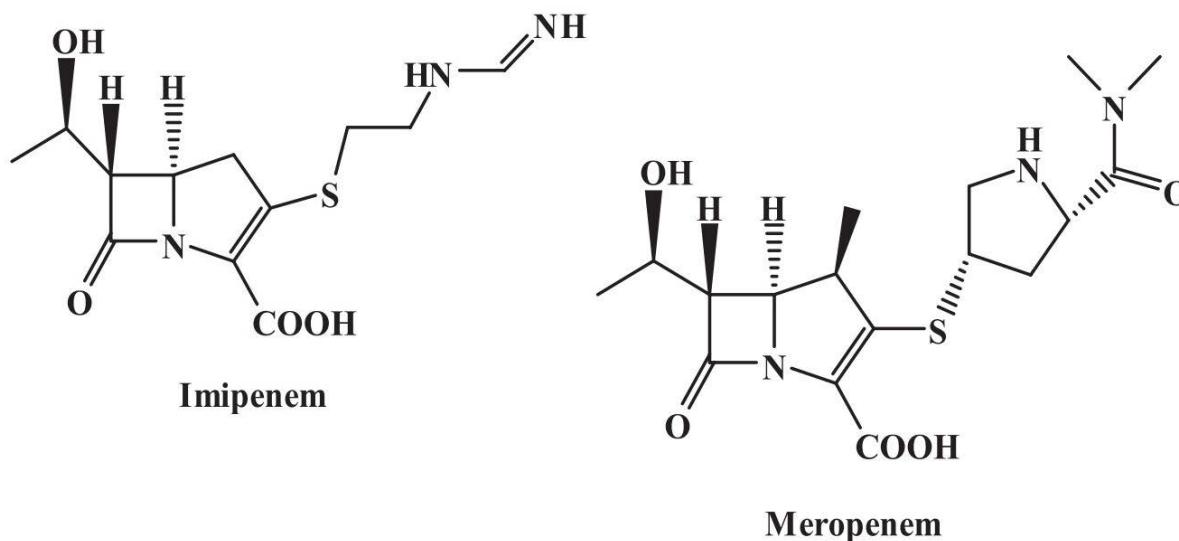
The sulphur atom of the thiazolidine ring has been externalized and replaced by a carbon atom (28). Carbapenems inhibit bacterial cell wall synthesis. Both IC and MEM exhibit activity against a wide range of Gram-positive and Gram-negative aerobic and anaerobic bacteria. They are quite stable against beta-lactamases, including extended-spectrum beta-lactamase producers (ESBLs). ESBLs are commonly found in *Klebsiella pneumonia, Escherichia coli* and other *Enterobacteriaciae* (29). Both agents have shown activity against Gram-negative bacteria such as *Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Stenotrophomous* species, *Acinetobacter baumanii* and *Enterobacteriaciae*. Gram-positive bacteria covered include *Staphylococcus* species, *Enterococcus* species and *Norcadia* species (17, 30-32). However, carbapenemases may hydrolyse carbapenems, rendering them inactive (29).

Resistance patterns

Extensive use of carbapenems may result in the development of resistance, especially among *Acinetobacter* species and *Pseudomonas aeruginosa*.

1.4.1. Imipenem/ cilastatin (IC)

The first carbapenem became commercially available in 1985 for the treatment of complex microbial infections (32). Imipenem, derived from thienamycin, showed significant affinity for penicillin binding proteins and was stable against β-lactamases. Imipenem was, however, prone to degradation in in the human kidneys by dehydropeptidase 1. Incorporation of an enzyme-inhibitor such as cilastatin was required to improve activity as well as prevent renal toxicity (29, 32). IC has been marketed by Merck Sharp and Dome with the trade name Tienam® in Saudi Arabia (8). The mode of action of IC allows for activity against Gram-positive and Gram-negative cocci and bacilli, both aerobes and anaerobes (32).

Dosing of IC

Both standard dosing of 500mg every six hours (q6h) and 1 gram every eight hours (q8h) results in a Minimum Inhibitory Concentration (MIC) of approximately the same time (29). IC is given as an intramuscular injection or intravenous infusion of at least 20 minutes. The United states FDA has approved the dose of IC from between 250mg q6h to a maximum of 1 gram q8h depending on the severity of the infection. The dose should be adjusted in patients with impaired renal function (creatinine $\leq$ 70 mL/min/1.73 m2) body weight less than 70 kg (33).

Pharmacokinetics and Pharmacodynamics of IC

IC given over 20 minutes result in plasma peak levels of 14 -24 mg/L (250mg dose), 21-56 mg/L (500mg dose) and 41-83mg/L (1 gram dose) (29). The plasma half-life is approximately 1 hour. After 1 hour of dosing the median concentration in the lung tissue is 5.6mg/kg, in the endometrial tissue 11.1 mg/kg, in the pleural fluid 22mg/kg, in the cerebrospinal fluid 2.6 mg/L

and in the interstitial fluid 16.4mg/L. Efficacy depends on time above the MIC, with the peak killing when 40% of the dosing interval has drug concentration higher than MIC (29).

Safety and tolerability of IC

The most common reported adverse effects observed in patients were thrombophlebitis/ phlebitis (3.1%), nausea (3.1%), vomiting (1.5%) and diarrhoea (1.8%). Seizure rate was found to be about 0.4% (29).

1.4.2. Meropenem (MEM)

MEM is a broad spectrum carbapenem that was developed and approved by the United States FDA later than IC (19, 30). Like IC, it interferes with bacterial cell wall synthesis with activity against most Gram-negative and Gram-positive bacteria. The high affinity for penicillin-binding proteins results in eventual cell death. MEM is quite stable against ESBLs and unlike IC it is much more stable against dehydropeptidase. It has been marketed in Saudi Arabia as Meronem®, manufactured by AstraZeneca (8). Meropenem has been reported to be somewhat more active against Gram-negative organisms and less active against Gram-positive than IC (19).

Dosing of MEM

The standard dose of MEM is from 500mg q8h to 1 gram q8h, given as an IV infusion of over 30 minutes or a bolus infusion of over 5-10 minutes (34). A maximum dose of 2 gram q8h has been used in bacterial meningitis (30). MEM has time-dependent bactericidal activity. This is best achieved when the plasma concentration remains above the MIC throughout the dosing interval The dose should be adjusted in patients with compromised renal function (creatinine clearance < 51 mL/min/1.73m^2) (34).

Pharmacokinetics and Pharmacodynamics

MEM given at a dose of 500mg achieves peak concentrations of about 23 mg/L, and after 1 gram achieves 49 mg/L. Administering 500mg or 1g of MEM as a bolus over 5 minutes achieves peak concentrations of 52 and 112 mg/L respectively. The peak concentrations achieved in various tissues were as follows : gynaecological tissues (0.3-10.2 µg/g, 500mg), skin (0.5-12.6 µg/g and 1.3-16.7 µg/g, 500mg and 1 gram), interstitial fluid (3.2 – 8.6 and 20.9 – 37.4 µg/g, 500mg and 1 gram), intra-abdominal tissue (2.5-3.9 µg/g, 1 gram), peritoneal fluid (7.4-54.6 µg/mL, 1 gram), bronchial mucosa (1.3-11.1 µg/g, 1 gram), lung tissue (1.4-8.2 µg/g, 1 gram). MEM distributes widely into tissues and fluids and has an apparent volume of distribution of between 12.5 and 20.7 litres. The elimination half-life is approximately 1 hour (30).

Safety and tolerability of MEM

Reported adverse effects (which occur in <3% of patients) includes nausea, vomiting and diarrhoea (2.5%). Seizures occurred in approximately 0.38% of patients (19).

1.5. Place in Therapy

The United States FDA has approved the usual IC dosage for mild to severe infections from between 500mg to 1 gram every eight to six hours. The approved indications includes endocarditis, polymicrobial infections, bacterial septicaemia, gynaecological infections, intra-abdominal infections (IAI), lower respiratory tract infections (LRTI), urinary tract infections (UTI), skin and skin structure infections (SSI), as well as bone and joint infections (33). MEM has been FDA-approved for moderate to severe infections, in the treatment of SSI, IAI, bacterial meningitis, at a dose of 500mg to 2 gram every eight hour (34).

1.5.1. Ministry of National Guard (MONG) Institutional Guidelines

The Ministry of National Guard (MONG) antimicrobial guidelines (15) restrict- IC to infection control practitioners, intensivists and haematology/oncology consultants, while MEM is restricted to infection control practitioners only. The following antimicrobial guidelines have been recommended at KAH:

1.5.1.1. Imipenem/ cilastatin

Acceptable uses:

a) Treatment of bacterial septicaemia

b) Treatment of LRTI

c) Treatment of bone and joint infections

d) Complicated abdominal infections

e) Urinary tract infections, if ESBL is suspected

Acceptable off-label uses

a) Fever in patients with neutropaenia

b) Treatment of cystic fibrosis

c) Infective endocarditis, due to penicillin, aminoglycoside, and vancomycin-resistant *Enterococcus faecalis.*

Unacceptable uses:

a) Central nervous system infection

b) For infections caused by pathogens susceptible to other β-lactams

c) Infections in patients with end-stage renal disease

d) Patients with a history of seizures or at risk of seizures

Dose:

0.5 – 1 gram given intravenously q6h

Adverse effects:

a) Seizures

b) Cardiovascular adverse effects: palpitations and tachycardia

c) Local infusion site reaction or induration and thrombophlebitis

d) Alteration in taste

e) Thrombocytopenia

1.5.1.2. Meropenem (15)

Acceptable uses:

a) Treatment of bacterial meningitis

b) Complicated skin and/or soft tissue infections

c) Complicated abdominal infections

Acceptable off-label use:

a) Treatment of healthcare-associated pneumonia

Fever in patients with neutropaenia unacceptable uses

    a) Community-acquired pneumonia

Dose:

    1 gram given intravenously q8h, maximum dose 2 gram q8h

Adverse Effects:

    a) Inflammation at the site of infusion/ injection

    b) Leukopenia, neutropenia and agranulocytosis

    c) Angioedema, erythema multiforme

    d) Hypersensitivity reaction, Stevens-Johnson syndrome

CHAPTER 2: LITERATURE REVIEW

2.1. Introduction

The principles of a cost-minimization analysis (CMA) require that the alternative medicines (or more broadly, the alternative interventions) being compared are considered, *a priori*, to be clinically equivalent. In order to justify the CMA approach used in this study, a literature review was first conducted to justify the *a priori* assumption of clinical equivalence of IC and MEM in the types of infections treated and the doses recommended in the KAH guidelines.

2.2. Literature search approach and methods

The sources used for the literature search included the Cochrane Library, Medline database, Trip database and Google Scholar. The search terms employed included: efficacy, safety, adverse reactions, effectiveness, pharmacoeconomic, bacterial infections, skin infections, sepsis, urinary tract infections, respiratory tract infections, hospital acquired infections, meropenem and imipenem. The study types sought included systematic reviews, meta-analyses, pharmacoeconomic evaluations, clinical trials, review articles and retrospective cohort studies comparing IC and MEM. All searches were saved in Endnote citation manager. Studies were grouped by infection types as listed in the tables below. Key questions sought were:-

a)   Are the results of the study valid?

b)   What are the results?

c)   Will the results help locally?

Studies included as justifying the assumption of equivalence were those matching the key search terms above, comparing IC with MEM. RCTs were considered the gold standard when comparing IC to MEM. Although RCTs were the main focus of the search, other studies like systematic reviews, meta-analyses, pharmacoeconomic studies and other review articles were reviewed so as to support the assumption of clinical equivalence of IC and MEM, or at least non-inferiority. Studies were critically appraised for quality and relevance using the "Critical appraisal skills programme , United Kingdom" tool (35). Some studies could not be appraised as only abstracts were available. Studies that did not demonstrate clinical and safety equivalence between IC and MEM or studies which showed superiority of one agent of the other, were also described. Details are given in section 2.3.8 together with justification for the value judgments made about the relative weight of the evidence retrieved.

Studies published in any language since the year 1995 were considered, although only those provided in English or in English translation could be included. The searches were last updated in October 2013.

2.3.   Literature retrieved

The outcome of the searches conducted is depicted in Figure 4.

Figure 4- Outcome of literature search
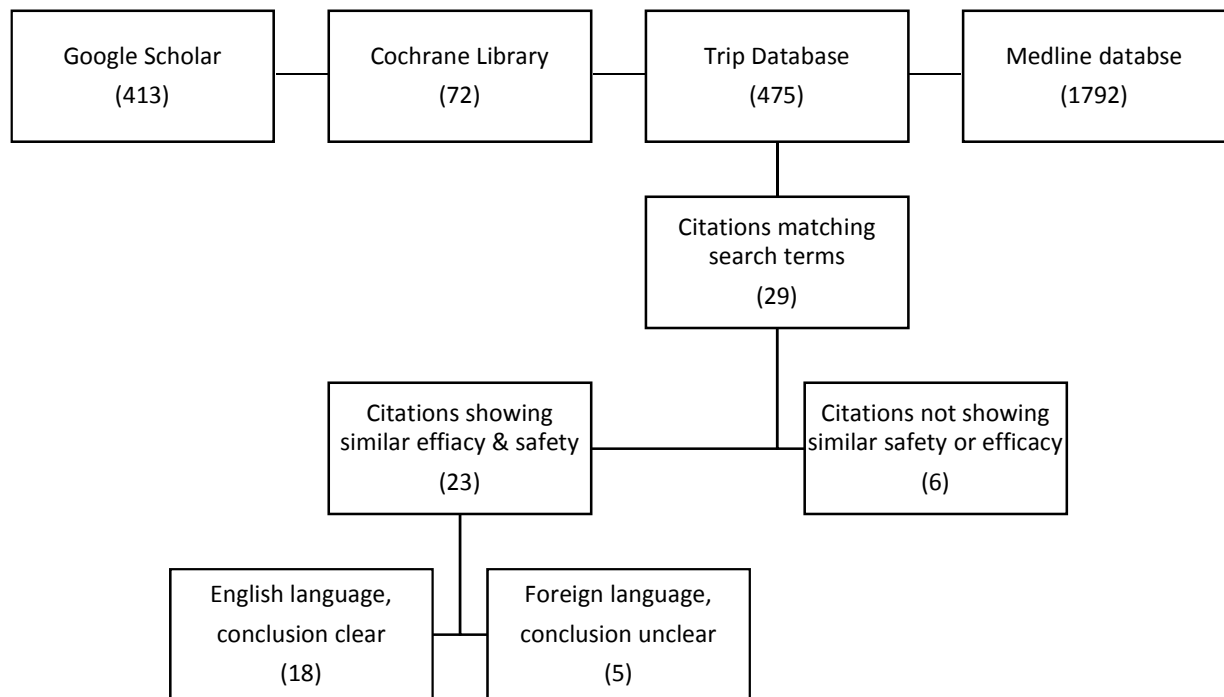
Searches conducted in Google scholar retrieved 413 studies, those in the Cochrane library retrieved 72 studies, while the Trip database returned 475 studies and the Medline database retrieved 1792 studies. Cochrane library included 1 review, 67 trials, 2 economic evaluations and 1 'other'. The Pubmed search retrieved 50 studies with search terms matching "meropenem AND imipenem and safety", 155 studies matching "meropenem AND imipenem AND efficacy", 127 studies matching "meropenem AND imipenem AND adverse", 1028 studies matching "meropenem AND imipenem AND bacterial infections" and 6 studies matching "meropenem

and imipenem AND pharmacoeconomic". Titles were reviewed so as to eliminate irrelevant topics as well as duplicates. Finally a total of 29 comparative studies were retrieved, matching the search criteria and applicable to the international context. The abstracts were reviewed to assess whether the published articles met the inclusion criteria. No local studies could be found which had been published in Saudi Arabia. Of the comparative studies retrieved, 23 showed similar efficacy or safety. Some studies could not be reviewed in detail, either due to being in a foreign language or where an unclear conclusion was recorded. Tables 1 to 3 summarise the 18 studies which were assessed as demonstrating the clinical equivalence of IC and MEM. These studies were available in the English language (at least as abstracts) and included clear conclusions, and met all inclusion criteria. The findings are then described in detail and related to the design features of the present study. Table 4 summarises the outcomes recorded in the 6 studies which did not show clinical equivalence.

2.3.1. Intra-abdominal infections (IAIs)

Five studies were retrieved; three were RCTs, one meta-analysis and one retrospective cohort studies. The study by Attanasio et al. (1) was a cost-effectiveness analysis. Table 1 summarises the studies that showed clinical equivalence of IC and MEM in the treatment of IAI.

Table 1- Studies showing clinical equivalency in IAI

Citation	Study Design	Daily dose	Sample	Study Endpoint	Results	Author's Conclusion
Zhanel et al. 1998 (36)	Review article, Comparative	All dosage ranges	N/A Severe bacterial infections	In vitro activity, pharmacokinetics, clinical uses and adverse effects	Results of individual studies reported	Literature supports the use of IC at a dose of 500mg q6h and MEM 1 g q8h for treatment of serious infections. IC appears more economical than MEM.
Attanasio E. et al. 2000 (1)	RCT, parallel over 20 centres	IC 1.5g MEM 2g	n = 287 > 18 years	Cost-effectiveness, clinical response and bacteriological response in patients with IAI.	Results of individual studies reported	No statistical difference in clinical, bacteriological response or adverse events. IC appears less costly.
Badia et al. 1999 (37)	Meta-Analysis	N/A	> 18 years	Cost-effectiveness in moderate to severe intra-abdominal infections	Results of individual studies reported	IC was shown to be as effective and less costly than MEM
Zanetti et al. 1999 (38)	Multicentre, open-label, RCT	IC 2g MEM 1.5g	n = 161	Clinical effectiveness in patients with moderately severe IAI	Results of individual studies reported	MEM is as clinically effective and well tolerated as IC
Geroulanos et al. 1995 (39)	multicentre, open, randomised study	IC 3g MEM 3g	n = 232	Clinical efficacy and tolerability in patients with IAI requiring surgery	Results of individual studies reported	MEM is as clinically effective and well tolerated as IC
Beketov et al. 2003 (40)	Retrospective Cohort	IC 1.5 g MEM 1.5g	n = 468	Efficacy, safety, economic outcomes in IAI	Results of individual studies reported	Most expensive treatment was MEM and IC. Both showed similar efficacy.

Key: IC = imipenem/ cilastatin; MEM = meropenem; IAI = Intra-abdominal infections; RCT = Randomized controlled trial; N/A = not available; g = gram; L = Italian liras; $ = United States dollar;

The studies in the literature review used varied doses of both carbapenems. The present study evaluated IC at a dose of 500mg q6h versus MEM 1gm q8h. This dosage has been supported by the KAH antimicrobial guidelines (15) as well as the United States Food and Drug Administration (FDA) (33, 34). This choice is also supported by a systematic review (36).

Zhanel et al. (36) completed a comparative review of IC versus MEM, looking at pharmacokinetics, clinical trials and adverse effects. The review was based on a MEDLINE search of the published literature from 1975 to 1997. The authors concluded that the use of IC at a dose of 500mg q6h and MEM 1 gram q8h in serious infections was supported by the available literature. In addition, it was found that IC 2 gram/ day ($98) appears more economical than MEM 3 gram/ day ($142/ day). Although this was a systematic review, no details were given in regards to the evaluation of the quality or relevance of the studies selected. Only prospective randomized trials published in peer reviewed journals were included. However, no direct comparisons were double-blinded. The methods of systematic review and statistical analyses were not mentioned. None of the trials included showed a statistically significant difference in outcomes (clinically or bacteriologically) between the two treatment groups. Both IC and MEM shared similar self-limiting adverse effects with notable concern expressed about the possibility of seizures in the IC group.

The study question was relevant to the present study as the infection types considered were comparable. These included IAI, respiratory tract infections, septicaemia, bacterial meningitis and febrile neutropenia. The present study did not include patients with bacterial meningitis or febrile neutropenia.

The economic analysis was less than ideal, as the authors only considered acquisition costs. At the time of the review, the acquisition cost of IC ($98) appears lower than that for MEM ($142) at the dose suggested.

Attanasio et al. conducted a cost-effective analysis of IC (1.5g daily) versus MEM (3g daily) in IAIs in multiple hospital settings (20 surgical centres), enrolling 287 patients (1). The University

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of York's Centre of Reviews and Dissemination has evaluated this study and found good features in terms of validity (accession number 12005000282). Effectiveness data were collected from 1991 to 1997, while cost data were collected from 1996 to 1997. However, all prices were as for 1997. The costing was carried out after the effectiveness analysis, which was in the form of a multi-centre randomized, parallel clinical trial. Patients included were over 18 years with non-life-threatening IAI. Patients who needed surgical intervention within 12 hours of traumatic bowel perforation or within 24 hours for perforation of gastroduodenal ulcer, or the administration of an antimicrobial treatment 48 hours before pre-study evaluation were excluded from the study. The direct costs included were those associated with diagnostic procedures, medicine acquisitions and administration, management of adverse events and hospitalization, based on official price lists for 1997. Indirect costs were not included. Sensitivity analysis was performed on effectiveness estimates and costs. Notably, the doses used varied from those applied in the present study at KAH, although the setting was broadly comparable and all relevant cost categories were included. The validity of the results were enhanced by the sensitivity analysis. The results showed: - IC costs = Lira 106,874 versus MEM = Lira 135,042. Attanasio et al. (1) found no statistical difference in clinical (98% IC versus 95% MEM, p = 0.439), bacteriological (96% IC, 98% MEM, p = 0.676) response, or in relation to adverse events.

Badía et al. conducted a meta-analysis of cost-effectiveness data for a range of antibiotics used in mild to moderate IAIs (37). Although the full study was only reported in Spanish, the abstract was available in English. In this analysis, outcomes were measured in natural units and only direct-health care costs were included. Although detailed data could not be obtained from the abstract, and the analysis was only based on retrospective data, this meta-analysis did show that

IC was clinically as effective (95.2% vs. 96.4%) and less costly than MEM (pesetas. 455 320 versus pesetas. 483 404). However, the exact doses used could not be extracted and the target population included a broader category of moderate to severe infection than that included in the present study.

Zanetti et al. conducted a multicentre, open-label, randomized trial comparing IC (2 gram/day) versus MEM (1.5 gram/day) in IAI, which showed IC to be as clinically effective and well tolerated as MEM (38). A clinical cure was achieved in 65/71 (93.8%) treated with IC compared with 60/64 (91.6%) treated with MEM.

Geroulanos et al. reported on a multicentre, open-label, randomized trial comparing IC (3 gram/day) versus MEM (3 gram/day) in 232 patients with moderate to severe IAI (39). Positive clinical responses were achieved in 83/88 (94%) treated with IC, compared with 79/82 (96%) treated with MEM. Bacteriological responses were also similar (81% versus 84%). A similar incidence of adverse events was observed between the both groups. The study concluded that IC was as effective and well tolerated as MEM.

Beketov et al. reported on a retrospective cohort study, which also showed IC and MEM to have similar efficacy, although IC was less costly (40). The comparisons in this study were complex though: empiric cefoperazone/sulbactam monotherapy was compared with the IC, MEM and the combination of cefepime plus metronidazole. Positive clinical responses in the MEM (87.5%) and IC (86.6%) were comparable, and were also not different from those achieved with cefepime/metronidazole (85.3%) and cefoperazone/sulbactam (86.8%). Although few details on the costing approach could be extracted, the authors reported that the total cost per 100 patients was 3 085 291 roubles for MEM and 2 653 388 roubles for IC.

2.3.2. Skin and skin structure Infections (SSIs)

Three studies were retrieved comparing IC and MEM in SSIs. Two were RCTs and one an open label prospective trial. Table 2 summarises the studies which showed clinical equivalence of IC and MEM in the treatment of SSI.

Table 2- Studies showing clinical equivalency in SSI

Citation	Study Design	Daily dose	Sample	Study Endpoint	Results	Author's Conclusion
Embil et al. 2006 (21)	International, multicentre double-blind RCT.	IC 1,5 g MEM 1.5g	n = 1076 ≥ 13 Years	Efficacy and tolerability in patients with SSI	Results of individual studies reported	IC or MEM appeared efficacious and well tolerated among patients with SSI, with or without DM
Fabian et al. 2005 (41)	Multicentre, international, double-blind, prospective randomized.	IC 1.5g MEM 1.5g	n = 1076	Clinical outcome in patients with SSI	Results of individual studies reported	MEM had comparable safety and efficacy to IC at the dosage 500mg q8h for each of the drugs
Nichols et al. 1995 (42)	Multicentre open-label prospective trial	IC 2g MEM 1.5g	n = 377	Efficacy and safety in patients with SSI	Results of individual studies reported	MEM was tolerated and as effective as IC.

Key: RCT = randomized controlled trial; IC = imipenem/ cilastatin; MEM = meropenem; ADE = adverse drug events; DM = diabetes mellitus

Embil et al. reported on a *post hoc* subgroup analysis of an international, multicentre, double-blind randomized trial in hospitalized patients, aged 13 years or older, with SSI (21). The subgroup comprised 398 diabetic patients out of a total sample of 1076. . Both IC and MEM were given at a dose of 500mg q8h (1.5 gram/day) for a minimum of 3 days. The primary efficacy endpoint was clinical outcome at 7 to 14 days after final administration of the study agent (test-of-cure visit). The clinical response rate in the subgroup was similar with IC (89.0%) IC and MEM (86.6%), and no differences in adverse events were noted. Although this study included younger patients (≥ 13 years), the mean age in the subgroup was 55 years. It was noted that a commercial sponsor (AstraZeneca) was acknowledged for their support for the study.

Overall, the results were taken to be directly applicable to the patients with SSI seen in the present study. Full details of the broader study were also available from a previous publication included here as Fabian et al. (41). This prospective, multicentre, international randomized double-blind study was one of the largest studies of hospitalized patients with SSI and has been frequently cited and considered to be robust. Cure rates were 82.9% (IC) versus 86.2% (MEM). Frequencies of ADEs and drug-related ADEs were similar between the 2 groups. This study has relevance to the context of the present study in terms of the clinical condition being treated and target population.

Nichols et al. reported on a multicentre, open-label, prospective trial comparing IC 500mg q6h (n=193) with MEM 500mg q8h (n=184) in SSI (42). No differences in clinical response (95% IC versus 98% MEM) or bacteriological response (IC 91% versus MEM 94%) were noted after an average of between 6 to 7 days' treatment. The authors concluded that MEM was as effective and well tolerated as IC.

2.3.3. Respiratory Tract infections (RTI)

Table 3 summarises the studies which showed clinical equivalence between IC and MEM in the treatment of RTI.

Three studies were retrieved comparing IC and MEM in respiratory infections. Two were RCT's and one meta-analysis.

Table 3 - Studies showing clinical equivalence in respiratory tract infections

Citation	Study Design	Daily dose	Sample	Study Endpoint	Results	Author's Conclusion
Xiao Ju, et al. 2001(43)	RCT	IC 2g - 3g MEM 1-1.5g	n = 52	Safety and efficacy in patients with bacterial infection	Results of individual studies reported	MEM is a potent antibacterial agent, can be recommended to treat mild to moderate or severe bacterial infections.
Song et al. 2001 (44)	RCT	N/A	n = 60	Cure rate, effective rate, and bacterial clearance rate in respiratory tract infections.	Results of individual studies reported	IC and MEM showed similar efficacy and safety profiles
Xiao H. et al. 2010 (45)	Meta-analysis	N/A	9 RCT's	Bacterial eradication, clinical cure rates and adverse reactions in respiratory tract infections.	Results of individual studies reported	No significant difference in clinical efficacy and adverse reactions with slightly higher bacterial eradication and clinical cure rates in the MEM group compared to IC.

Key: RCT = randomized controlled trial; IC = imipenem/ cilastatin; MEM = meropenem; ADE = adverse drug events; 95% CI = 95% confidence interval; N/A = not available

All three studies in patients with lower respiratory tract infections were conducted in Chinese subjects, and could be obtained in abstract form only. As no details of the target population were provided, their applicability to the local context of the present study could not be established.

Xiao-Ju et al. reported on a randomized controlled trial of IC (1 gram q12h or q8h) versus MEM (500mg q12h or q8h (43). Cure rates were 65.38% (IC) versus 73.08% (MEM); effective responded patients 92.31% (IC) versus 96.15% (MEM); bacterial eradication rates 96.15% (IC) versus 100% (MEM); adverse reactions 7.69% (IC) versus 11.54% (MEM). This was small study, with only 52 participants, but did show equivalence in terms of clinical response and bacterial eradication rates.

Song et al. conducted an RCT in 60 patients with respiratory tract infections (44). The cure rate, effective rate and bacterial clearance rate for MEM were 80.0%, 93.3%, 92.3%, respectively and IC were 76.7%, 90.0% and 91.3%, respectively. Rate of adverse reactions for both was 3.3%.

Similar cure rates and bacterial clearance rates were shown for IC and MEM. The authors also concluded that safety profiles were similar.

Xiao H et al. reported on a meta-analysis of 9 RCTs, retrieved by searching the PubMed database and China National Knowledge Infrastructure database between 1983 and 2009 (45). These authors used a dated method of assessing study quality (the Jadad scale). Heterogeneity was examined by Revman5.0 and Stata 10.0. Publication bias was assessed using Egger's test and Begg's test. MEM showed higher bacterial eradication rate compared with IC in moderate or severe pulmonary infection (OR: 1.62, 95% CI: 1.03-2.53). Clinical cure rate displayed a borderline statistical significance (OR: 1.39, 95% CI: 1.00-1.94). Clinical efficacy rate and incidence of adverse reactions did not show any significant difference between the two drugs (P=0.05). The authors concluded that there was no significant difference in clinical efficacy and adverse reactions with slightly higher bacterial eradication and clinical cure rates in the MEM group compared to IC.

2.3.4. Urinary Tract Infections (UTIs)

Only one comparative study of IC and MEM in UTIs was retrieved. Cox et al. conducted a prospective, stratified, randomized, multicentre open-label, parallel group trial comparing IC 500mg q6h (n=119) and MEM 500mg q6h (n=116) in adult ($\geq$ 18 years old), hospitalized patients with complicated UTIs requiring intravenous antibiotics (25). The focus of infection in this study was defined well. The sample size was large, but neither participants nor study staff were blinded. Clinical response in both the IC and MEM groups was 99%. A positive bacteriological response was achieved by 81% in the in IC group and 90% in the MEM group. The authors concluded that MEM is a safe and effective alternative to IC. The inclusion and

exclusion criteria applied in this study were similar to those applied in the present study. Clinical response was evaluated at the end of treatment and follow up done after more than 21 days.

2.3.5. Sepsis

Only the abstract for one small open label, prospective RCT (n=53) comparing IC (2 gram/day) versus MEM (2 gram/day) in hospitalized Chinese septic patients could be found, reported by Kuo et al. (46). . The study reported no difference in clinical (76% IC versus 84% MEM) and bacteriological (75% IC versus 80% MEM) outcomes. The authors concluded that MEM was as effective and well tolerated as IC in bacteraemia patients.

2.3.6. Bacterial Infections

Two RCTs was retrieved comparing IC with MEM in bacterial infections. These were defined as LRTIs, UTIs, SSIs as well as IAIs and Sepsis.

Three additional studies were retrieved which reported on outcomes in a range of bacterial infections. Hou et al. reported on a multicentre, open-label, RCT evaluating the efficacy and safety of IC versus MEM in 182 hospitalized Chinese patients with LRTIs, UTIs and other infections including SSI (47). . Patients aged ≥ 16 years old received 500mg – 1 gram of either antibiotic q12h for 7-14 days. The study excluded patients with severe cardiac, hepatic, renal or hematopoietic abnormalities. Withdrawal criteria were established for in cases where pathogen was resistant, where a negative culture was obtained within 72 hours, and when serious adverse events occurred. The study followed Good Clinical Practice guidelines and was notable for a low withdrawal rate (20 patients). Cure rates were 57% in the IC group and 66% in the MEM group (P=0.298). Overall efficacy rates were 87% in the IC group and 90% in the MEM group (P=0.595). For LRTI the clinical efficacy rates were 77% and 86% for IC and MEM

respectively, 100% for UTI's and 89% for IC and 85% for MEM (P=0.219). The difference between the groups was not statistically different. Adverse drug events were observed in 8.6% of IC patients compared to 9.7% in MEM group. (P=0.812). The results showed no statistical difference between the 2 groups in terms of efficacy and safety. Although the dosing used differed from that in the present study, the results were considered to be applicable. The target population was similar (LRTI, UTIs and SSI) and could be generalized to the setting of the present study.

Vewaest et al. conducted a multicentre, open-label, randomized, parallel-group trial evaluating IC and MEM (1 gram/day) in 212 intensive care patients aged ≥ 18 years with bacterial infections involving LRTI, IAI and sepsis (17). . Overall efficacy rates were 68.1% in the IC group versus 77.0% in the MEM group (P=0.185).Both drugs had similar response rates in terms of LRTIs and sepsis, however MEM performed better in IAI. This was a well-conducted randomized trial, which should have increased the validity of the findings. However the method of randomization was not mentioned. There was no blinding in this study, which could have introduced bias. The patient population was similar to that targeted in the present study in terms of baseline demographics as well as the primary infections. Clinical cure was well defined using APACHE II scoring system and follow up was 2-4 weeks.

Colardyn et al. conducted a randomized, prospective multicentre study for the treatment of serious infections in 204 adult patients (≥18years) (48). Both IC and MEM were given at a dose of 1 gram q8h as monotherapy. Infections included IAI, SSI, LRTI, UTI, bacteraemia and a case of meningitis. Clinical response was seen in 77% of cases with IC and 76% of cases with MEM.

Bacteriological eradication rated were also not statistically different and adverse events were considered to be similar for both groups (IC=12 and MEM =9). This study included 1 case of meningitis, which the present study excluded. The study further excluded patients with central nervous system disease, osteomyelitis, endocarditis or cystic fibrosis. Since there was no blinding, the possibility of bias could not be excluded. Clinical definitions were not as rigid as might be expected. Follow up was variable (2-4 weeks or 4-6 weeks). Adverse events were not clearly defined and the study noted only observed occurrences. However, the study population was similar in terms of baseline characteristics as well as including patients from both intensive care and general wards.

2.3.7. Studies which showed differences in outcomes between IC and MEM

Edwards et al. (2) performed a cost-utility analysis simulating the ICU processes using costs and QALY, in a United Kingdom hospital setting (ICU). This economic analysis found MEM to be cost-effective when compared to IC. It was not clear if the authors' performed a systematic review. The viewpoint of the NHS was used in the study and the costs were not detailed. Direct costs were apparently used, including hospital stay and resource consumption. Some data were obtained from expert opinion. A published systematic review and clinical trials were used. The study used utility values appropriate for a United Kingdom setting, which might not be easily translated to other settings. IC costs were £15,585.30 compared with £14,938.06 for MEM. The QALYs gained were 7.413 QALY for IC versus 7.495 QALY for MEM. Clinical response (7.4% IC versus 9.5% MEM) and bacteriological response (80.4% IC versus 84.6% MEM) was recorded. The study uses transitional probabilities deduced from a systematic review, using a Markov model approach and concluding superiority of MEM. The study concluded that MEM is significantly more effective and less costly than IC.

Table 4 - Studies which showed differences in clinical outcomes

Citation	Study Design	Sample	Study Endpoint	Results	Author's Conclusion
Edwards. et al. 2006 (2)	Pharmaco-economic	n = 133, patients with severe infection	Cost-effectiveness, clinical response and bacteriological response in patients with severe infection.	Results of individual studies reported	MEM was cost effective when compared to IC for the treatment of severe infections in hospitalized patients.
Edwards et al. 2005 (49)	Systematic review	n > 3,802	Clinical, bacteriologic response, mortality and adverse events	Results of individual studies reported	MEM is significantly more effective than IC in clinical response, bacteriologic outcomes and is associated with fewer adverse events in the treatment of severe infections
Novelli et al. 2005 (50)	RCT, open-label	n = 20	Pharmacokinetic parameters: Peak serum concentration, Area under curve and volume of distribution in patients with sepsis	Results of individual studies reported	IC showed more favourable pharmacokinetic profile than MEM
Kohno et al. 1998 (51)	Clinical trial	n = 2053	Clinical and bacteriological response	Results of individual studies reported	MEM showed superiority in terms of clinical efficacy
Maggioni et al. 1998 (52)	Multicenter RCT	n = 105	Clinical, bacteriological and safety outcomes	Results of individual studies reported	Better clinical response and side effect profile observed in the MEM group
Shah et al. 1996 (53)	Randomised parallel study, non-blinded	n = 66 adult patients	Clinical efficacy and safety outcomes	Results of individual studies reported	IC and MEM showed similar efficacy, however MEM showed better tolerability

The costing data used, in particular the resource consumption, was not clear. Edwards et al. (49) also performed a systematic review supported by AstraZeneca, the manufacturer of MEM. Clinical response was reported to be statistically higher for MEM than IC (RR 1.04, 95% CI: 1.01, 1.06). Bacteriologic response was also statistically higher with MEM than with IC (RR 1.05, 95% CI 1.01, 1.08). No difference in mortality (RR 0.98, 95% CI: 0.71, 1.35) was reported.

Fewer adverse effects were observed in the MEM group compared to the IC group (RR 0.87, 95% CI: 0.77, 0.97). Only the abstract was available and the level of significance could not be ascertained. The authors concluded that MEM was clinically and bacteriologically superior to IC and had fewer side effects. These conclusions were not in agreement with several studies outlined above. In addition the systematic review by Hoffman et al. (54) did not agree with the conclusions that MEM is safer than IC. Ten studies did not agree with this study, which showed similar tolerability as, listed in Table 6. The applicability of pharmacoeconomic evaluation to the local setting was questionable. However the systematic review was the only study of good quality which found superiority in efficacy and safety, favouring MEM. Overall, the balance of evidence still indicates the clinical equivalence of IC and MEM as summarized in Table 6.

Novelli et al. (50) suggested that IC showed more favourable outcomes when compared to MEM. The study endpoints in this case were pharmacokinetic parameters. The mean peak serum concentration was higher for IC than for MEM (90.1 ± 50.9 vs 46.6 ± 14.6 mg/L, $p < 0.01$); the area under the serum concentration-time curve was also higher for IC (216.5 ± 86.3 vs 99.5 ± 23.9 mg/L, $p < 0.01$), while the mean volume of distribution and mean total clearance were significantly higher for MEM than for IC (25 ± 4.1 vs 17.4 ± 4.5L, $p < 0.01$ and 191 ± 52.2 vs 116.4 ± 42.3 mL/min, $p < 0.01$, respectively).Clinical, bacteriological or safety endpoints were not considered and as such, conclusions of efficacy and safety could not be deduced from this pharmacokinetic study.

Kohno et al. (51) reviewed phase II and phase III trials of the four available carbapenems. The authors suggested that MEM showed superiority in terms of clinical efficacy, but referenced other double-blind studies that showed no difference between IC and other carbapenems. Clinical efficacy rates reported were 79% for IC and 100% for MEM.

Maggioni et al. (52) conducted a multicenter RCT evaluating clinical, bacteriological and safety outcomes in obstetric and gynaecological infections, the authors reported a better clinical response and side effect profile in the MEM group. Clinical cure for IC was 84.6% and for MEM was 100% (p = 0.026). IC showed more side effects (15.1% versus 11.5%, level of significance not reported). Patients with obstetric and gynaecological infections were not included in this study and these data were thus excluded from the evaluation.

Shah et al. (53) found MEM to be better tolerated than IC, however clinical efficacy was found to be similar. Cure rates were 60% with IC and 58% with MEM. Nausea and vomiting occurred in 7/33 patients on IC versus 2/33 on MEM. This study was not in agreement with the ten studies that showed no difference in safety outcomes as listed in Table 6. Nevertheless it did conclude that there was no difference in clinical efficacy between IC and MEM.

2.3.8. Adverse Drug Events (ADEs)

The safety of IC versus MEM, with particular focus on the risk of seizures, was the subject of a systematic review reported by Hoffman et al. (54). Studies were retrieved from MEDLINE for the period 1966 to 2007, and included many of the studies described above. Four RCT's showed similar safety outcomes. The largest trial by Verwaest et al. (17) reported IC = 3/105 (2.9%) and MEM = 4/107 (3.7%) drug-related seizure in patients with CNS disease. In the second trial by Colardyn et al. (48) , patients with CNS disease were excluded with adverse effects in 12 patients (12%) in the IC group and 9 (10%) in the MEM group. The third trial by Garau et al. (55) excluded patients with CNS disease or previous history of seizure. Drug-related adverse events occurred in 11 (15%) of IC patients and 13 (17%) of MEM group. Two seizures were found in each group. Observations of 1754 patients by Calandra et al. (56) treated with IC 2gram/ day in phase III clinical trial were reviewed to determine the risk of seizures . The results reported 52

patients (3%) had seizures and 16 (0.9%) were classified to be possibly, probably, or definitely IC related seizures. Of these patients, the majority had a background of seizure-risk. In a review of almost 5000 patients on MEM (57); overall incidence of seizures were reported in 22 (0.46%) of patients. The overall seizures considered to be related to MEM were 4 (0.08%). In 278 patients treated for meningitis 20 (7.2%) experienced seizures with MEM compared to 26 (9.8%) patients treated with cephalosporins. Similar findings were found in several other studies. The author found that elderly patients, patients with low body weight, at risk of CNS disease, history of seizure and renal dysfunction appears to be associated with increased risk of drug related seizure. The authors highlighted one paediatric study (3) which is often cited as the reason for IC associated seizures. Seizure rates were nonetheless shown to be similar when either IC or MEM were used.

2.3.9 Pharmacoeconomic review

Four studies Table 5 showed that IC is less costly than MEM. Only the study by Attanasio et al. (1) used well-described pharmacoeconomic principles, as described in section 2.3.1. Badia et al. (37) measured direct health cost using a meta-analysis approach to cost effectiveness data. However, the details of this study could not be obtained as it was in a foreign language. The study by Zhanel et al. (36) was less than ideal as it only included acquisition costs, while in Beketov et al. (40) the costing approach was not sufficiently detailed to allow interpretation. The study by Edwards et al. (2), supported by AstraZeneca,used well-described pharmacoeconomic principles and showed that MEM was significantly less costly than IC.

Table 5 Summary of pharmacoeconomic studies

Citation	Study Design	Daily dose	Sample	Study Endpoint	Results	Author's Conclusion
Attanasio E. et al. 2000 (1)	RCT, parallel over 20 centres	IC 1.5g MEM 2g	n = 287 > 18 years	Cost-effectiveness, clinical response and bacteriological response in patients with IAI.	Results of individual studies reported	No statistical difference in clinical, bacteriological response or adverse events. IC appears less costly.
Badia et al. 1999 (37)	Meta-Analysis	N/A	> 18 years	Cost-effectiveness in moderate to severe intra-abdominal infections	Results of individual studies reported	IC was shown to be as effective and less costly than MEM
Zhanel et al. 1998 (36)	Review article, Comparative	All dosage ranges	N/A Severe bacterial infections	In vitro activity, pharmacokinetics, clinical uses and adverse effects	Results of individual studies reported	Literature supports the use of IC at a dose of 500mg q6h and MEM 1 g q8h for treatment of serious infections. IC appears more economical than MEM.
Beketov et al. 2003 (40)	Retrospective Cohort	IC 1.5 g MEM 1.5g	n = 468	Efficacy, safety, economic outcomes in IAI	Results of individual studies reported	Most expensive treatment was MEM and IC. Both showed similar efficacy.
Edwards. et al. 2006 (2)	Pharmaco-Economic, Systematic review	varied	n = 133, patients with severe infection	Cost-effectiveness, clinical response and bacteriological response in patients with severe infection	Results of individual studies reported	MEM was cost effective when compared to IC for the treatment of severe infections in hospitalized patients.

2.4. Summary of literature review

A fundamental prerequisite for performing a cost minimization analysis in this study was establishing clinical equivalence between IC and MEM, or at least non-inferiority in both directions. The evidence sought were comparative studies focusing on IAI, SSI, LRTI, UTI, sepsis, bacteriological outcomes, and safety. In addition, pharmacoeconomic studies were being sought. The literature review focused on establishing that IC is clinically equivalent to MEM in clinical, bacteriological and safety outcomes.

In terms of a hierarchy of evidence, the search found 2 meta-analyses, 12 RCTs, 1 prospective cohort and a retrospective cohort study that supported the position of clinical equivalence between IC and MEM. The six studies that did not show clinical equivalence were a pharmacoeconomic review, two systematic reviews and 3 RCTs. There were 4 pharmacoeconomic evaluations showing IC to be less costly than MEM. Of the most robust evidence were: a meta-analysis by Xiao H et al. (45), which was well-detailed. The second meta-analysis could only be retrieved as an abstract, as the original was in the Spanish language. Among the RCTs, 1 was blinded (41), while 11 were open-label trials. Two systematic reviews were selected. One pharmacoeconomic (1) review was considered to be of good validity.

The key findings of this appraisal provided convincing evidence of the clinical equivalence of IC and MEM. These findings answer the search questions in the following way:

a) IC is clinical equivalent to MEM in IAI, SSI, LRTI, UTI and sepsis

b) IC has an equivalent bacteriological response to MEM

c) IC is as safe as MEM

d) IC is less costly than MEM

e) The dose of IC 500mg q6h and MEM 1 gram q8h is supported by literature as equipotent.

The evidence for clinical equivalence was evaluated as follows:

Table 6 - Summary of critical appraisal

	Critical appraisal findings	Supported by
1	IC clinically equivalent to MEM in patients with IAI	No difference in clinical efficacy supported by studies (1, 36-40, 48).
2	IC clinically equivalent to MEM in SSI	No difference in clinical efficacy supported by studies (21, 41, 42, 48).
3	IC clinically equivalent to MEM in LRTI	No difference in clinical efficacy supported by studies (17, 43-45, 47, 48).
4	IC clinically equivalent to MEM in UTI	No difference in clinical efficacy supported by studies (25, 47, 48).
5	IC clinically equivalent to MEM in Sepsis	No difference in clinical efficacy supported by studies (17, 46).
6	IC bacteriologically equivalent to MEM	No difference in bacteriological outcomes supported by studies (1, 25, 39, 44, 46).
7	IC as safe as MEM	No difference in adverse drug events supported by studies (1, 17, 21, 25, 38, 39, 41, 42, 45-48, 54).
8	IC less costly than MEM	IC less costly than MEM supported by studies (1, 36, 37, 40) .
9	IC 500mg q6h and MEM 1gram q8h	This dosage supported by Zhanel et al. (36), United states FDA (33, 34) and our hospital Antimicrobial guidelines (15).

Key: IAI = intra-abdominal infection, SSI = skin and skin structure infection, LRTI = lower respiratory tract infection, UTI = urinary tract infection, IC = imipenem/ cilastatin, MEM = meropenem.

CHAPTER 3: METHODS

3.1. Introduction

This chapter sets out to describe the research methods employed, the type of research, study design, study population, inclusion and exclusion criteria, data collection methods, definitions and pharmacoeconomic approach.

3.2. Type of Research

This study was a retrospective, single-centre cohort employing cost minimization principles. The CMA assumes that consequences are equivalent while considering the least expensive alternative (13, 58). As outlined in the literature review, IC is considered to be clinically equivalent to MEM in terms of safety and efficacy. An institutional review indicates that an interchange program of IC with MEM could save the institution more than SAR 2 million. As the initial review only included acquisition costs of the drugs, a costing analysis of this nature was considered to include resource costs relevant to the primary infection.

3.3. Study Design

A cost minimization analysis of IC versus MEM in moderate to severe infections was conducted at the King Abdulaziz National Guard Hospital, Al-Ahsa (a 300 bed tertiary care centre). Between January 2012 and December 2012, all patients receiving IC 500mg every six hours and MEM 1 gram every eight hours for moderate to severe infection were included in the study.

The perspective of the economic evaluation was that of the Ministry of National Guard in Saudi Arabia that provides health-care to eligible dependents. The eligible dependents include employees of the National Guard, their families, staff and their families. The majority of the

patients at the hospital receive free medical treatment while approximately 20 beds are reserved for cash paying private patients. Only direct costs were included in the study, based on the October 2013 hospital business centre pricing. Medicine acquisition prices were obtained from the October 2013 Saudi Food and Drug Administration (SFDA) Human Drug pricing list (8). Direct costs included medications, supplies, laboratory tests, health-care professionals' time and hospitalization costs(13). All costs are expressed as Saudi Riyals (SAR).

3.3. Target Population

Patients on IC or MEM with moderate to severe infection, eligible to receive treatment at our institution.

3.4. Study Population

3.4.1. Inclusion criteria:

a) Adult patients ($\geq$ 18 years old).

b) Patients diagnosed with moderate to severe infection, including SSI, sepsis, IAI, respiratory tract infections, UTI and HAI who were prescribed IC 500mg every six hours intravenously (2 gram per day).

c) Patients diagnosed with moderate to severe infection, including SSI, sepsis, IAI, respiratory tract infections, UTI and HAI who were prescribed MEM 1 gram every eight hours intravenously (3 gram per day).

3.4.2. Exclusion Criteria:

Patients excluded from the study were:

a) those that were pregnant

b) those with known or suspected meningitis

c) those diagnosed with microorganisms resistant to IC or MEM

d) patients with a documented hypersensitivity or prior contraindication to IC or MEM.

3.5. Sampling

The study set out to capture a year's sample including 100 patient files with 50 patients in each arm. The study period included 1 January 2012 until 31 December 2012.

3.6. Data Collection

Data were extracted from the electronic and paper medical records maintained by the King Abdulaziz National Guard Hospital information system. Records were searched from 1 January 2012 until 31 December 2012. The search included any patient either on IC or MEM during the study period. The search results were exported to Microsoft® Excel. The search fields included patients' medical record number, name, date of birth, study drug (either IC or MEM), dosage, admission date and number of doses given. Patients were matched as per the inclusion and exclusion criteria. Data on patients' gender, age, weight, diagnosis, medical history, laboratory test (including renal function and haematological status), recorded comorbid illnesses and previous medicines allergies, prescribed antifungals or antibiotics and microbiological tests were extracted from the hospital's electronic medical record, with the assistance of the hospital information management department. Information about consultant and physician visits was extracted from the paper based physician notes, as were clarifications of the recorded diagnosis in cases where electronic records were incomplete.

3.7. Variables

The following variables were captured in relation to each patient and his/her hospital stay:

1. Baseline demographics:
   1.1. age
   1.2. gender
   1.3. weight
   1.4. height
2. Diagnosis and primary infection
3. Doses administered of IC or MEM
4. Doses administered of concomitant antibiotics or antifungals
5. Microbiology and source of infection.
6. Sensitivity or resistance patterns of identified micro-organisms
7. Number and type of laboratory procedures used to test for sensitivity patterns, monitoring of primary infection failure or superinfections, source of infection
8. Laboratory tests conducted:
   8.1. full blood count
   8.2. liver function tests
   8.3. renal function
   8.4. coagulation studies
9. Vital signs including temperature
10. Recorded adverse drug events
11. Physician consultations
12. Nursing visits
13. Pharmacist processing and preparation time
14. Pharmacy aide delivery time
15. Daily consumables used in the administration of medicines
16. Dates of admission and discharge

From the variables listed above, the following outcomes were documented:

a) adverse drug events (ADE) associated with either IC or MEM, using previously published criteria (29)

b) length of hospitalization

c) length of antibiotic stay (LOAS); defined as the number of hospital days during which the patient was being treated for the diagnosed infection, including any treatment associated with treatment failure or related adverse effects

d) resource consumption, limited to direct medical costs of managing the primary infection based on the institutional perspective.

3.8.   Definitions

3.8.1 Definitions of moderate to severe infections

The diagnosis of moderate to severe infection was based on the treating physician's documented clinical decision, using the criteria below:

a) **Skin and skin structure infections (SSI) –**

restricted to signs and symptoms associated with cellulitis, infected wounds, infected skin ulcers, and abscesses (20, 48).

b) **Sepsis - :**

defined as a fever with temperature above 38.3 degrees Celsius, with chills, leucocytosis, hyperventilation, hypothermia, skin lesions, septic embolism, change in mental status, hypotension, disseminated intravascular coagulation, or organ failure (17, 26).

c) **Intra-abdominal Infections (IAI) - :**

evidence of abscess, or peritonitis originating from the stomach, duodenum, biliary tract, pancreas, appendix, small intestine and colon (16, 17, 48).

d) Lower respiratory tract infections (LRTIs) - :

evidence of pulmonary infiltration thought to be due to infection on the chest X-ray and at least two of the following criteria: purulent sputum (<10 squamous epithelial cells, > 25 white blood cell counts (WBCs) and a pathogen should be cultured), fever and leucocytosis (16, 17).

Urinary Tract Infection (UTI) - :

evidence of dysuria, frequency, urgency, suprapubic pain, and/or haematuria, fever greater than 38 degrees Celsius, urinalysis, history of previous UTI, urine culture showed positive bacteriological growth (24, 48).

Hospital Acquired Infection (HAI) -:

defined as late onset infection (> 72 hours after admission), post-surgical infection, or early onset (and community acquired, with onset considered as early onset (< 72 hours after admission) (27).

3.8.2 Adverse drug events (ADE):

Adverse drug events (ADEs) associated with IC or MEM were identified based on physician documentation and the records extracted from the hospital information system. The following circumstances were considered to be indicative of an adverse drug event associated with IC or MEM:

1. seizure diagnosed by the physician, within twenty four hours after either IC or MEM was administered.

2. anti-epileptic medication (phenytoin, carbamazepine, phenobarbital or levetiracetam) prescribed within twenty four hours of initiating IC or MEM

3. skin reactions (rash, pruritus, urticaria, erythema multiforma, and Stevens-Johnson syndrome)

4. gastrointestinal disturbance such as antibiotic-associated diarrhoea, nausea or vomiting. A *Clostridium difficle* culture was considered as antibiotic-associated diarrhoea if it was confirmed immediately after initiation of the study drug. This was further verified if any medication was started to treat the infection like oral vancomycin.

5. changes in liver function tests of more than 3 times the upper normal limit (aspartate aminotransferase > 100 units/ L or alanine aminotransferase > 100 units/L), and 3 times the upper normal limit of total bilirubin (>60µmol/L) (54, 59)

6. changes in renal function (creatinine clearance < 50ml/min)

3.9. Costing

Pricing was obtained from the financial sector of the hospital's business centre. The national drug pricing was obtained from SFDA. The most recent pricing available at the time was taken in October 2013 from the business centre as well as the SFDA Human Drug List (http://www.sfda.gov.sa). Direct medical costs include medications, laboratory costs, health care provider costs, hospitalization costs, consumables and administration costs. Direct non-medical costs (transportation and food) were not included in the study. Indirect medical costs (lost income) and intangible costs (pain and suffering) were excluded as incompatible with the perspective of the present study. The perspective was that of the payer, a government institute. Costs associated with support personnel such as maintenance, housekeeping, patient escort and administration were assumed to be fixed and were not included in the study. Laboratory data unrelated to the primary infection or super infections were not considered in the study. Investigators' and data collectors' fees were excluded. Discounting was not considered as the

study period was for a year. Pricing was in Saudi riyals (SARs). One SAR has been fixed at

approximately 0.27 United States dollars (USD) for the last 10 years.

Drugs were priced on the generic brands available in the institution. The Business Center pricing

as at October 2013 was as shown in Tables 7 to 12.

Table 7 - Cost of hospital stay (daily and other charges)

Cost of Hospital Stay	
Type of ward or service	**Cost (SAR)**
Critical Care unit/ day	1500
High Stay ward/ day	900
General ward/ day	500
Consumables ICU/ day	250
Consumables General Ward/ day	50
Administration set + 50ml normal saline or equivalent for intravenous infusion/ dose	11

Key: ICU = Intensive care unit

Table 8 - Personnel costs

Personnel Costs	
Type of Service	**Cost (SAR)**
Intensive care consult/ visit	1000
General ward consult/ visit	200
Physician consult/ visit	200
ICU Nurse/ Day	300
General ward Nurse/ Day	100
Pharmacist / minute	1.2
Pharmacy Aide/ minute	0.4

Key: SAR = Saudi riyal, ICU = Intensive care unit; HS = step-down unit; GW = general ward

Table 9 - Laboratory costs

Laboratory	Cost (SAR)
CBC	80
Basic Screen	240
LFT	200
PT/PTT/INR	80
Vancomycin level	180

Key: SAR = Saudi riyal, CBC = complete blood count; LFT = liver function test; PT = prothrombin time; PTT = partial thromboplastin time

Basic Screen includes blood urea nitrogen, electrolytes (sodium, potassium and chloride), blood glucose and serum creatinine. LFTs include alanine transaminase, aspartate aminotransferase, alkaline phosphatase, total protein and bilirubin.

Table 10 - Cost per laboratory culture

Cultures	Cost (SAR)
Tracheal	150
Throat	150
Sputum	150
Urine	180
Blood	170
Skin	150
Wound	200
Nare (MRSA)	300
Rectal	150
Body Fluid	170
TB	600
C.difficle	150
Faecal/ Stool	150
Cather Tip	150
Respiratory	190
Fungal	180

Key: SAR = Saudi riyal

Table 11 - Antifungal costs per unit

Antifungal	Cost (SAR)
Amphotericin IV	444.33
Caspofungin 50mg IV	2548.45
Fluconazole IV	77.1
Fluconazole 50mg IV	8.36
Fluconazole 150mg IV	25.2
Voriconazole 200mg IV	587.75

All costs are expressed as unit costs (cost per vial)

Table 12 - The SFDA Drug Pricing October 2013 (based on the available generic brand)

Drug	cost (SAR)	Drug	cost (SAR)
Amoxicillin 250mg PO	0.91	Ethambutol 400mg PO	0.86
Amoxicillin/ clav 600mg IV	10.18	Gentamicin 80mg IV	13.54
Amoxicillin/ clav 625mg PO	3.30	IC 500mg/ 500mg IV	70.40
Azithromycin 250mg PO	12.24	INH 100mg PO	0.07
Azithromycin 500mg IV	60.25	Linezolid 600mg IV	301.58
Cefazolin 1gram IV	8.30	Linezolid PO	250.00
Cefepime 1gram IV	40.45	MEM 1gram IV	151.26
Ceftazidime 1 gram IV	57.30	Metronidazole 500mg IV	8.15
Ceftazidime 2 gram IV	114.60	Metronidazole 500mg PO	0.32
Ceftriaxone 1gram IV	51.75	Moxifloxacin 400mg IV	155.05
Cefuroxime 500mg PO	8.18	Moxifloxacin 400mg PO	16.40
Cefuroxime 750mg IV	15.00	Nitrofurantoin 100mg PO	0.78
Cephalexin 500mg PO	2.00	Norfloxacin 400mg PO	1.74
Ciprofloxacin 200mg IV	63.45	Piperacillin Tazobactam IV	101.80
Ciprofloxacin 250mgPO	2.28	Pyrazinamide 500mg PO	0.60
Clarithromycin 250mg PO	4.31	Rifampicin 300mg PO	2.70
Clindamycin 150mg PO	1.29	Streptomycin IV	4.00
Clindamycin 600mg IV	21.10	Tigecycline IV	215.13
Cloxacillin 500mg IV	17.28	Trimeth/ sulfamethox DS PO	2.33
Colistin IV	35.05	Trimeth/ sulfamethoxaz IV	10.83
Erythromycin 250mg PO	0.55	Trimeth/sulfamethoxaz PO	1.18
Erythromycin IV 500mg	22.90	Vancomycin 1gram IV	64.35

Key: SAR = Saudi riyal, PO = oral; IV = intravenous, IC = imipenem/ cilastatin; MEM = meropenem

3.10. Pharmacoeconomic analysis

3.10.1 Cost minimization analysis

As this is a cost-minimization analysis, the assumption of equivalent efficacy was demonstrated by the literature retrieved and cited and not the outcomes of patients treated, whose cost data are being sought in this study. Evidence of the outcomes in each case was documented by the attending physician in the clinical notes. Clinical success was therefore dependent on the source of infection and defined by clinical improvement in signs and symptoms that would warrant resolution of fever or clinical signs of infection, discontinuation of antibiotics or discharge from the hospital without re-admission within 10 days or eradication of baseline positive microbiological pathogens.

3.10.2 Perspective and timescale

The economic analysis was based on our institutional perspective. The study period began at the point the primary infection was diagnosed. The LOAS was used to determine the time period of the costing analysis.

Costing data relating to the primary infection was included. This included:

1.   total amount of study agent (IC or MEM) per day,

2.   ancillary antibiotics used for the study period,

3.   any non-study medicines related to super infections or treatment failure

4.   any failed antibiotics started prior to the study drug. These were medicines that were
        discontinued as they proved to be unsuccessful in treatment.

5.   standard laboratory tests such as microbiological culture studies, vancomycin levels, complete blood count (CBC), basic screen and coagulation profile

6.   costs related to adverse events

7.   costs related to all, health care worker visits

8.   medication delivery costs.

Health care worker costs included daily critical care units (CCU) consultation, CCU nursing costs per day, general ward consultation, physician consultation, general ward nursing costs and pharmacy processing and preparation time. Included in the study was the costs relating to hospital stay in CCU, step-down unit and general ward. Pharmacy aide delivery time was considered. Daily consumable charges were based on the institutional charges and included in the costs.

Support personnel such as maintenance, housekeeping, patient escort and administration costs were assumed to be fixed and were not included in the study. Laboratory data unrelated to the primary infection or super infections were not considered in the study. Investigators' and data collectors' fees were excluded. Discounting was not considered as the study period was for a single year.

3.10.3 Sensitivity Analysis

One-way sensitivity analysis was performed, in Microsoft® Excel 2010, by increasing and decreasing each parameter by 20%, while observing the impact on the results. The change in a single parameter assisted in identifying those factors that had the greatest impact on the conclusions of the study (total costs). The higher number of CCU days in the IC group was

expected to influence the overall average daily costs. One-way sensitivity analysis was carried out on the following:

a) Mean daily CCU day costs

b) Mean daily step-down costs

c) Mean daily general ward (GW) costs

d) Mean daily vial costs

e) Mean daily administration sets costs

f) Mean daily laboratory costs

g) Mean daily laboratory culture costs

h) Mean daily CCU consultation costs (specialist fees)

i) Mean daily GW consultation costs (specialist fees)

j) Mean daily physician costs

k) Mean daily CCU nurse costs (critical care nurse fees)

l) Mean daily GW nurse costs

m) Mean daily Pharmacist costs (processing, preparation and dispensing)

n) Mean daily Pharmacy aide costs (delivery costs)

o) Mean daily ADE costs

A threshold analysis was performed, in Microsoft® Excel using 'what-if-analysis'. It was performed on those parameters thought to impact on the conclusions of the study. A threshold analysis was performed on:

a) CCU days

b) step-down days

c) general ward days

d) ADEs

e) vial costs

f) administration sets

g) pharmacists costs

Hypothetical values were run through each parameter to find the threshold value at which the conclusion changed. The parameter in questions was varied, while the other parameters were kept at their original value (base value). The input and output results were then displayed graphically to assess the threshold value at which the results (mean total costs) of the study would change significantly. The objective was to find the threshold value at which IC became less costly than MEM. It was assumed that total costs should be less than SAR 3795.00 if the conclusions of the study would change. This value was obtained using the independent sample T-test so as to obtain a p-value less than 0.05.

3.11. Statistical analyses

Statistical analysis was done in coordination with the King Abdullah Medical Research Center using SPSS version 21. An independent sample T-test was used to test the difference between the means as well as the level of significance. The test compares the mean scores of the two

independent groups. The independent T-test assumes that the dependent variables are normally distributed with the two comparators having equal variance on the dependent variable. Independent sample T-test was performed on the following parameters:

a) Baseline demographics (age, weight and height)

b) Hospital days (CCU days, step-down days and GW days)

c) Personnel visits (consultant, physician, nursing, pharmacist and aide visits)

d) Administration sets

e) Doses administered of IC or MEM

f) Doses of concomitant antibiotics or antifungals

g) LOAS

h) Peak temperature recorded

i) WBC

j) Costs related to hospital stay (CCU, step-down and GW)

k) Costs related to laboratory tests and cultures

l) Resource (personnel costs)

m) Cost of ADEs

Chi square tests of independence were performed on categorical variables on the following parameters:

a) Gender

b) Clinical success

c) Renal function

d) Number of positive infections

e) ADEs

3.12. Reliability and Validity of Data Source

The reliability and validity of the data sources was dependent on the accuracy and completeness of information recorded. As the hospital is accredited by the Joint Commissions International, medical records were relatively complete. Pricing used was the most recent (October 2013), supplied by the business centre. Data were captured in the relevant data collection sheet and was subsequently verified by a second pharmacist (Analyn Crisostomo). Where necessary, corrections were made during the verification process. As with any retrospective review, limitations in the dataset were expected. Nevertheless, every attempt was made to ensure that the dataset was an accurate representation of the target population. Certain parameters had to be cross-verified using secondary data sources.

Some examples include:

a) Identifying primary infection using laboratory cultures with physician diagnosis

b) Identifying positive infection using WBC counts or identifying fever

c) Adverse drug event diagnosis confirmed by treatment with corticosteroids, antihistamines or in the case of seizure using anti-seizure medication.

For interpretation of clinical, statistical and pharmacoeconomic findings the following disciplines were routinely consulted:

a) Microbiologist

b) Infection control physician

c) Gastroenterologist

d) Quality Management Physician

e) Clinical Pharmacist

f) Biostatistician

3.13. Bias and Limitations

Bias may have been introduced in the following ways:

a) Studies that do not incorporate randomization and blinding may be subjected to bias.

b) The ICU clinical pharmacists were aware of the higher utilization of MEM.

c) PI was aware of the unpublished review that estimated a cost saving by utilizing IC instead of MEM.

d) Physicians were aware of a case of seizure with IC and showed preference to use MEM.

e) National costs of drugs and procedures were used, some companies may offer discounts.

f) Information bias where investigators look for particular diagnosis.

To minimize the chance of bias the following steps were taken

a) A clearly defined population that have the same risk of developing the outcome of interest. The population expressed in this study reflects real world patients that one would encounter in any hospital in Saudi Arabia.

b) Results were expressed as average daily costs, so as to limit the impact of differences in the average LOAS.

c) National Costs may be generalized to other institutions in Saudi Arabia and may represents a more standardized approach to costing data, increasing external validity.

d) Equivalence studies were evaluated for robustness so as to prove clinical equivalence, and those studies which did not show equivalence were considered and balanced against the predominant viewpoint.

e) Diagnosis was verified at various levels including laboratory data, clinical records and physician diagnosis.

f) An independent pharmacist was selected to verify all data collected. If the PI showed any bias the independent double check was implemented to rectify any oversight.

3.14. Ethics

The protocol received approval from the King Abdullah International Medical Research Centre (reference number RRE12/011) (Appendix 1) eastern region of Saudi Arabia, as well as the Biomedical Research Ethics Committee at the University of Kwa-Zulu Natal in South Africa (reference number BE: 273/13). (Appendix 2)

The information sought was not sensitive in nature, allowing King Abdulaziz International Medical Research Center ethics committee approval. The review of subject's information was only limited and no harm to the subject's status, employability or insurability could occur. The Biomedical Ethics Research Committee of the University of Kwa-Zulu Natal provisionally approved the proposal pending several queries. Following resolution of these queries final approval was obtained.

3.15. Storage of Data

The master list (electronic record) was kept till the final analysis of the data following which the identification of all patients was deleted from the file. During the study period and analysis, the master list was kept in a secured locked cabinet in the pharmacy director's office. The master list data collection sheets process was then valued in Saudi Riyals and exported to SPSS for statistical analysis. Principal Investigator (PI) kept the list and was shared with the data collector (Analyn Crisostomo). Only the PI had access to the file. Following the completion of collection of data and primary analysis, all the identification parameter such as medical record number was immediately deleted from the file. Each record was given a unique identification number.

CHAPTER 4: RESULTS

4.1. Introduction

This chapter provides analytical and descriptive data of the findings. It includes patient characteristics, length of hospital stay, clinical findings and economic outcomes. Primary outcomes considered were the pharmacoeconomic impact of IC and MEM. Costing data represents the institutional perspective and includes resource costs. Secondary outcomes reported include clinical and safety findings. Raw data was provided by the hospital information management department using the electronic and paper-based patient records. The population represented patients that are eligible for treatment at the King Abdulaziz National Guard Hospital in Saudi Arabia. No data from the private sector was used in this study. Therefore, the data represents a government costing perspective.

4.2. Overview of Data Management

An account of the data collection is necessary in providing a background of the sample selected and outcomes in this study. The data included any patient with mild to moderate bacterial infections with IAI, SSI, LRTI, UTI and sepsis. The data is not representative of patients with meningitis, pregnant patients or paediatric patients. Patients with mild to moderate renal impairment were considered in the study as these may add to costs. The primary infection was reported by the diagnosing physician using the criteria outlined in the method of this study. Some patient days had to be corrected and 1 patient diagnosis was rectified after confirming with the records in the patient file, patient history and laboratory findings. In cases where the primary infection was not clearly identified in the electronic record, the paper-based physician notes were used and verified by the parameters defined earlier in the study. A total of 44 patients receiving

IC and 44 receiving MEM could be evaluated clinically, as shown in Figure 5. The plan was to include 50 patients in each group from 1 January 2012 until 31 December 2012. However it was found that only 45 patients on IC could be used for this study, due to the limited usage of the drug. MEM was used much more frequently, however only 44 patients were finally selected due to the inclusion and exclusion criteria. Furthermore, one file in the IC group and one file in the MEM group could not be accessed as it was locked by medical records. Seven patients did not meet the study criteria. Patients excluded from the study were due to:

a) One patient diagnosed with meningitis

b) One patient found to be pregnant

c) One patient was less than 18 years old

d) Two files were locked by Health Information Management Department

e) Two patients with only a single dose given and drug discontinued.

Statistical analysis was done with consultation of the King Abdullah International Medical Research Center, Department of Biostatistics using SPSS version 21.

Figure 5 - Schematic representation of sample

100 patients with mild to moderate infection with IC or MEM

Patient on IC (n=45)

5 Patients excluded

1 file locked

44 files accessible

Patient on MEM (n=45)

1 file locked

44 files accessible
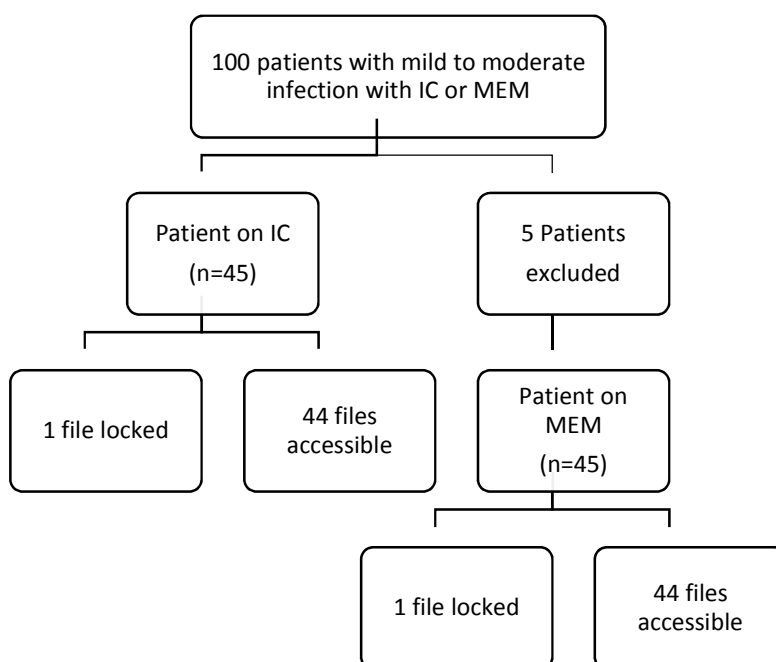
4.3. Baseline Characteristics

Baseline characteristics are summarized in Table 13. Independent sample T-tests showed no significant difference in baseline characteristics in terms of mean age, weight and height. The Chi-Square test showed no significant difference in gender between the groups.

Table 13 - Baseline characteristics

	IC (n = 44)	MEM (n = 44)	*p value*
Mean Age in years (SD)	65.64 (19.04)	64.11 (21.28)	0.724
Mean weight in kg (SD)	71.31 (15.81)	68.80 (21.92)	0.538
Mean height in cm (SD)	159.32 (11.15)	157.82 (10.06)	0.509
Male (%)	21 (47.73%)	20 (45.45%)	0.831
Female (%)	23 (52.27%)	24 (54.55%)	

Key: SD = standard deviation

4.4. Number of Hospital Days

Numbers of hospital days are summarized in Table 14. Although there was a significant greater number of mean critical care days in the IC group compared to the MEM group ($p = 0.030$), the mean number of step-down days showed no significant difference ($p = 0.375$). No statistically significant differences were seen in mean general ward days or in the mean length of antibiotic stay (LOAS), as shown in Figure 4.

Table 14 - Hospital days

	IC (n = 44)	MEM (n = 44)	*p* *value*
Mean CCU days (SD)	13.93 (19.11)	6.86 (9.40)	0.030
Mean Step-down Days (SD)	4.23 (5.39)	3.25 (4.89)	0.375
Mean general ward days (SD)	10.64 (18.49)	13.66 (20.66)	0.472
Mean LOAS (SD)	11.18 (6.34)	9.57 (5.67)	0.212

Key: IC = Imipenem/ cilastatin, MEM = meropenem, CCU = critical care days; SD = standard deviation; LOAS = length of antibiotic stay

Figure 6 - Mean hospital days
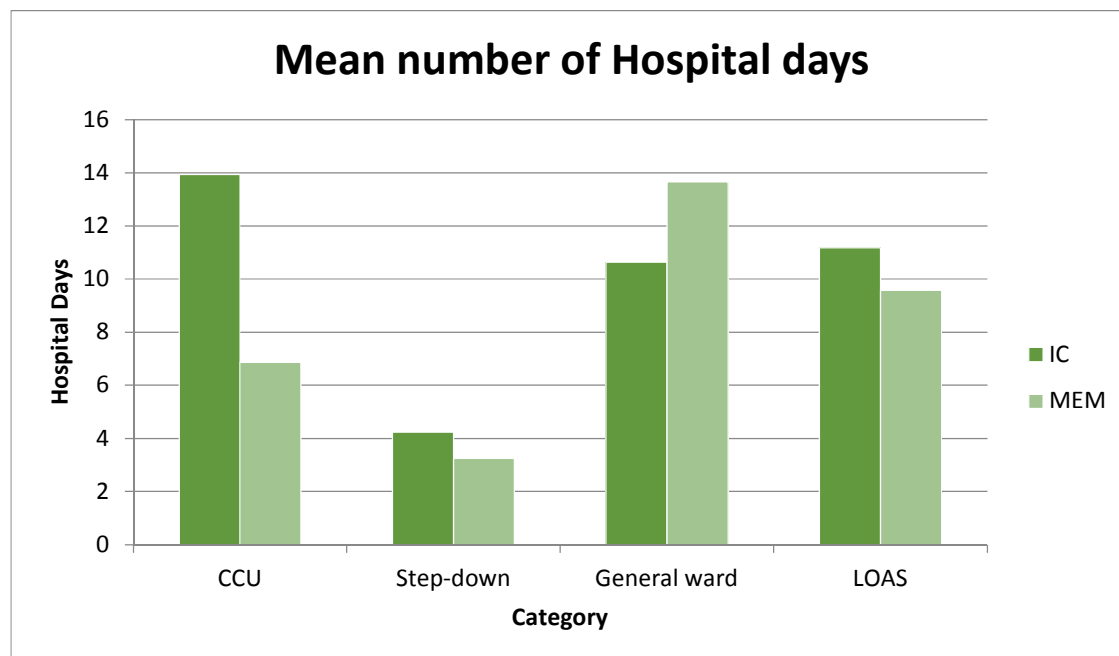
Key: IC = Imipenem/ cilastatin, MEM = meropenem

4.5. Clinical Characteristics

Clinical success rates (as defined in section 3.8. and 3.10.1.) are shown in Table 15, and were not statistically different between IC and MEM (p = 0.661). Independent sample T-test showed no significant differences between IC and MEM in terms of mean peak temperature (in degrees Celsius) recorded (p = 0.597) and mean WBC (10^9L) recorded (p = 0.401). Chi-square test showed no significant difference in renal function between the groups. Similarly the numbers of infections between the groups were not significantly different, as depicted in Figure 7.

Table 15 - Clinical characteristics

	IC (n = 44)	MEM (n = 44)	P value
Clinical Success	26 (59.1%)	28 (63.6%)	0.661
Mean Peak Temperature in ºC (SD)	37.98 (0.82)	37.89 (0.78)	0.597
Mean WBC 10^9 L (SD)	19.27 (10.89)	22.57 (23.44)	0.401
Normal renal function	35 (79.5%)	34 (77.3%)	0.796
Moderate renal impairment	9 (20.5%)	10 (22.7%)	0.796
Number of positive Skin Infections	7 (15.9%)	7 (15.9%)	0.99
Number of positive Sepsis cases	13 (29.5%)	16(36.4%)	0.496
Number of positive IAIs	5 (11.4%)	3 (6.8%)	0.458
Number of positive LRTIs	9 (20.5%)	7 (15.9%)	0.580
Number of positive UTIs	21 (47.7%)	22 (50.0)	0.831
Number of positive HAIs	16 (36.4%)	9 (20.5%)	0.098

Moderate renal impairment with creatinine clearance from 30 to 50 ml/minute and normal renal function greater than 50 ml/ minute.

Figure 7- Site and number of infections
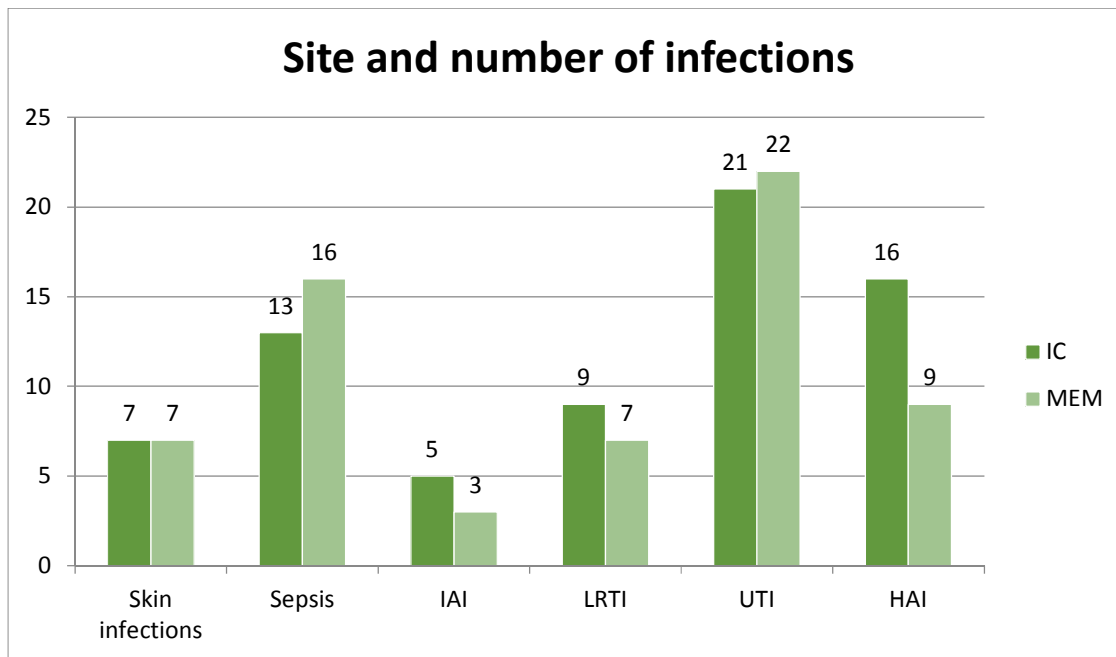
Key: IAI = intra-abdominal infection; LRTI = lower respiratory infection; UTI = urinary tract infection; HAI = hospital acquired infection

4.6. Adverse Drug Events (ADEs)

Gastrointestinal ADEs occurred in 1 (2.3%) of the patients on IC versus 3 (6.8%) of the patients on MEM. These ADEs included nausea, vomiting and diarrhoea, as well as any *Clostridium difficile* culture found immediately after initiation of the medicine confirmed. This was confirmed by any supportive measure taken for treatment, such as administration of oral vancomycin. General ADEs occurred in 1 (2.3%) patient on IC and 1 (2.3%) patient on MEM. General ADEs took into account skin reactions, rash, pruritus, urticaria, erythema multiforma, and Stevens-Johnson syndrome. Laboratory ADEs occurred in 5 (11.4%) patients in the IC group versus 6 (13.6%) patients in the MEM group. One case of seizure associated with IC was documented. It was noted that the case of seizure occurred in a high-risk patient with moderate renal impairment. Overall the ADEs were similar for both groups, as shown in Table 16.

Table 16 - Adverse drug reactions (ADEs)

	IC (n = 44)	MEM (n = 44)	P value
Gastro-intestinal ADE	1 (2.30%)	3 (6.80%)	0.616
General ADE	1 (2.30%)	1 (2.30%)	0.99
Laboratory ADE	5 (11.4%)	6 (13.60%)	0.747
Seizure	1 (2.30%)	0 (0%)	0.99

4.7. Hospital Resources

The number of resources used was expected to be higher in the IC group due to the higher number of critical care days in this group. Utilisation of key personnel resources is shown in

Table 17 - Personnel

	IC (n = 44)	MEM (n = 44)	P value
Mean number of Consultant Visits (SD)	24.68 (20.96)	18.00 (14.89)	0.088
Mean number of Physician Visits (SD)	40.93 (41.68)	21.93 (18.53)	0.007
Mean CCU Nurse days (SD)	13.93 (19.11)	6.86 (9.40)	0.030
Mean General ward Nurse days (SD)	14.86 (19.49)	16.91 (21.56)	0.642
Mean Pharmacist minutes (SD)	620.11 (409.78)	392.05 (297.96)	0.004
Mean Pharmacy Aide minutes (SD)	620.11 (409.78)	392.05 (297.96)	0.004
Administration Sets (SD)	41.34 (27.32)	25.14 (17.13)	0.001

Key: SD = standard deviation; CCU = critical care days. Mean visits are expressed per patient

The mean number of consultant visits was not significantly higher in the IC group than the MEM group (p = 0.088). The mean number of physician visits was higher in the IC group compared to the MEM group (p = 0.007), as were the mean ICU nurse days (p = 0.030). The mean general ward nurse days were not statistically different (p = 0.642). The mean pharmacist time included the time to process the order and included technician preparation time of the intravenous minibag. It was estimated that each minibag takes 15 minutes to prepare. The mean pharmacist time (in minutes) was significantly higher in the IC group compared to the MEM group (p =

0.004). The pharmacy aide time considered the time to deliver the study drug to the units to be 15 minutes per item. The mean pharmacy aide time appeared significantly higher in the IC group compared to the MEM group (p = 0.004*).* The mean number of administration sets used in the IC group was also significantly higher than in the MEM group (p=0.001).

4.8.   Economic Evaluation

Resource utilization costs are listed in Table 18 as the mean resource cost per day. Comparison of the mean daily costs using independent sample –T tests demonstrated no significant difference in terms of mean daily CCU and step-down costs. Mean CCU days for the IC group cost SAR 1,022.73 (95% CI 807.86 to 1,237.59) and for the MEM group were SAR 784.09 (95% CI 553.67 to 1014.51), These mean costs were significantly different (p = 0.13). The mean step-down costs were not significantly different (p = 0.99). Mean general ward costs were significantly lower in the IC group than the MEM group (p = 0.016*).* A significant lower medicine acquisition vial cost was observed for IC (SAR 250.63, 95% CI 238.06 to263.20) compared to MEM (SAR 393.48, 95% CI 366.12 to 420.84) (p < 0.001). However there was a significantly higher cost attached to administration sets in the IC group (SAR 39.16, 95% CI 37.2 to 41.13) than in the MEM group (SAR 28.00, 95% CI 26.61 to 29.39) (p < 0.001). Mean daily laboratory costs in the IC group were not significantly different when compared to the MEM group (p =0.379), however the costs of mean daily laboratory cultures were significantly lower in the IC group compared to the MEM group (p = 0.014). Mean CCU consultations costs were not significantly different between the groups (p = 0.13), nor were mean daily GW consultations (p = 0.939) and staff physician consultations (p = 0.056).

Mean CCU daily nursing costs were not significantly different (p = 0.13), nor were mean daily GW nursing costs (p = 0.956) However, mean daily pharmacists costs were significantly higher

in the IC group (SAR 64.08, 95% CI 60.87 to 67.30) compared to the MEM group (SAR 46.82, 95% CI 43.57 to 50.08) (p < 0.001). Mean daily pharmacy aide costs were also significantly higher in the IC group than the MEM group (p < 0.001). There was no difference in the mean costs of ADEs between the two groups (p = 0.333).

Overall there was no difference in the mean total daily costs between IC (SAR 4784.46, 95% CI 4140.68 to 5428.24) and MEM (SAR 4390.14, 95% CI 3785.82 to 4994.45) (p = 0.37), as shown in Table 18- Resource utilization costs.

Table 18- Resource utilization costs

Average Daily Costs	IC				MEM				P value
	Mean	Confidence Interval Lower	Upper	SD	Mean	Confidence Interval Lower	Upper	SD	
CCU	1,022.73	807.86	1,237.59	706.73	784.09	553.67	1,014.51	757.89	0.130
Step-down	572.73	439.58	705.88	437.95	572.73	439.58	705.88	437.95	0.99
GW	372.16	305.83	438.49	218.16	465.91	427.15	504.67	127.49	0.016
Vials	250.63	238.06	263.2	41.34	393.48	366.12	420.84	89.99	<0.001
Admin Sets	39.16	37.20	41.13	6.46	28.00	26.61	29.39	4.57	<0.001
Laboratory tests	904.96	658.61	1,151.31	810.29	761.32	545.84	976.81	708.77	0.379
Lab. cultures	86.61	74.32	98.90	40.42	129.64	97.48	161.8	105.78	0.014
CCU consult	681.82	538.57	825.06	471.16	522.73	369.11	676.34	505.26	0.13
GW Consult	205.26	114.73	295.79	297.77	200.47	114.08	286.86	284.15	0.939
Staff Physician	264.48	222.84	306.13	136.98	215.55	186.25	244.86	96.39	0.056
CCU Nurse	204.55	161.57	247.52	141.35	156.82	110.73	202.9	151.58	0.13
GW Nurse	92.88	85.13	100.63	25.49	93.18	85.43	100.93	25.50	0.956
Pharmacist	64.08	60.87	67.30	10.57	46.82	43.57	50.08	10.71	<0.001
Pharmacy Aide	21.36	20.29	22.43	3.52	15.61	14.52	16.69	3.57	<0.001
ADE	1.05	0	2.11	3.48	3.78	-1.77	9.32	18.24	0.333
Totals	4,784.46	4,140.68	5,428.24	2,117.50	4,390.13	3,785.82	4,994.45	1,987.70	0.37

Figure 8 - Resource utilization costs

Resource Utilization Costs
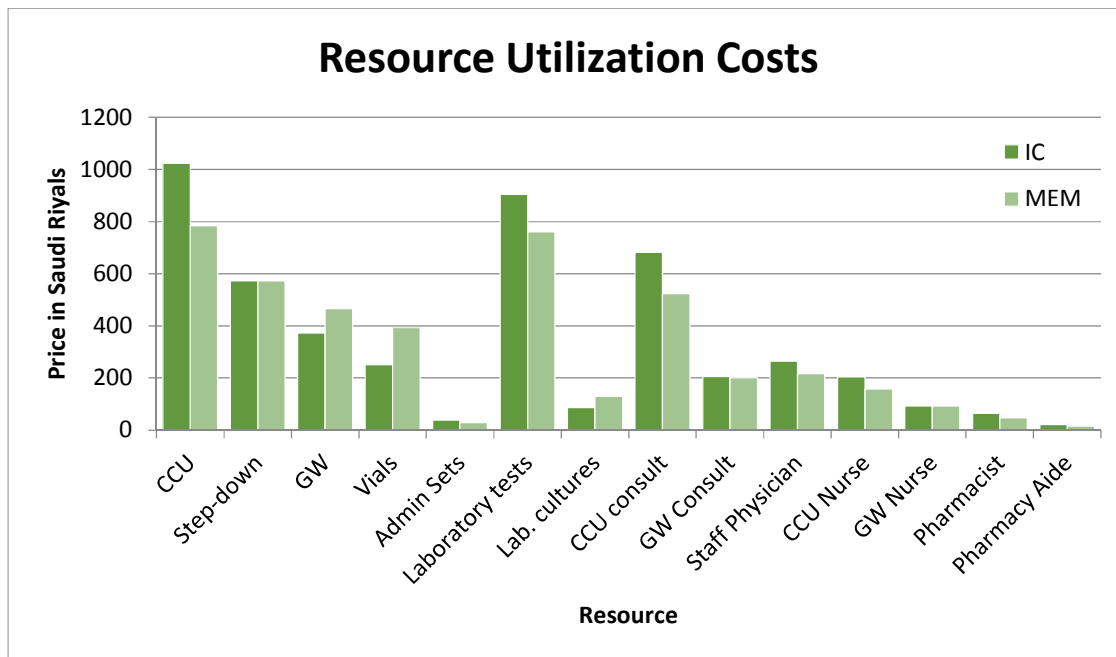
Figure 9 - Mean total costs of IC and MEM
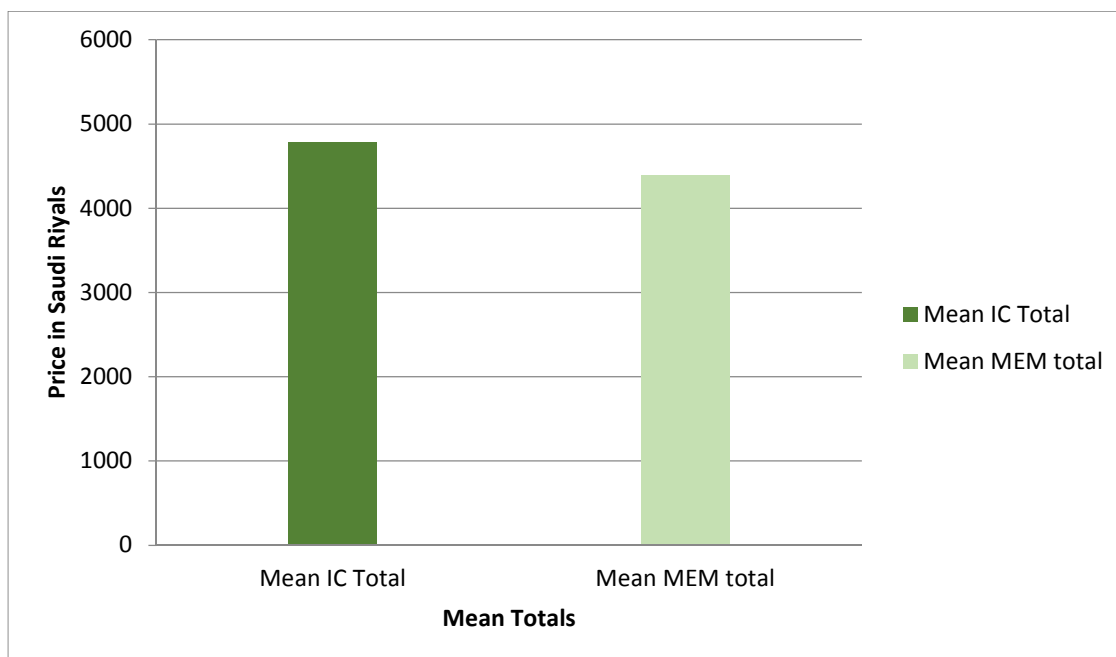
4.8.1. One-way sensitivity analysis

One-way sensitivity analysis was performed in Microsoft ® Excel by varying the mean cost of
each parameter of IC and MEM. A 20% variation from the mean parameter cost produced the
following outcomes with IC:

The mean parameter cost was increased and decreased to assess those parameters with the
greatest impact on the total costs. Changes in the base value (IC = SAR 4,784.46 and MEM =
SAR 4,390.13) were noted.

Table 19 – One-way sensitivity analysis with IC

Parameters	Low	High	% change
CCU days	4,579.91	4,989.00	4.28
Step-down days	4,669.91	4,899.00	2.39
GW days	4,710.02	4,858.89	1.56
Vials	4,734.33	4,834.58	1.05
Admin Sets	4,776.62	4,792.29	0.16
Laboratory tests	4,603.46	4,965.45	3.78
Laboratory cultures	4,767.13	4,801.78	0.36
CCU consult	4,648.09	4,920.82	2.85
GW Consult	4,743.40	4,825.51	0.86
Staff Physician	4,731.56	4,837.35	1.11
CCU Nurse	4,743.55	4,825.37	0.85
GW Nurse	4,765.88	4,803.03	0.39
Pharmacist	4,771.64	4,797.27	0.27
Pharmacy Aide	4,780.18	4,788.73	0.09
ADE	4,784.25	4,784.67	0.00

One-way sensitivity analysis with a 20% change in IC parameters shows that the parameters,
which exerts the greatest change in the mean total cost are:

a) CCU days with a 4.28% change in the total cost

b) Laboratory tests with a 3.78% change in the mean total costs

c) CCU consultation charges with 2.85% change in the total costs

d) Step-down days with a 2.39% change in the total costs

e) GW days with a 1.56% change in the total costs

Figure 10 - One way sensitivity analysis with IC (mean value = SAR 4,784.46)
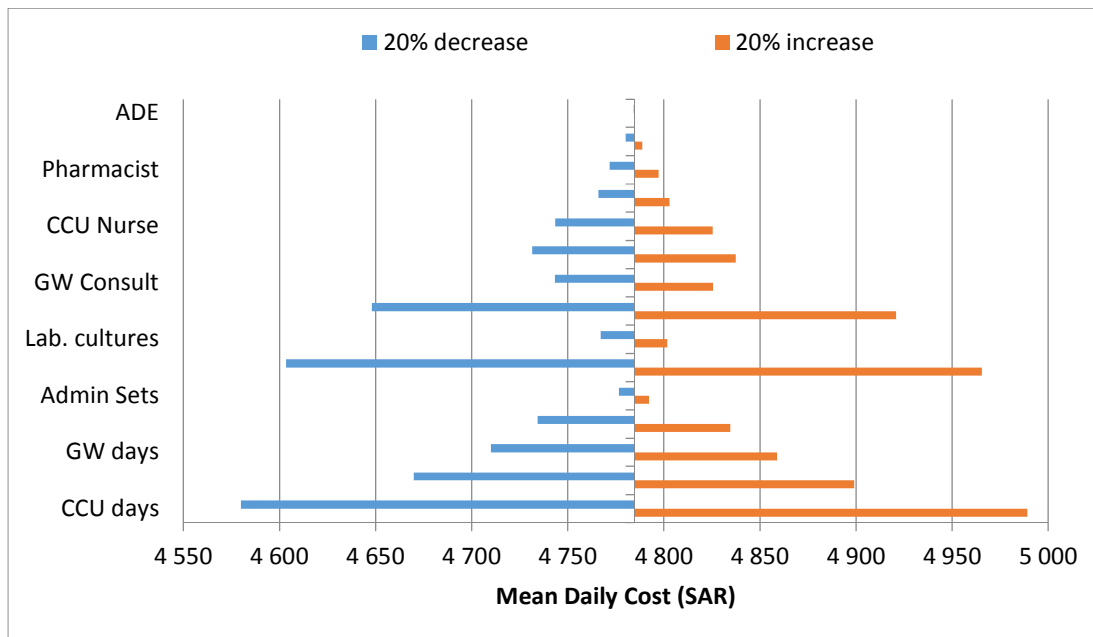
The parameters which least affected the total costs in the IC group were:

a) ADE with 0.004% change in the mean total cost

b) Pharmacy Aide with 0.09% change in mean the total cost

c) Administration sets with a 0.16% change in mean the total costs.

d) Pharmacists with a 0.27% change in the mean total cost

e) Laboratory cultures with a 0.36% change in the mean total cost

f) GW nursing with a 0.39% change in the mean total cost

One-way sensitivity analysis with a 20% change in MEM parameters shows that the parameters, which exerts the greatest change in the mean total cost are:

a) CCU days with a 3.57%% change in the mean total cost

b) Laboratory tests with a 3.47% change in the mean total costs

c) CCU consultation charges with 2.38% change in the mean total costs

d) Step-down days with a 2.61% change in the mean total costs

e) GW days with a 2.12% change in the mean total costs

A 20% variation from the mean parameter cost produced the following outcomes with MEM:

Table 20 - One-way sensitivity analysis with MEM

MEM	20% decrease	20% increase	% change
CCU days	4,233.31	4,546.95	3.57
Step-down days	4,275.58	4,504.67	2.61
GW days	4,296.95	4,483.31	2.12
Vials	4,311.43	4,468.82	1.79
Admin Sets	4,384.53	4,395.73	0.13
Laboratory tests	4,237.86	4,542.39	3.47
Laboratory cultures	4,364.20	4,416.06	0.59
CCU consult	4,285.58	4,494.67	2.38
GW Consult	4,350.03	4,430.22	0.91
Staff Physician	4,347.02	4,433.24	0.98
CCU Nurse	4,358.76	4,421.49	0.71
GW Nurse	4,371.49	4,408.76	0.42
Pharmacist	4,380.76	4,399.49	0.21
Pharmacy Aide	4,387.01	4,393.25	0.07
ADE	4,389.37	4,390.88	0.02

One way sensitivity analysis with MEM (base value = SAR 4,390.13)

Figure 11- One way sensitivity analysis with MEM (mean value = SAR4,390.13)
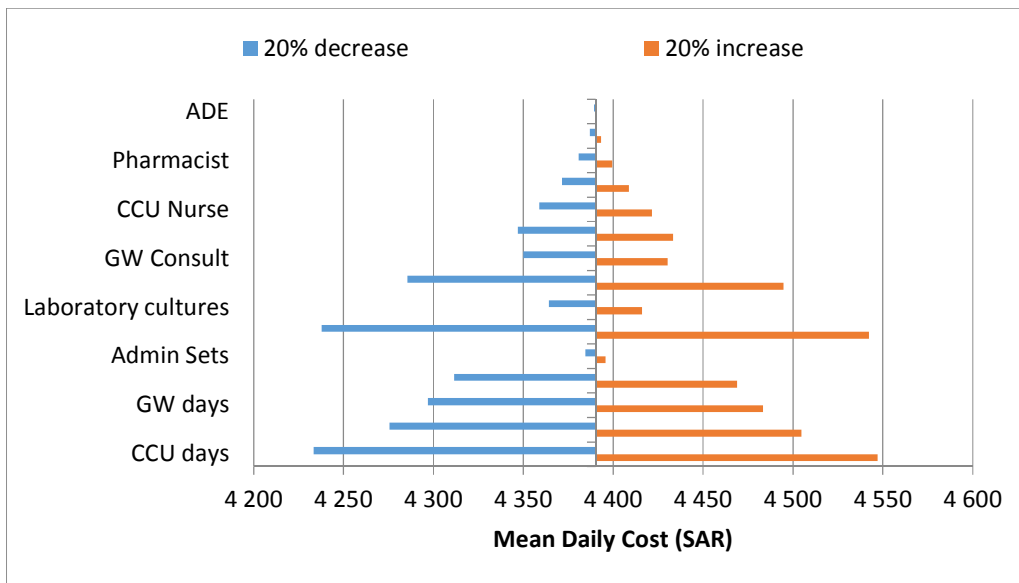
The parameters which least affected the total costs in the MEM group were:

a) ADE with 0.02% change in the mean total cost

b) Pharmacy Aide with 0.07% change in the mean total cost

c) Administration sets with a 0.13% change in the mean total costs

d) Pharmacists with a 0.21% change in the mean total cost

e) GW nursing with a 0.42% change in the mean total cost

f) Laboratory culture with 0.59% change in the mean total cost

4.8.2. Threshold Analysis

A threshold analysis was performed on parameters so as to assess the value at which our conclusions change. The value of the parameter was being sought that agreed with our initial assumption that IC is less costly than MEM. It was assumed, using independent sample T-test

comparison of the mean, with p <0.05, that the conclusion will change in favour IC as being

significantly less costly, if the total costs were below SAR 3,795.00. Our initial unpublished

study assumed that acquisition costs significantly impacts the total health care costs. Using the

parameters of the acquisition costs, the input value was varied to assess the threshold at which

the total costs in the IC group would be less than SAR 3,795.00. The parameters included vial

costs, ADEs, administration sets and pharmacists' costs.

Figure 12 - Impact of variations in ADEs, vial costs and pharmacists costs
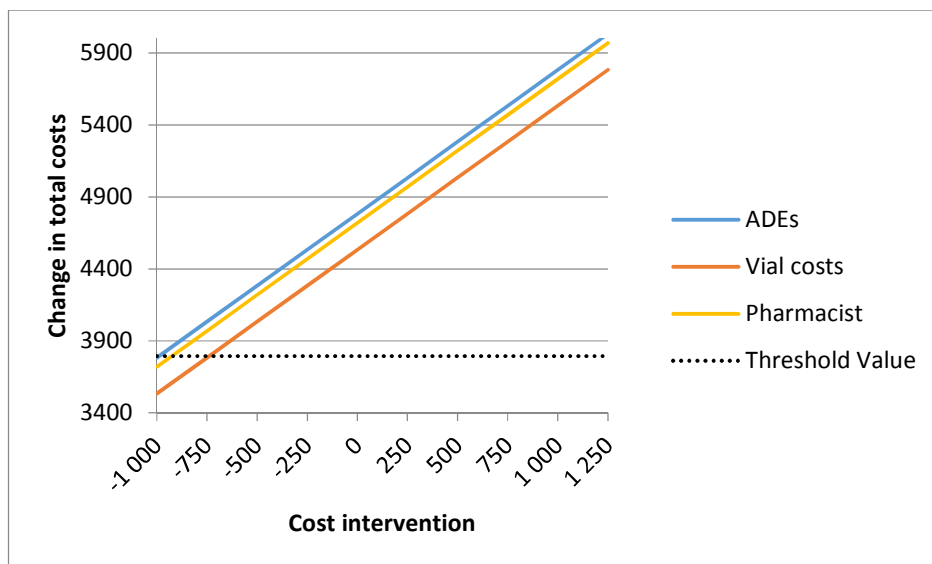
 The threshold analysis found that variations in ADEs, vial costs, administration costs and

pharmacists' costs did not affect the conclusion even if the input value of each of the acquisition

costs parameter was set at SAR 0.00. Input and output values are listed in Table 21 **-**

Table 21 - Impact of variations in ADEs, vial costs, administration sets and pharmacist costs on total costs

Cost Intervention	ADEs	Vial Cost	Administration Sets	Pharmacist Costs
-1,000	3,783.41	3,533.83	3,745.30	3,720.38
-750	4,033.41	3,783.83	3,995.30	3,970.38
-500	4,283.41	4,033.83	4,245.30	4,220.38
-250	4,533.41	4,283.83	4,495.30	4,470.38
0	4,783.41	4,533.83	4,745.30	4,720.38
250	5,033.41	4,783.83	4,995.30	4,970.38
500	5,283.41	5,033.83	5,245.30	5,220.38
750	5,533.41	5,283.83	5,495.30	5,470.38
1,000	5,783.41	5,533.83	5,745.30	5,720.38
1,250	6,033.41	5,783.83	5,995.30	5,970.38

Acquisition costs threshold values for each parameter was less than 0 (Table 22).

Table 22 - Threshold value of acquisition costs parameter at which IC is less costly than MEM

Parameter	Threshold
ADEs	-988.41
Vial costs	-738.83
Administration sets	-950.30
pharmacist cost	-925.38

Threshold analysis was done on those parameters that had the greatest effect on the total cost of treatment. The value was being sought of each parameter that would change our conclusion i.e. the point at which IC becomes less costly than MEM. The total value was once again set to SAR 3,795.00. Parameters included was hospital days (CCU, step-down and GW), as these were found to impact total costs the most.

Figure 13 - Impact of variations on CCU, step-down and GW costs
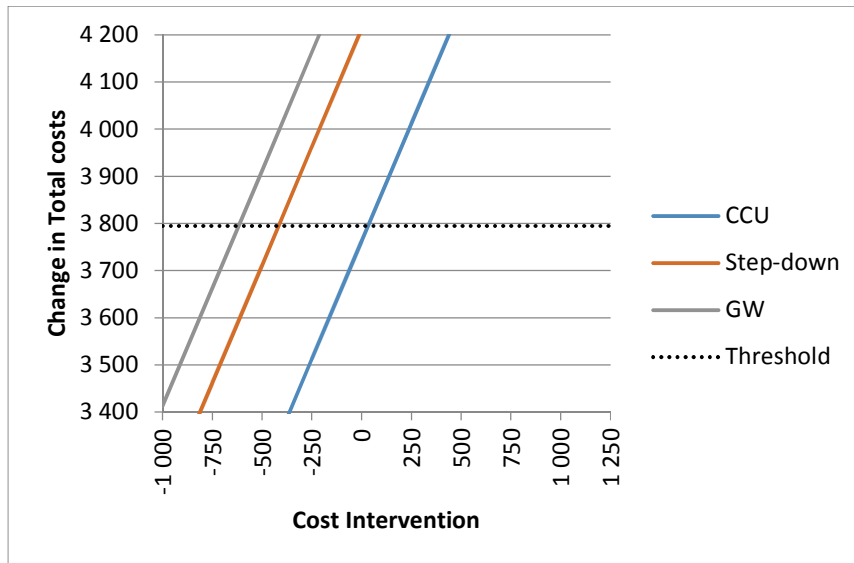
The threshold analysis found that variations in step-down costs and GW costs did not affect the

conclusion even if the input value of each of the acquisition costs parameter was set at SAR 0.00.

However the threshold value of CCU was SAR 33.27. Input and output values are listed in

Table 23.

Table 23 - Impact of variations in CCU, step-down and GW costs on total costs

	CCU	Step-down	GW	Threshold
-1,000	2,762	3,211.73	3,412.30	3,795.00
-750	3,012	3,461.73	3,662.30	3,795.00
-500	3,262	3,711.73	3,912.30	3,795.00
-250	3,512	3,961.73	4,162.30	3,795.00
0	3,762	4,211.73	4,412.30	3,795.00
250	4,012	4,461.73	4,662.30	3,795.00
500	4,262	4,711.73	4,912.30	3,795.00
750	4,512	4,961.73	5,162.30	3,795.00
1,000	4,762	5,211.73	5,412.30	3,795.00
1,250	5,012	5,461.73	5,662.30	3,795.00

Acquisition costs threshold values for each parameter was less than 0, except CCU which was

SAR 33.27. Threshold values for hospital days are listed in Table 24.

Table 24 - Threshold value of hospital days at which IC is less costly than MEM

Parameter	Threshold
CCU days	33.27
Step-down days	-416.73
GW days	-617.30

Costs related to primary infection and superinfections

Other costs related to primary infection and superinfections are listed in Table 25. This includes

add-on antibiotics, previously failed antibiotics and antifungals used to treat either the primary

infection or superinfections. Independent sample T-tests found no significant difference in mean

daily costs between antifungals, ancillary antibiotics or previous failed antibiotics between the

two groups.

Table 25 - Costs related to primary infection and superinfections

Mean Cost/day	IC		MEM		
	Mean	SD	Mean	SD	P value
Antifungal	80.05	250.72	139.88	430.24	0.428
Ancillary Antibiotics	189.24	211.07	207.58	196.30	0.674
Previous Antibiotics	116.30	278.04	46.94	68.33	0.112

CHAPTER 5: DISCUSSION

5.1. Introduction

This chapter will discuss the results of this study within the context of carbapenem usage in a 300-bed government hospital in Saudi Arabia, and also in relation to the available published literature. It will discuss the setting of the study; baseline characteristics focusing on the primary objectives of the study (cost minimization analysis).

Several factors prompted the need for a pharmacoeconomic evaluation of IC and MEM. These included an institutional review of antimicrobial restriction, and concerns about usage and costs. Most importantly, the acquisition costs of IC were noted to be less than those for MEM (SAR70.4 versus SAR 151.26 per vial). In addition, published pharmacoeconomic evaluations are limited in Saudi Arabia (4). To our knowledge, no published pharmacoeconomic evaluations comparing IC and MEM in adult patients had been conducted in Saudi Arabia. There have been several international pharmacoeconomic evaluations done (1, 2, 37) with conflicting results. Using data based on the local perspective therefore had the potential to provide insight into the factors influencing local practice and medicines selection. Government institutions in Saudi Arabia, providing free medical treatment, may adopt similar costing strategies that are unique to this region.

A retrospective review of 100 files were planned, but only 88 patients records met the study criteria. The type of research was based on staffing, budgeting constraints, and the small sample size. However, a double-blinded randomized control trial would have been optimal. The number of patients on IC, that met the study criteria, was limited to only 45 for the year 2012. In addition one file could not be retrieved by the hospital information management department, leaving 44

clinically evaluable charts. MEM patients numbered 44 with 6 charts not meeting the study criteria as mentioned in the method section above. The review included adult patients ($\geq$ 18 years), as the paediatric population weights and dosing vary considerable. The patients with moderate to severe infections with SSI, IAI, LRTI, sepsis, UTI and HAI were considered, as these are the main indications of carbapenems approved by the institution guidelines. Furthermore, a wealth of literature supports the use of IC and MEM for the indications described. In addition, the literature review provides evidence showing that IC and MEM share similar efficacy and tolerability profiles. Bacterial meningitis was not included as this group is at-risk for seizures. Pregnant patients were also excluded due to the unpredictable pharmacokinetic parameters in this population. In order to minimize bias a clearly defined population was used, that have the same risk of developing the outcome of interest.

A cost-minimization analysis was considered based on the clinical equivalence studies above, assuming similar efficacy and safety profiles between IC and MEM cited in the literature review. Thus equivalency studies were presented to reinforce our assumption of clinical equivalency. Institutional antimicrobial guidelines(15) recommend IC at a dose of 0.5 to 1 gram every 6 hours and MEM at a dose of 1 gram every eight hours for mild to moderate infections. The United States FDA recommendations (33, 34), reinforced by the literature review (36) supports the institutional guidelines. Therefore the study dosage of IC 500mg q6h and MEM 1gram q8h was selected. The cost-minimization was performed following a previously unpublished institutional review that suggested a substantial saving, had the institute enforced the antimicrobial restriction guidelines. It was suggested that an interchange program of MEM with IC would drive down costs. On the other hand, physicians showed preference to MEM, due to

the apparent risk of seizures with IC (60). This has led to an increased usage of MEM, substantially impacting the hospital budget.

5.2. Findings

5.2.1. Comparative review

The approach used was to seek evidence from clinical trials of the clinical equivalency between IC and MEM in terms of efficacy and safety. A literature review of 18 studies comparing IC to MEM concluded that IC is as effective and well tolerated in mild to moderate infections. None of the 18 studies included a non-inferiority study design. The six studies which showed superiority of either agent were not considered to alter this overall judgment. The justification for this conclusion was provided in section 2.3.8. The studies by Edwards et al. (2, 49) were not in agreement with the conclusions drawn in the 18 studies that showed clinical equivalence.

Four studies showed that IC was significantly less costly than MEM. Only one well-designed pharmacoeconomic study by Attanasio et al. (1) had well described costing data measuring direct costs. Details of the costing approach for two studies were not clear, while the third measured acquisition costs. One study by Edwards et al. (2) applying pharmacoeconomic principles found MEM to be significantly less costly than IC.

Evidence retrieved suggests the following:

a) Literature supports the rationale of the study dose of IC 500mg q6h and MEM 1gram q8h

b) No significant difference in clinical, bacteriological and adverse effects of IC and MEM in patients with IAI

c) No significant difference in clinical, bacteriological and adverse effects of IC and MEM in patients with SSI

d) IC and MEM showed similar efficacy and safety profiles in patients with respiratory tract infections

e) IC and MEM showed no significant difference in clinical or bacteriological outcomes in patients with UTI

f) IC is as well tolerated and effective as MEM in patients with sepsis

g) Four RCTs showed similar safety profiles between IC and MEM

Based on the above; IC at a dose of 500mg q6h (cost = SAR 281.60 per day) is an attractive alternative to MEM 1gram q8h (cost = SAR 453.78 per day), particularly in mild to moderate infections. These studies show that both drugs share similar clinical efficacy and tolerability profiles. Carbapenems should be avoided in elderly patients, patients with low body weight, at risk of CNS disease, history of seizure and renal dysfunction. Our review was in agreement with the 18 studies showing that IC is as effective and well tolerated as MEM. However, this study was not in agreement with the pharmacoeconomic conclusions in the studies above. The economic evaluation is discussed in section 5.1.6. It must be further mentioned that future research might access studies using a formal non-inferiority approach rather than the assumed equivalency approach that was used in the studies retrieved.

5.2.2. Baseline Characteristics

Baseline characteristics in our study were not significantly different in terms of the mean age, weight and height (Table 13). A significant greater number of CCU days in the IC group was found when compared with the MEM group (13.93 vs. 6.86, $p= 0.030$). Higher number of

critical care days was associated with higher total costs in the IC group. Outliers were identified in the IC group with 1 patient in the ICU as much as 102 days. The intensive care pharmacist's intervention (interchanging MEM with IC) resulted in more patients using IC in CCU compared to the general wards. PTC recommendations were implemented to reduce costs. Our hospital does not have clinical pharmacists in the step-down units and general wards resulting in much more erratic use of MEM in these areas. However overall costs per day were not affected significantly in the critical care areas. There were no significant difference in step-down days and GW days in both groups.

5.2.3. Clinical efficacy and safety outcomes

As this is a cost-minimization analysis, the assumption of equivalent efficacy was demonstrated by literature retrieved and cited and not the outcomes of patients treated, whose cost data are being sought in this study. Nevertheless the clinical efficacy and safety outcomes found in this study agreed with the studies cited in the literature review chapter. This study focused on patients diagnosed with skin infections (SSI), intra-abdominal infections (IAI), respiratory tract infections, urinary tract infections (UTI), hospital acquired infections (HAI) as well as those with sepsis. Equivalency studies with a pharmacoeconomic evaluation showed IC to be less costly than MEM (1, 37, 40). It was noted that Edwards et al. (2) did not agree with this finding.

Clinical success rates (59.1% in IC group versus 63.6% in the MEM group, $p = 0.661$) were not significantly different. The number of positive infections appeared similar. LOAS were not statistically different in both groups (mean IC =11.18 and MEM = 9.57, $p = 0.212$). The clinical efficacy data between IC and MEM in this study agreed with the studies cited in the literature review. IC and MEM showed no difference in their clinical efficacy

The overall ADEs were not significantly different between the groups. It was found that ADEs were under reported when compared to published studies (54). In this regard ADEs was confirmed by objective parameters. These include initiation of anti-seizure medication if the patient had a seizure, corticosteroid and anti-histamines for rash and therapies for antibiotic associated diarrhoea. Although more patients had gastrointestinal ADEs in the MEM group, it was not significantly different when compared to IC. These were mainly antibiotic associated diarrhoea after *C. difficle* culture was taken. Antibiotic diarrhoea was confirmed by comparing the patient record to the physician notes or the patients were started on supportive measures or therapies like vancomycin oral. Other objective measures included laboratory ADEs. One patient on IC had a seizure associated with IC administration. This concern among health care workers prompted the avoidance of IC in our hospital. One study (3), which is often quoted to highlight the seizures of IC may have also influenced the poor usage of IC. The study suggests that IC may be associated with drug-related seizure events. It must be pointed out that Hoffman et al. (54) found no difference in seizure rates between IC and MEM, and that elderly patients, patients with low body weight, at risk of CNS disease, history of seizure and renal dysfunction appears to be associated with increased risk of drug related seizure The patient was at risk for seizures as she was geriatric patient with moderate renal impairment. This study excluded patients with bacterial meningitis due to this population being at risk for seizures. In addition our hospital guidelines (15) does not advocate its use in those at seizure risk and patients with poor kidney function. Our study did not show significant difference in in ADE's between IC and MEM, agreeing with Hoffman et al. (54).

5.2.4. Hospital resources

The number of physician visits were significantly higher in the IC group when compared to MEM (mean IC= 40.93, SD = 41.68 versus mean MEM = 21.93, SD 18.53). This was attributed to more CCU days found in the IC group which necessitated more physician visits. Similarly more CCU nurse days were found in the IC group, related to more patients in the IC group in critical care areas. As expected the mean pharmacists' time (in minutes) was significantly higher in the IC group compared to the MEM group (mean IC = 620.11, SD 409.78 versus mean MEM = 392.05, SD = 297.96). The institute prepares both antibiotics in the intravenous admixture room. Both antibiotics are prepared as a late-mix just before the dose is due. IC was given 4 times daily while MEM was given 3 times daily. The delivery by the pharmacy aide showed more delivery time with IC compared to MEM, again this is attributed to the 4 times daily versus 3 times daily of IC and MEM respectively. For the same reason, more administration sets and minibags were required for the IC group. The results clearly demonstrate that significantly more time is required per day to prepare IC compared with MEM. Overall more hospital resources are required in the preparation, dispensing and administration of IC compared to the MEM group, except in mean number of consultant visits and mean number of nurse general ward visits.

5.2.5. Costing

The October 2013 business centre and SFDA Human Drug List pricing was used corresponding to the final ethics approval obtained in October 2013. In addition, the most updated costing was being sought. A standardised approach to the pricing was used rather than the actual hospital cost. Standardised figures are more generalizable to other government health sectors, as these include the standard list prices. The prices used were indicative of the generic medicine brands

available at our institution. Costs per day were calculated rather than total cost per patient so as to limit the impact of differences in LOAS.

5.2.6. Economic Evaluations

Total hospital days, especially the total CCU days in the IC group was significantly higher. This was attributed to the clinical pharmacist's intervention of interchanging MEM with IC. The greater usage of IC with more "sicker patients" affected the number of hospital days. The longer CCU days was believed to influence costing, especially in the IC costs. The cost per day of a CCU day is highest (SAR 1500) compared to a step-down (SAR 900) unit or a general ward (SAR 500). Patients varied significantly in regard to the number of CCU days. Daily costs would allow comparison of the two antibiotics while minimizing bias due to length of hospital stay. In this regard, all costs were reflected as cost per day.

Independent sample T-tests showed no significant difference in terms of mean daily hospital costs in CCUs (IC = SAR 1,022.73, 95% CI [807.86, 1,237.59] and MEM = SAR 784.09, 95% CI [553.67, 1014.51], p = 0.13); and step-down costs (IC = SAR 572.73, 95% CI [439.58, 705.88] and MEM = SAR 572.73, 95% CI [439.58, 705.88], p = 0.99). However the GW costs in the IC group was significantly lower in the IC group (SAR 372.16, 95% CI [305.83, 438.49] compared to MEM at SAR 465.91, 95% CI [427.15, 504.67], p = 0.016). Although total CCU costs were higher, cost per day was not statistically different between the two groups, except in the GW days. More patients in the MEM group spent a greater number of days in the GW unit, which drove up mean costs in this group.

The mean total daily costs of vials in the IC group were much lower than MEM (SAR 250.63 vs. 393.48). This was expected as the cost of a vial of IC = SAR 70.4 versus MEM = SAR 151.26. IC given 4 times daily would result in daily costs of SAR 281.60 versus MEM given 3 times daily at SAR 453.78. The mean costs in our study were mean costs reflecting dose changes as well. In the institution, previous unpublished study, this difference in acquisition costs amounted to a significant saving of more than SAR 2 million riyals for the organization. This makes IC an attractive choice as a carbapenem in patients with moderate to severe infections. However the institutional review did not include resource costs associated with the primary infection. Our study included personnel costs, administration costs, length of hospital stay, laboratory charges, delivery costs and costs related to ADEs. The administration sets costs were higher in the IC than MEM (SAR39.16 vs. SAR 28.00). Pharmacy preparation time and costs was significantly higher in the IC group than the MEM group (SAR 64.08 vs. SAR 50.08). Pharmacy aide delivery time and costs were much higher in the IC group compared to the MEM group (SAR 21.36 vs. SAR 15.61). The administration, preparation, dispensing and delivery costs were related to the frequency of the dosing times; with IC given every 6 hours versus MEM given every 8 hours. As a result costs were higher in the IC group. Overall the acquisition costs of IC were significantly lower in the IC group, while costs in the preparation, dispensing, administration sets, and deliveries were higher in the IC group. No significant difference was found in terms of average daily nursing costs between the two groups. The business centre costs for nursing were not related to the number of patient visits. Consultant, physician and nursing costs were not affected by the frequency of administration costs; rather they were affected by the number of CCU days, whereas administration sets, pharmacy aide delivery time and pharmacists' time were related to the frequency.

Laboratory tests mean costs per day were not significantly different between the groups. The laboratory cultures mean costs per day was significantly higher in the IC group. This may be attributed to the higher number of CCU patients that require more critical care and more cultures.

Despite significant differences in acquisition costs, laboratory culture costs, pharmacist and pharmacy aide costs, the total average costs per day was not significantly different between the 2 groups (SAR 4,784.46 IC and SAR 4,390.13 MEM, *p = 0.370*). Our review may have agreed with literature review in terms of the clinical and safety outcomes, we found no difference in the overall mean total daily costs between the 2 drugs.

The studies by Attanasio et al. (1), Beketov et al. (40) and Zhanel et al. (36) showed both agents to be clinically effective and showed IC to be less costly. These three studies only considered patients with IAI, whereas our study included a larger definition as outlined in the methods chapter. Our study was in agreement with similar clinical efficacy; however the total costs were not significantly different between the two groups which was similar to the findings of Badia et al. (37). Attanasio et al. (1) included direct costs such as diagnostic procedures, drug acquisition and administration, management of adverse events and hospitalization. Our study included similar direct costs as well as pharmacist time and delivery costs. Zhanel et al. (36) showed similar cost-effectiveness as Attansio et al. (1), however the details of the cost analysis were not available.

The greater number of CCU days in the IC group seems to be the reason for driving up the total costs in the IC group. However mean total daily costs were not significantly different. Although the costing details for Badia et al. (37) were not available our study was in agreement that there

were no significant differences in the total costs between IC and MEM, clinical efficacy and safety.

Other costs related to the primary infections were not significantly different.

Local perspective

It must be pointed out that some resource costs are unique to the local perspective. These include resource costs that are fixed in the institution and not related to the number of patient visits. Nursing services costs have daily rates rather than cost per visit. IC requires more frequent administration and costs were expected to be higher. However, with fixed costs, this was not apparent. Other costs like consumables were also fixed. Most resources were variable and based on the number of patient days or related to the frequency of administration.

Sensitivity Analysis

A one-way sensitivity analysis varying the resource costs by 20% showed that the mean total costs were sensitive to hospital days, laboratory tests and CCU consultations charges (Table 19 and Table 20). These findings did not support our hypothesis that acquisition costs and costs related to administration times play a major role in total daily costs. The sensitivity analysis found that ADEs, pharmacy aide delivery costs, pharmacist costs, administration costs, and nursing costs were the least sensitive parameters in relation to the total costs. The sensitivity analysis sheds light on the factors that influence costing of the primary infection. Our study shows that costs related to the LOAS and consultation charges may affect total costs much more than acquisition costs or ADE costs.

A threshold analysis was performed on the hospital days, acquisition costs and personnel costs. The only parameter found to change the conclusion was CCU days. If the CCU value was less than SAR 33.27, average total costs of IC would be less costly than MEM. Our conclusion did not change for the rest of the parameters even if the parameter value was set to SAR 0.

5.3. Limitations

Our study was a retrospective single-cohort study that reflects the practices of our institution. A double blind randomized controlled multi-centre trial would have been optimal. However due to the limitations of budgeting and manpower, ethical approval, blinding and randomization could not be achieved. Sample size was small. Only 44 patient's files could be evaluated due to the lack of patients prescribed IC and patients that met the inclusion criteria.

Missing information could have added to the bias; however every effort was made to accurately identify missing information. Primary infection was based on the physician diagnosis. Some of the files had incomplete documentation and in this case the physician notes had to be consulted as defined in the methods section as well as laboratory cultures. Every attempt was made to obtain correct diagnosis based on physician notes and definitions above. Two files were inaccessible as they were locked by the Hospital Information Management Department for review. The ADEs were confirmed using objective parameters.

The costing of drugs was taking from the SFDA human drug list pricing (8). The cost of resources was taken from the hospital's business centre section. This may not reflect the true costs that the institution would pay. Suppliers may offer discounts to government institutions.

Experts may argue that the societal perspective may be the only true measure of a pharmacoeconomics evaluation as it measures the benefits to the community as a whole. However, this study considered the provider perspective so as to provide guidance on hospital formularies in the region.

The PI was aware of the PTC review of IC and MEM as well as the cost-saving interventions. The data was double-checked by a second pharmacist to ensure that any oversight was correctly rectified.

Only equivalence studies were being sought (citation bias). A wealth of evidence exists showing similar efficacy between the drugs. Some studies have shown differences in terms of efficacy and cost-effectiveness; however the perspective of a cost minimization analysis is based fundamentally in proving their similarities rather than a difference. Some experts (58) may disagree with a cost minimization analysis, however based on the institutional perspective antimicrobial Guidelines (15), these two antibiotics are clinically equivalent in terms of efficacy and safety, as described in the introduction of this paper.

Despite these limitations, our study has given insight into the factors influencing hospital budgets at our institution.

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1.   Introduction

The overriding purpose of this study was to find the least costly alternative of 2 therapeutically equivalent alternatives (IC 500mg q6h versus MEM 1 gram q8h) in a tertiary care hospital in Saudi Arabia. The purpose of this chapter is to conclude and summarise the findings of this study and recommend strategies ensuring efficient budget utilization of IC and MEM at our institute. To achieve that goal it has become necessary to explore the field of pharmacoeconomics, in Saudi Arabia, using cost minimization analysis in an environment that has limited research in this field. Studies of this nature could help PTC formulary decision in providing the most effective, equitable and efficient services for our population, within the resources entrusted to us.

In addition to looking at acquisition costs, this study aimed to look at hospital resources and personnel costs that influence costs in our setting. Recommendations for future research of IC and MEM are also recommended in this chapter.

6.2.   Conclusions

The outcomes of this retrospective review of 88 adult patients in a tertiary care institute in Saudi Arabia, found that although IC acquisition costs is significantly less that MEM, the mean total costs per day was not significantly different between IC and MEM. This study supports the PTC recommendation of carbapenem selection by restricting MEM to infection control physician only. In addition, costs related to frequency of administration times were higher in the IC group compared to MEM, however not significantly impacting mean total costs. This included pharmacy aide delivery, pharmacist preparation and administration sets used.

The study showed that those factors with the greatest impact on hospital costs were related to the hospital stay, especially CCU days. Mean total costs were also sensitive to CCU consultant visits and laboratory cultures associated with CCU admission.

Threshold analyses found that reduction of CCU day costs was the only factor which could change the conclusion; other parameters did not change the conclusion of the study, even if the input parameter was SAR 0.00.

The secondary outcomes agreed with previous findings that IC 500mg q6h is as effective and well tolerated as MEM 1 gram q8h.

Carbapenems should be avoided in elderly patients, patients with low body weight, at risk of CNS disease, history of seizure and renal dysfunction.

This study has shown that while acquisition costs of IC at a dose of 500mg q6h may be less costly than MEM 1 gram q8h, mean total costs per day was not significantly different between IC and MEM, indicating that medicine costs are only a small element of the overall costs of managing moderate to severe infections.

6.3. Recommendations

The following recommendations are based on the analysis and interpretation of the study. The perspective of the recommendations is that of a Saudi Arabian government sector hospital in adult patients with mild to moderate infection.

1. Interchanging MEM 1 gram q8h with IC 500mg q6h reduces cost per day, however this is not a major component influencing total daily costs related to the primary infection.

2. Enforce PTC recommendation of using IC as the first line carbapenem in moderate to severe infections

3. IC 500mg q6h is as effective and well tolerated as MEM 1 gram q8h in moderate to severe infections

4. Carbapenems should be avoided in patients at risk of seizures including elderly patients, patients with low body weight, at risk of CNS disease, history of seizure and renal.

5. More robust pharmacoeconomic studies are needed in Saudi Arabia. It would have been optimal if conditions favoured a blinded randomized control trial. Comparative studies could use the non-inferiority approach rather than attempting to prove equivalence.

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APPENDICES

Appendix 1 - - King Abdullah International Medical Research Centre approval

Kingdom of Saudi Arabia
National Guard Health Affairs
King Abdulaziz Hospital
Al Ahsa

المملكة العربية السعودية
الحرس الوطني – الشؤون الصحية
مستشفى الملك عبدالعزيز با
الاحساء

King Abdullah International Medical Research Center - Eastern Region

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RESEARCH OFFICE

MEMORANDUM
Ref #: KAIMRC-ER/CRO/04/13

DATE   :   **13 JANUARY 2013**
                 01 Rabi Al Awal 1434

TO   :   **DR. IMRAAN JOOSUB**
                 Principal Investigator - RRE12/011
                 Pharmacy Supervisor, Pharmaceutical Care
                 King Abdulaziz Hospital, NGHA, Al Hasa

FROM   :   **DR. RIFAT REHMANI**
                 Chairman, Clinical Research Office – Eastern Region
                 King Abdullah International Medical Research Center – Eastern Region
                 King Abdulaziz Hospital, NGHA, Al-Ahsa

SUBJECT   :   PROTOCOL # RRE12/011 – "Cost Minimization Analysis of Meropenem versus Imipenem/Cilastatin in Moderate to Severe Infections at a Tertiary Care Hospital in Saudi Arabia"

After careful scientific evaluation of the above-mentioned proposal, as per comments and suggestions of the respective reviewers and in behalf of the committee, I am grateful to inform you that your Research Proposal has been **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.

Kindly observe the retrospective research guidelines in conducting your data collection in accordance with APP 1427-08.

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

Your dedication and continued collaboration to our organization will lead to the fulfillment of our goal.

Thank you and best regards.

cc: KAIMRC-ER
       FILE
                                                           13/01/2013/RRA

Appendix 2 - Final approval - University of KwaZulu-Natal

UNIVERSITY OF ™
KWAZULU-NATAL

INYUVESI
YAKWAZULU-NATALI

03 October 2013

Mr I Joosub
Department of Pharmacy
P.O Box 2477
King Abdul-Aziz National Guard Hospital
Kingdom of Saudi Arabia
31982
imraan007@gmail.com

PROTOCOL: Cost Minimization Analysis of Meropenem versus Imipenem/ Cilastatin in Moderate to Severe Infections at a tertiary care hospital in Saudi Arabia. REF: BE273/13.

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 11 July 2013.

The study was provisionally approved pending appropriate responses to queries raised. Your responses dated 02 September 2013 to queries raised on 27 August 2013 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from 03 October 2013.

This approval is valid for one year from 03 October 2013. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be RATIFIED by a full Committee at its next meeting taking place on 12 November 2013.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor D.R Wassenaar
Chair: Biomedical Research Ethics Committee

Professor D Wassenaar (Chair)
Biomedical Research Ethics Committee
Westville Campus, Govan Mbeki Building
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Telephone: +27 (0)31 260 2384 Facsimile: +27 (0)31 260 4609 Email: brec@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx
Founding Campuses: ■ Edgewood ■ Howard College ■ Medical School ■ Pietermaritzburg ■ Westville

INSPIRING GREATNESS

Appendix 3 - Data Collection Sheet

Data Collection

MRN:			ID:			Weight (kg):	
Gender:			Date of Admission:			Age (years):	
Days in ICU:			Date of Discharge:			Height (cm):	
Past Medical History:			Days in General Ward:			LOS-AR:	
Diagnosis			Days in ICU:			Drug Name:	
Hepatic Status:			Renal Status:			Allergy:	

Sensitivity	1		2		3		4		5
Resistance:	1		2		3		4		5
Ancilliary Abx	1		2		3		4		5
Dose:									

Date:																Tot.
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Tot.
Daily Dose:																
Cultures Taken																
Dx Tests																
Highest Temp																
WBC																
CBC																
Basic Screen																
Serum Cr.																
LFT																
Antibody Screen																
ABORH																
PT/PPT																
INR																
# Consultant Visits																
# Physician Visit																
Nurse Visit																
Ancillary Staff Visit																
# IV Admin Sets																
Clinical Success																
Other Abx																

ADR/ADE											
HBA1C											
Pathology											
Lactic Acid Serum											
GTP											
Cardiac Enzymes											
Troponin											
Vancomycin level											
Troponin											
Vancomycin level											

Date:						
Source of Infection						
Positive/ Negative						
Microbiology 1						
Microbiology 2						
Microbiology 3						
Microbiology 4						
Microbiology 5						

Notes:

_____

_____

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Abbreviations:		Admin:	Administrations	Focus of ingection see notes (skin, intra-abdominal, urinary etc.)		
Tx:	Treatment	LOS:	Length of Stay	ADE:	Adverse Drug Event	Abx: Antibiotics
DC:	Discontinued	Micro:	Microorganisms	ADR:	Adverse Drug Reaction	Dx: Diagnostic

Name of Data Collector: _____

Focus of infection (positive culture or physician documentation)

☐ Skin infection: cellulitis, infected skin ulcers, infected wounds, and abscess would be used.

☐ Sepsis: sepsis, fever with temperature above 38.3 degrees Celsius, chills, leukocytosis (WBC above normal), hyperventilation, hypothermia, skin lesions, septic embolism, change in mental status, hypotension, disseminated intravascular coagulation, organ failure are considered. Should be diagnosed by physician.

☐ Intra-abdominal infections: evidence of abscess or peritonitis (inflammation of abdominal lining) originating from stomach, duodenum, biliary tract, pancreas, appendix, small intestine and colon.

☐ Lower respiratory tract infections (LRTIs) (2): pulmonary infiltration thought to be due to infection in the chest X-ray and at least two of the following criteria: purulent sputum (<10 squamous epithelial cells, > 25 WBC's and a pathogen should be cultured), fever and leukocytosis (WBC > 12).

☐ Urinary tract infections (UTI), evidence of dysuria, frequency, urgency, suprapubic pain, and/or hematuria, fever greater than 38 degrees Celsius urinalysis, history of previous UTI, urine culture showed positive bacteriological growth would be considered

☐ Hospital-acquired infection is was defined as late onset infection (> 72 hours after admission), post-surgical infection and community acquired considered as early onset (< 72 hours) (1-6)

Adverse Events Associated study drug (after initiation of drug)

Seizure diagnosed on the day the study drug was administered: YES/ NO

Anti-epileptic drug initiated after administration of study drug:

Phenytoin ☐   carbamazepine ☐   phenobarbital ☐   levetiracetam ☐

General Adverse Events related to study drug

Skin reactions ☐   rash ☐   pruritis ☐

Urticaria ☐   erythema multiforma ☐   SJS or other ☐

GI disturbance (N,V,D) ☐   COMMENTS:_____

Lab Adverse Events within 24 hours of initiating study drug

Elevated ALK (>150U/L), AST(>34 U/L) or ALT(>55 U/L)   ☐

Renal   CrCl < 50ml/min   ☐

Bilirubin T (>20.5µmol/l)   ☐

Notes: