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DRUG UTILIZATION REVIEW OF MEROPENUM

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Abstract

Meropenem is known as a most effective drug for the treatment of multi-drug resistant gram negative bacterial infections. The higher incidence of empirical prescription for this drug in hospitals will potentially increase the prevalence of resistance, making it an important candidate for execution of drug utilization evaluation (DUE).

The primary objective of the study was to assess the Meropenum prescribed cases and evaluation of its appropriateness. A retrospective study was conducted to evaluate the appropriate use of Meropenum. A total of 50 Meropenum prescribed cases were assessed in our study, which revealed 84% of empirical use and 16% of specific use.

The culture sensitivity test was performed in 82% of cases and in 18% of cases the culture sensitivity test was not performed. The maximum dose in all 50 cases was 1g and minimum dose was 100mg. The maximum duration was 14 days and minimum duration of therapy was 2 days. The dose given to patients was accurate as per renal status in 88% of patients and 12% of patients received inappropriate dose as per renal status. Out of 50 collected cases 98% of patients responded to Meropenem therapy while 2% patients didn't respond to the therapy.

Keywords:
Meropenem, chemical structure, pharmacokinetics and dynamics, side effects and clinical pharmacology

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Introduction:

1.1. Background study

Appropriate use of antibiotics is associated with detrimental effects including emergence of antibiotics resistance affecting treatment outcome. The Centers for Disease Control and Prevention estimated 23,000 deaths per year in the USA due to infections by antibiotic resistant microorganisms. Therefore, curbing antibiotic resistance is a major public health priority. Epidemiological studies have shown a relationship between carbapenem use and resistance. Carbapenem intermediate or resistant Enterobacteriaceae, including Klebsiella pneumonia carbapenemase producing bacteria, are of increasing concern and have rapidly spread worldwide.

Meropenem, a parenteral carbapenem antibiotic, have a broad spectrum of antibacterial activity in-vitro with the majority of gram-negative, gram-positive and anaerobic microorganisms being highly susceptible to the drug. Meropenem is likely to have the greatest value for empiric treatment of life threatened infections or those caused by multi-drug resistant pathogens.

Due to resistance to destruction by most β-lactamase enzymes, carbapenems are often used as last-line therapy for infections due to multidrug-resistant gram-negative bacilli. However, there have been an alarming emergence of carbapenem-resistant bacteria including acinetobacter spp. and pseudomonas aeruginosa over recent decades.

Drug utilization studies are performed to analyze and manage data obtained over a certain period of time or to evaluate the effects and resistance achieved by therapeutic interventions. Moreover, the patterns of use are evaluated to obtain the information necessary to update prescribing policies as well as to provide proper feedback to the healthcare professionals that prescribe meropenem as a treatment plan. The high rate of prescribing meropenem in hospitals will definitely increase the prevalence of resistance, making it an important candidate for drugs utilization evaluation (DUE) studies. Therefore, this study was conducted to evaluate the use of meropenem in MTI- Hayatabad Medical Complex.

Meropenem is a new carbapenem antibacterial recently introduced and marketed in many countries. The first member of this class, imipenem, was introduced into the market as medicine to treat life threatened disease in 1980s. These antibacterial drugs share a number of significant advantages over other types of antibacterial. In particularly, they offer the broadest antibacterial spectra of any class, which includes virtually all clinically important gram-negative and Gram-positive aerobic and anaerobic microorganisms. This activity is due in part to high degree of stability shown by carbapenem to β-lactamase. This property is becoming important in view of the increasing incidence of Enterobacteriaceae strains which produce broad-spectrum β-lactamase. However, there are important differences between meropenem and imipenem. Imipenem is susceptible to be metabolized by renal dehydropeptidaase-1 (DHP-1).

Consequently, the drugs must be administered in combination with cilastin a DHP-1 inhibitor. In contrast, meropenem is somewhat stable to this enzyme and does not require co-administration with a DHP-1 inhibitors.

Also, there are differences in the antibacterial spectra of these two agents. Meropenem shows somewhat better activity against Enterobacteriaceae and Pseudomonas aeruginosa, while imipenem is more potent against some gram-positive cocci. Meropenem may be better tolerated than imipenem/cilastin, particularly by the gastrointestinal tract with regard to nausea and vomiting and central nervous system. In addition, Meropenem unlike imipenem/cilastin, can be given by intravenous bolus injection.Therfore, meropenem monotherapy is an attractive choice for the empirical treatment of moderate or severe bacterial infections.

1.2 Chemistry:

Meropenem (4R, 5S, 6S)-3-[[(3S, SS)-5-(dimethylcarbamoyl)-3-pyrrolidinyl] thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo [3, 2, 0] hept-2-ene-2-carboxylic acid, is among the newer semisynthetic beta-lactam antibacterial agent belonging to the carbapenem class. Meropenem differs chemically from imipenem by possessing a 1 beta-methyl group on the carbapenem moiety and substituted 2’ sides chain. The 1-b-methyl substituent provides stability to human renal dehydropeptidase-1 (DHP-1),

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an enzyme that hydrolyses imipenem. Meropenem can therefore be administered as a single agent, unlike imipenem which must be co-administered with cilastin, a DHP-1 inhibitor, to prevent the degradation of the molecule and nephrotoxic effects. The 2'side's chain of meropenem provides enhanced activity against P.aeruginosa.

1.3 Pharmacodynamics:

As with other β-lactam antibiotics, carbapenems (meropenem) are inhibitors of cell wall biosynthesis specifically, they prevent transpeptidation, which is an integral step to the structural integrity of the bacterial cell wall. Inhibition of peptidoglycan crosslinking results in cell wall lysis and ultimately cell death such as, carbapenems are classified as bactericidal (that cause cell death). Broadly speaking, as a compound class, carbapenems show limited permeability of the outer membrane protein (OMP) prions to facilitate their entry into the gram-negative bacteria; for example, OprD is implicated as a key transport channel for carbapenems, facilitating entry into pseudomonas aeruginosa. Carbapenems inhibit the penicillin-binding protein (PBP) family of enzymes by acylating the targets. Carbapenem affinity for the different PBPs varies between bacteria, and gram-negative PBPs are structurally different from those of Gram-positive organism. A range of PBPs exist and are targeted by different carbapenem: for example, PBP2 is the primary target of meropenem in Escherichia coli, whereas high-affinity binding to PBP1, PBP2 and PBP4 is observed in Staphylococcus aureus.

The basis for this inhibition is the similarity of the β-lactam core to the d-Ala-d-Ala terminus of the peptidoglycan substrate. This structural similarity facilitates covalent binding and thus irreversible inhibition of the target enzymes.

1.4. Pharmacokinetics:

Meropenem has linear pharmacokinetics and distributes into a broad range of body fluids and tissues. Mean value for peak plasma concentration (Cmax) in healthy volunteers were 54.8-61.6 mg/L after single dose meropenem 1g. These values were similar 1 hour after either bolus or infusion administration. Means value for elimination half-life ($T_{1/2}$) were 1.0-1.4 hours , and volume of distribution was 12.5-23L. Meropenem is largely excreted renally with 54-79% of a 1g dosage excreted unchanged in the urine and 19-27% excreted as an inactive metabolites. Unlike imipenem, meropenem is stable to human renal dehydropeptidase-1. Data relating to the effects of serious infections on the pharmacokinetics of meropenem are limited, but the changes seen in studies in small numbers of patients appear to result from factors other than infection (such as recent surgery). However, dosage adjustments are necessary in patients with renal impairment. Meropenem is primarily excreted through kidne ys because of this, total body and renal clearance of meropenem decrease and $T_{1/2}$ increases, as creatinine clearance decreases. Patients with renal failure requiring continuous veno-venous haemofibrilation may require higher dosages of meropenem than the dose recommended for their level of renal impairment in order to maintain adequate serum concentrations. Hepatic impairment had no significant effect on the pharmacokinetics of meropenem.

1.5 Therapeutics:

Meropenem is a broad-spectrum antibacterial used for the treatment of a wide range of infections including polymicrobail infections in adults and children. It has comparable efficacy to imipenem/cilastin and various other treatment regimes. Its greatest value may be empiric monotherapy in the treatment of serious infections, or those caused by multiple-resistant pathogen, or for mixed infection usually requiring antibiotics combinations. It has been found effective in intra-abdominal and soft tissue infections as well as in febrile neutropenia, urinary tract infections, and meningitis. Meropenem is effective in dosages of 1.5-3.0 g daily for the treatment intra-abdominal infections, lower respiratory tract infections, obstetrics and gynecological infections and sepsis.

Table 1.5.

S/No	Name of disease	Unit	Route of administration	References
1	Febrile neutropenia	1g	I.V , in every 8 hours	19

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2	Intra-abdominal infection	1g	I.V , in every 8 hours	20
3	Meningitis	2g	I.V , in every 8 hours	21
4	Soft/skin tissue infection	0.5g	I.V , in every 8 hours	22
5	Urinary tract infection	0.5g	I.V , twice daily	23

1.6 Contraindications:

Meropenem is contraindicated in those who are hypersensitive to it. Precautions must be taken when prescribing meropenem to those with renal impairment, with epilepsy, or a history of seizures or neurological disorders, with hepatic dysfunctions and in those who have had an anaphylactic reactions to the β-lactam antibiotics.

1.7 Adverse effects:

The overall incidence of adverse effects leading to drug withdrawal and mortality are similar among meropenem, imipenem/cilastin and combination regimens. Adverse effects most frequently associated with meropenem are diarrhea, rash, nausea/ vomiting and local inflammation at the site of injection. However, there are important differences in the tolerability of meropenem and imipenem. Unlike imipenem, meropenem does appear to be any more likely induce seizures than other β-lactam antibiotics. Also, meropenem seems less likely to cause nausea and vomiting and inflammation at IV sites. While rapid infusion of imipenem significantly increases the frequency of nausea and vomiting, administration of it IV bolus injection is generally well tolerated.

1.8 Antibacterial activity:

Studies have shown that meropenem freely penetrates Enterobacteriaceae and Pseudomonas aeruginosa. Similar to other β-lactam antibacterial agents, meropenem binds covalently to penicillin binding proteins (PBP). PBPs are essential for bacterial cell wall biosynthesis and this disruption leads bacterial cell death. In Escherichia coli, the main target of both meropenem and imipenem is PBP2. However, in pseudomonas aeruginosa, ameropenem unlike imipenem has high affinity for both PBP2 and PBP3.

A comprehensive overview of the antibacterial activity of meropenem and a comparison with imipenem and various other antibacterial agents is provided in the review by Edward and Wiseman et al. Meropenem has broad spectrum of antibacterial activity which encompasses the majority of clinically important aerobic nutritionally fastidious, with anaerobic bacteria. The widely accepted susceptibility breakpoints for meropenem are 4-8 mg/l for full and intermediate susceptibility respectively and 216mg/l for resistance, these remain to be confirmed by NCCLS.

The spectrum of activity of meropenem is similar to that of imipenem. However meropenem is more active against in-vitro than imipenem against Enterobacteriaceae and other Gram-negative aerobes and a little less active against some aerobes Gram-positive cocci.

Meropenem exhibits a high degree of potency against non-fermenters. It is generally 2-4 fold more active than imipenem against most pseudomonas spp. And 4 times more potent against Burkholderiucepaciu. Indeed, meropenem was the most potent antimicrobial tested in a recent study involving 1991 clinical isolates of pseudomonas aeruginosa; 98.9% of isolates were fully susceptible to meropenem. Meropenem, in common with most β-lactam agents, is not active against stenotrophomonas (Xanthomonas) maltophilia. The activity of meropenem in-vitro against bacterial strains resistant to other antimicrobials has also been evaluated. Meropenem retains activity against penicillin-resistant streptococcus pneumonia, although its MIC in these strains is increased to 1 mg/l. Meropenem has demonstrated a high degree of activity against Enterobacteriaceae and pseudomonas aeruginosa strains with resistance to fluoroquinolones, aminoglycosides or other beta lactam. In one study 95% of 144 Gram-negative bacilli isolates resistant to ciprofloxacin, cefoperazone and/ or amikacin were susceptible to meropenem. Other study showed meropenem to be at least 4-fold more active than imipenem against most strains of gram-negative bacilli with resistant to other β-lactam agents. Meropenem has also demonstrated activity against strains of anaerobic organism resistant to cefoxitin, clindamycin and metronidazole.

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Table 1.2. In-vitro antibacterial activity of meropenem against clinically important Gram-negative and gram-positive aerobes:

S/No	Organism	Number of strains	MIC_{90} Of meropenem mg/l
	Gram-positive		
1	Staphylococcus aureus (MS)	3417	0.25
2	Staphylococcus epidermidis (MS)	1317	4
3	Streptococcus pyrogene	392	<0.06
4	Streptococcus pneumoniae (PS)	708	0.13
5	Streptococcus pneumoniae (PR)	143	1
6	Enterococcus faecalis	1698	8
7	Listeria monocytogenes	155	0.25
	Gram-negative		
8	Escherichia coli	3683	0.06
9	Citrobacter freundii	656	0.13
10	Klebsiella pneumoniae	1241	0.06
11	Enterobacter cloacae	1201	0.25
12	Serratia marcescens	764	0.25
13	Proteus mirabilus	1398	0.13
14	Proteus vulgarus	377	0.25
15	Salmonella spp.	308	8
16	Acinecobactor calcoaceticus	461	2

Table 1.2: Compiled internationally from 122 laboratories (reproduced with permission). MS, methicillin-susceptible; PS, penicillin-susceptible; PR, penicillin resistant. Including β-lactamase positive or ampicillin resistant strains.

Carbapenem, unlike other β-lactam agents exert a post-antibiotics effects (PAE) with Gram-negative bacilli. Meropenem has also demonstrated a PAE with staphylococcus aureus, Enterococcus faecalis, Pseudomonas aeruginosa and Bacteriodesfragilis. With respect to Enterobacteriaceae, meropenem induced a PAE with 80% (12/15) of strains tested.

1.9 Clinical Pharmacology:

The usual dosage of meropenem in adult is 500 mg to 1g IV three times daily. The dosage depends on the type and severity of infection, known or suspected susceptibility of the pathogen(s), and the clinically status of the patient. Febrile episodes in neutropenic patients should be treated with 1g of meropenem three times daily and in meningitis a dosage of 2g three times daily should be used. Meropenem dosage should be reduced in patients with impaired renal function (creatinine clearance <51 ml/min). A dosage of 500mg every 24hrs has been recommended in patients undergoing continuous arteriovenous haemofiltration (based on a normal dosage of 1 g 8 hourly). Patients undergoing hemodialysis should receive 500mg every 48-72 hours and after hemodialysis. No dosage adjustment is required in patients with impaired hepatic function. The recommended dosage for the treatment of most infections in infants and children between 3 months and 12 years of age is 10-20 mg/kg three times daily, depending upon the type of severity of infection, the known or anticipated susceptibility of the pathogen and the patient's condition. Pediatric patients with febrile neutropenia should receive meropenem 20mg/kg three times daily and a dosage of 40mg/kg three times daily is recommended for the treatment of meningitis. The adult dosage should be used for children who weight more than 50kg. Meropenem has not been studied in children with renal impairment and therefore no dosage recommendations can be made for this patient group. Also at present, there are no dosage recommendations for meropenem in neonates. In clinical studies to date, the maximum daily dosage

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of meropenem administered was 6g in adults and 120mg/kg in children; the maximum duration of treatment was 52 days in adults and 18 days in children.

Table 1.3: Recommendations for meropenem dosage in adults with renal impairment (reproduced with permission of Aids International Limited)

CL_{CR}(ml/min)	*Dose (mg)*	*Dosage interval (hr)*
>50	0.5-1000	8
26-50	500-1000	12
10-25	500	12
<10	500	24
0 (CAVHD)	500	24
0 (hemodialysis)	500	48-72 and after hemodialysis

1.10 Mechanism of resistance:

Resistance to β-lactam antibacterial agents can result from a number of mechanisms and may be intrinsic or acquired. Reduced susceptibility to the carbapenems, although less common than with other β-lactam agents, has been observed in bacteria (such as P.aeruginosa) that exhibit multiple resistance mechanisms; in addition there are increasing numbers of reports of organisms with acquired carbapenemase. In spite of the wide spread use of meropenem, there has been no clinically significant resistance seen in P.aeruginosa or Klebsiella, Enterobacter or Serratia spp. The potential of antibacterial agents to select resistant strains and the incidence of cross-resistance should be considered when choosing an antibacterial agents although data are limited. In 1 in-vitro study, meropenem selected resistant strains of Enterobactercloacae to a greater degree than imipenem (although data from MYSTIC indicate that meropenem is highly active against this pathogen); in another study, neither meropenem nor imipenem selected for mutant isolates of P.aeruginosa that were cross-resistant to other β-lactam agents. Cross-resistance data from isolates Of P.aeruginosa. However, suggest that imipenem-resistant strains are more likely to be susceptible to meropenem than vice versa.

1.10.1 Production of β-lactamases:

The production of enzymes capable of hydrolyzing β-lactam rings enables certain bacteria to inactive β-lactam antibacterial agents. Carbapenems such as meropenem are highly resistant to hydrolysis by serine-based β-lactamases (such as chromosomal and plasmid-mediated β-lactamases produced by most Gram-negative bacteria). This may be of clinical significance; 1 study (reported as an abstract) found that mortality rates in 80 patients infected with extended spectrum β-lactamases producing strains of K.pneumoniae were significantly lower in those who received a carbapenem in the first 5 days of treatment, compared with those who received other antibacterial agents (5 vs 43% p=0.01). However, carbapenems are susceptible to the metallo-β-lactamases (Bush groups 3a and 3b) and clavulanic acid inhibited carbapenemase (group 2f) produced by S.maltophilia and some Flavobacterium spp. Acquired metallo-β-lactamases conferring resistance or decreased susceptibility to carbapenems have been reported in resistant isolates of P aeruginosa from 1 patient in Italy and Japan ; a specific metallo-β-lactamases (IMP-1) has also been reported in Japanese isolates of Serratiamarescens and in 1 case , a Japanese isolate of K.pneumonia.

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Carbapenemase resistance is also increasingly common in clinical isolates of acinetobacter, with plasmid-mediated carbapenemase and metallo-β-lactamases reported.

1.10.2 Alteration in permeability:

Carbapenem enter Gram-negative bacteria by passive diffusion through porins in the cell membranes. The zwitter ionic nature and low molecular weight of meropenem mean that it is able to penetrate most cells. However, organisms that lack porins can have decreased susceptibility to carbapenems because of the reduction in permeability. Deficiency of outer membrane porins proteins D2 is associated with decreased susceptibility to carbapenems, but not other β-lactam agents in the addition, a number of different porins deficiencies associated with decreased susceptibility have been described in isolates of P.aeruginosa. One in-vitro study also found that meropenem selected tor porins deficient mutant of K.pneumoniae. However, clinical data indicate that isolates of K.pneumoniae are still highly susceptible to meropenem. Some organisms with these deficiencies may demonstrate a reduction in susceptibility only if they also hyper produce β-lactamases. Multidrug efflux pumps capable of excreting antibacterial agents have been detected in some Gram-negative bacteria including P.aeruginosa and these can also contribute towards decreased susceptibility to carbapenems. These pumps are usually capable of excreting a broad range of antibacterial agents including β-lactam, fluoroquinolones and tetracyclines. It is unclear how common they are among resistant bacterial isolates.

1.11. Problem statement:

1.11.1 Inappropriate prescribing of meropenem:

In clinical settings leads to increased risk of antibacterial resistance and poor patient outcomes.

1.11.2 Lack of regular DUR:

Lack of regular drug utilization review of meropenem results in its overuse, misuse and irrational prescribing patterns in hospitals.

1.11.3 Inadequate monitoring:

Inadequate monitoring of meropenem use compromises treatment effectiveness and may increase healthcare costs and hospital stay duration.

1.11.4 Absence of standard guidelines:

Absence of standardized guidelines for meropenem prescribing contributes the variation in usage across different healthcare facilities.

1.11.5 Limited awareness:

Limited awareness among healthcare professionals about the pharmacoeconomics impact of meropenem overuse hinders optimal antibiotic stewardship practices.

1.12 Significance of study:

1.12.1 Promote rational use:

The study helps ensure meropenem is prescribed based on appropriate clinical indications, minimizing misuse and overuse.

1.12.2 Prevent antimicrobial resistance:

Evaluating usage patterns supports strategies to combat rising resistance to carbapenem antibiotics like meropenem.

1.12.3 Improve patient safety:

DUR identifies inappropriate dosing, frequency or duration that may harm patients ensuring safer antibiotic therapy.

1.12.4 Enhance antibiotics Stewardship:

The study supports hospital stewardship programs by guiding interventions to optimize antibiotics use.

1.12.5 Reduces healthcare costs:

Rational use decreases unnecessary prescriptions, lowering drug costs and hospital stays.

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1.12.6 Supports policy development:
Findings can inform evidence-based guidelines and institutional protocols for meropenem use.
1.12.7 Educational value:
It raises awareness among healthcare providers about appropriate antibiotics prescribing practices.

1.13 Aims and objectives:
The aim of the study is to evaluate the use of meropenem against the standard criteria.

- To check the indication of meropenem.
- To check the dosage of meropenem in different indications.
- To check the duration of meropenem therapy in different conditions.
- To check that whether the serum creatinine and CBC was checked before and during the course of therapy.
- To check that whether the temperature was recorded 4 hourly,
- To check that whether the C/S test was performed prior to the therapy.
- To check that whether the C/S test showed the growth of meropenem susceptible microorganisms.

Literature review:
Meropenem utilization evaluation in referral teaching hospital in Iran, 2018. This study aimed to evaluate the use of meropenem, an extended-spectrum antibiotic, in a referral teaching hospital to detect different types of errors in its prescription.
Drug use evaluation of meropenem at a tertiary care university hospital: A report from Northern Iran, 2015, Ebrahim Salehifar, Afshin sheva, Mona Moshayedi. The inappropriate use of antibiotics remains the primary factor in antimicrobial drug resistance. In this study, we evaluate the use of meropenem in surgical/medical wards of Imam Khomeini Tertiary Refferal Hospital, Sari, Iran
Evaluation of the inappropriateness of meropenem prescribing at a tertiary care hospital: A retrospective study in Oman, 2020, Dania Al-Hadithi, Ibrahim Al-Zakwani, Abdullah Balkhair, Yousaf M Al-Suleimani. The aim of this study was to evaluate the use of meropenem in terms of indication and continuation of treatment at Sultan Qaboos University Hospital (SQUH), Muscat, Oman.
Retrospective review with threat of infectious disease consultation and sustained reduction in meropenem use over four yours, 2021. Nandita S Mani, Kristine F lan, Rupali Jain, Elizabeth M Krantz,
A retrospective study was conducted at the University of Washington Medical Center (UWMC) and Harborview Medical Center (HMC) to evaluate the impact of the policy on antimicrobial consumption and clinical outcomes pre- and post-intervention during a 6-years period.
Meropenem use and therapeutic drug monitoring in clinical practice: A literature review 2021, Nadine A Steffens, Estevan S Zimmermann, Sabrina M Nichelle, Natalia Brucker. The main parameter associated with its therapeutic success is the percentage of time that the levels remain above the minimum inhibitory concentration.
Drug Utilization Evaluation of Meropenem and Vancomycin in febrile Neutropenic patients, 2015. Sudhakar, Rahamada Safna, Mariyam, Ashok Kumar T.R.
The purpose of the present study is to evaluate the use of meropenem and vancomycin in Febrile Neutropenia patients.
Retrospective drug evaluation review of meropenem and the role of infectious disease pharmacist in specialized cancer care hospital, 2022.Muhammad Rehan Khan, Zikria Saleem, Narjis Batool, Mahrukh Babar, Aleena Shabbir The objective of this study was to review the use of meropenem in cancer patients and to evaluate the impact of clinical pharmacist's intervention in this practice to reduce possible risks associated with use of meropenem.
Impact of an electronic alert on prescription patterns of meropenem, Variconazole and caspofungin 2021, Katharina Kusejko, Nadia Eberhard, Sandra E. Chaudron, Dirk Saleschus antimicrobial stewardship

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programs promotes the appropriate use of antimicrobial substances through the implementation of evidence-based active and passive intervention.

Adherence to antimicrobial agent recommendations and utilization during drug shortages 2023, the study objectives were to characterize utilization of antimicrobial agents with established restrictions during a medication shortage, access utilization of shortage antimicrobials following shortage resolution and examine use of recommended alternatives antimicrobials during the shortage period. Victoria Urban, Brian R Lee, Jennifer L Goldman, Ashley Duty, Ann L Wirtz.

Maximizing cost savings and clinical outcomes: A retrospective analysis of antimicrobial stewardship for meropenem utilization in Saudi Arabia, 2025, to evaluate trends in meropenem utilization, compliance, consumption and cost across consecutive quarters from April 2022 to December 2023. Rawan T Tafish, Reem Al-Zayer, Faisal Al-Anazi, Jida Al-Mulki.

Trends in meropenem antibiotics utilization, costs and market dynamics in Medicaid: A retrospective analysis from 1991 to 2023, 2025. Marwan A Alrasheed, Abdulrahman A Alsuhibani. This study aimed to analyze longitudinal trends in carbapenem use, market dynamic and economic impact within Medicaid from 1991 to 2023.

Prospective drug utilization evaluation of three broad-spectrum antimicrobials: Cefepime, piperacillin-tozabactum and meropenem,2006, D Ravesh, E Muallem-Zilcha, A Greenberg, Y Wiener-well, Y Schlesinger, A M Yinnon. To evaluate guidelines for appropriate use of these drugs.

Impact of the acceptance of the recommendations made by a Meropenem Stewardship Program in a University hospital : A pilot study by Jorge Alba Fernandez,2022

Evaluation Criteria and Rationality Analysis of Drug Utilization of Meropenem in a Tertiary Medical Institution in Beijing / Asian Journal of Social Pharmacy, 2025, Zhang Qiming, Huang Zhe (School of Business Administration, Shenyang Pharmaceutical University, Shenyang 110016, China)

Methodology:

This study was a retrospective drug utilization study carried out in the medical and pads ward of multispecialty 1300 bedded tertiary care hospital MTI-HMC. The hospital also provides services in pathology, gastroenterology, infection, critical care, pediatrics, neonatology, surgery, ENT, gynecology, pulmonary and neurology.

2.1 Study duration:

The study was conducted for the period of 1 month from 20th September to 19th December 2025 in study hospital.

2.2 Study objects and information retrieval:

All those patients who were prescribed with meropenem were included in this study. Subjects were identified from the daily review of patients profile and their medication chart in each of the participating wards. The data was collected on a pre-designed data collecting form. All the relevant information were extracted by thorough reviewing of patient profile and were recorded on a data collection form. In case of any query or difficulty in interpretation of any information, resident doctors were consulted to built a consensus on any existing issue. The confidentiality of patients was highly maintained.

2.3 Study population:

Record of 50 patients were subjected to the evaluation process. The demographic characteristics of the patients are shown in the table:

Patient Age(Days)	
Mean	8121.46 days
Median	5110.0
Range	28461

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Gender	Percentage
Male	75.5
Female	25.5
Clinical departments	
Medical-B	52
Peads-B	48

Result and conclusion:

Result of 50 patients were subjected to the evaluation process. The demographic characteristics of the patients are shown in the table 3.1 in total of 50 patients 75.5% were male and 24.5% were female. Their mean age was 8121.46 days (range: 28461). They were utilizing services of medical-B wad (52%) and peads ward-B (48%).

Table: 3.1

Patient Age(Days)	
Mean	8121.46 days
Median	5110.0
Range	28461
Gender	Percentage
Male	75.5
Female	25.5
Clinical departments	
Medical-B	52
Peads-B	48

Table: 3.2

Indication of therapy:

Indication of therapy:	Percentage of patients
Empirical therapy	84
Directed / Definite	16

All the 50 patients were started on meropenem empirically, until the C/S test results were obtained. Out of 50 patients 16% patients were switch to directed meropenem therapy after their C/S reports were obtained that showed growth of meropenem susceptible microorganism (MO). While 84% of 50 patients continue to receive meropenem empirically because their C/S tests did not show growth of MO, but as the infections indicators were present so they continued to receive meropenem until their condition got improved.

Table: 3.3

Indication / uses:

Indication	percentage
Pyrexia of unknown origin	50
Enteric fever	28
Dengue	4

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Malaria	2
Severe Infection	20

Out of 50 patients 50% patients received meropenem empirically for pyrexia of unknown origin (PUO) where other antibiotics did not respond, 28% patients received meropenem for multi drug resistant enteric fever, 4% patients received meropenem empirically in dengue fever while 2% patients received meropenem empirically in malaria where other antibiotics did not respond and 20% patients received meropenem in severe infections where all other antibiotics did not work.

Table: 3.4

Dose adjusted as per renal status:

Dose adjusted as per renal status:	Percentage
Yes	88
No	12

In total of 50 patients 80% patients received accurate dose as per their renal creatinine clearance value while 12% received inaccurate dose of meropenem as per their renal creatinine clearance values.

Table: 3.5

Duration of therapy:

Duration of therapy	Percentage
1-3 days	32
3-7 days	52
1-2 weeks	16

32% of patients received meropenem for 1-3 days, 52% of patients received meropenem for 3-7 days and 16% patients received meropenem for 1-2 weeks. Proper duration of therapy was not allowed in any case due to patient's overflow, as soon as the patient got afebrile for 48 hours and her/his infection indicators were disappeared for 24-48 hours the drug was stopped and the patient was discharged without completion of the course of therapy.

Table: 3.6

Justification for use:

Justification for use	Percentage
C/S performed	82
C/S showed growth of MO	14.3
Pre-treatment Serum Creatinine checked	69.4
Pretreatment and CBC checked	71.4
Creatinine checked at intervals during the cause of therapy	98
CBC checked at intervals during the course oftherapy	98
Temperature recorded 4 times daily	100
Other antibiotic tested on patients prior to Meropenem therapy	28
Other antibiotics used prior to hospital admission	100

Out of 50 cases, in 82% patients the C/S test was performed but positive culture test results were obtained in only 14.3% of patients while the remaining 87.5% of cases showed negative culture results. In 69.4% of patients serum creatinine was checked prior to begin the meropenem therapy and in 98% patients it was checked during the course of therapy.

The temperature was recorded 4 hourly in 100% of patients out of 50 cases.

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In 28% patients different antibiotics were used prior to meropenem therapy in hospital but they did not respond to it because of which they were started on meropenem therapy. Out of 50 patients, all the patients received antibiotics prior to admission to hospital.

Table: 3.7

Outcome of the therapy:

Outcome of therapy	Percentage
Patient condition improved	98
Patient is not responding to therapy	2

98% patients out of 50 cases, got improved with meropenem therapy while 2% did not respond to meropenem therapy.

Table: 3.8 Overall criteria-wise compliance:

Criteria	Total	Compliance %	Non-compliance %
Cultures showed growth of MO	50	14.3	85.7
Pretreatment TLC and Neutrophil count obtained	50	71.4	28.6
Pretreatment serum creatinine obtained	50	69.4	30.6
TLC and neutrophil count monitored at regular intervals	50	98	2
Serum creatinine monitored at regular intervals	50	98	2
Dosage individualization as per renal function status	50	88	12

The compliance level of different criteria based parameters were checked in all 50 cases and the following results were obtained. In 14.3% of cases the culture showed growth of microorganism while 85.7% cases showed non-compliance with respect to the growth of microorganism.

Out of 50 cases, the compliance level of pretreatment TLC and neutrophil count obtained, was 71.4% and non-compliance level was 28.6% while the compliance level of pretreatment creatinine was 69.4% and non-compliance level was 30.6%

The compliance level of TLC and serum creatinine obtained during the course of therapy was 98% and non-compliance level was 2%.

The compliance level of dosage of individualization as per renal status was 88% and non-compliance level was 12%.

Table: 3.9 Dose and dosing frequency during meropenem:

Dose (mg)	Dosing frequency	Frequency	Percentage
500	TDS	10	20
500	BD	3	6
500	OD	1	2
1000	TDS	13	26
1000	BD	5	10
1000	OD	4	8
750	TDS	5	10
700	TDS	1	2
450	TDS	1	2
400	TDS	2	4
300	TDS	3	6
250	TDS	1	2
100	TDS	1	2

The maximum dosage in all 50 cases was recorded to be 1000mg TDS while the minimum dosage was 100mg TDS. The most frequent dosage in all 50 cases was 500 mg TDS (Frequency=20). The dosage were adjusted aas per creatinine clearance and the body weight of the patients.

Table: 3.10 Indication and dosage:

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Pyrexia of unknown reason (PUR):

Dose (mg)	Dosing frequency	Frequency
500	TDS	7
1000	TDS	5
500	BD	2
1000	BD	3
750	TDS	2
700	TDS	1
400	TDS	1
300	TDS	2
100	TDS	1

In pyrexia of unknown origin the maximum dosage of meropenem was 1g TDS (frequency=5) while the minimum dosage was 100mg TDS (frequency=1). The most frequency dosage of meropenem in PUO was 500mg TDS.

Table: 3.11

Enteric fever:

Dose (mg)	Dosing frequency	Frequency
500	TDS	2
1000	TDS	4
1000	OD	3
750	TDS	2
400	TDS	2

In enteric fever the most frequent dosage was 1g TDS (frequency=2), while the maximum dosage was 1g TDS and minimum dosage was 400mg TDS.

Table: 3.12 Dengue fever:

Dose (mg)	Dosing frequency	frequency
1000	TDS	1
500	TDS	1

In enteric fever, maximum dosage was 1g TDS while the minimum dosage was 500mg TDS.

Table: 3.13 Malaria:

Dose (mg)	Dosing frequency	Frequency
1000	TDS	1

Out of 50 cases, only in 1 case the meropenem was used in malaria fever, having a dosage of 1g TDS.

Table: 3.14 severe infection:

Dose (mg)	Dosing frequency	Frequency
1000	TDS	1
1000	BD	2
500	TDS	1
500	BD	1
300	TDS	3
450	TDS	1
100	TDS	1

The most frequent dosage in severe infection was 300mg TDS (3), while the maximum dosage was 100mg TDS and the minimum dosage was 1oomg TDS.

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Conclusion:

In this study we conclude that in almost all patients meropenem was started as empirically therpy in cases where other antibiotics did not work. i.e. in 50% cases meropenem was used empirically in pyrexia of unknown origin. In 28% of cases it was used empirically in enteric fever, in 4% of cases empirically in dengue, in 2% of cases it was used empirically in malaria and in 20% cases it was started as empirically therapy and the accurate dosage of meropenem was based on creatinine clearance of the patients i.e. in 88% out of 50 cases the dose was accurate while in 12% cases the dose was inaccurate as per renal status. The most frequent dosage of meropenem in POU was 500mg TDS and inn enteric fever the most frequent dosage was 1g TDS. The meropenem was also used in dengue (frequency=2) and malaria (frequency=1) where other antibiotics failed to work. In 84% of cases the meropenem was continued as empirical therapy until the patient was discharged while in 16% of cases the meropenem therapy was switched to directed therapy upon reviewing of C/S test that showed growth of meropenem susceptible microorganism.

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Conflict of Interest:
The authors declare that they have no conflict of interest.

Ethics Approval:
The study was directed in harmony with the ethical principles of biomedical research. Ethical approval was acquired from the related Institutional Ethics Committee prior to data collection.

Informed Consent:
As this was a surveying study based on anonymized patient medical histories with no direct patient participation, the necessity for informed consent was waived by the Institutional Ethics Committee.

Data Availability:
The datasets generated and/or examined during the current study are accessible from the corresponding author upon sensible request, subject to institutional and ethical regulations.

Author Contributions:

Dr. Sami Ullah Jamal: Conceptualization, study design, data collection, data analysis, manuscript drafting, and corresponding author.
Dr. Muhammad Tariq Noor: Supervision, methodology, critical revision of the manuscript, and final approval.
Dr. Iftikhar Ahmad Zegar: Data interpretation, manuscript review, and editing.
Dr. Jawad Sahak: Data collection, literature review, and manuscript editing.
All authors read and approved the final version of the manuscript.

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