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ORIGINAL ARTICLE

Carbapenems A Novel Drug Class: Evaluation of Comparative Efficacy against In Patients & Out Patients Resistant Isolates

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ABSTRACT
Carbapenems consider to be the most important beta lactamase antibiotics. Meropenem and imipenem are a very well develop antibiotics of this group. Both of these drugs are use against nosocomial and polymicrobial infections and could use against various pathogens. Cilastatin sodium should mostly prescribe with imipenem in combination because of DHP-1 renal degradation. In this study we aimed to determine the comparative efficacy of meropenem vs imipenem in out patient's vs in patients. For the purpose of this study data were collected from OP and IP through different sources of isolates like blood CS, urine CS, pus CS etc and then samples were examined for the activity of meropenem vs imipenem. Heeding to the results meropenem is highly sensitive to gram positive strains including coagulase negative staphylococci (44%), E.coli (108%), klebsiella pneumonia (50%) and pseudomonas aeroginosa(60%) while that of imipenem is highly sensitive to gram negative strains and also active against ESBL and staphylococci MRSA. After careful consideration it was concluded that carbapenems is an efficacious group of beta lactamse and a drug of choice in very resitant type bacterias like ESBL but they cant use empiricaly as imipenem could develop seizure so it should be use according to prescriber's or physician's choice

Key words: *carbapenems, comparison of meropenem vs imipenem, efficacy in OP & IP, in vitro, susceptibility, clinical isolates.*

Abbreviations:*OP= Out patients, IP=In patients, CS=Culture sensitive, HVS= High vaginal swab, ESBL=Extend spectrum beta lactamase.*

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INTRODUCTION

Since 1940s beta lactam antibiotics are using clinicaly very significantly. Carbapenems comes under a beta-lactam group of antibiotic and it has broad specrum of activity against gram +ve and gram –ve isolates. Thienamycin was the first carbapenem introduced in 1970s. Imipenem is rapidly or fastly degraded by the proximal renal tubular enzyme i:e. dehydropeptidase-1 (DHP-1) so should be co administer with cilastatin that could inhibit the enzyme DHP-1 .[1-5]. The co administration of cilastatin with imipenem is also favourable to prevent nephrotoxicity in vulnerable individuals. Meropenem was the second one carbapenem discovered in America and it could be administer alone no DHP-1 inhibitor is required for co-administration with meropenem as it is not so nephrotoxic , Etrapenem proved to be highly effective against blood stream inection[6-9]

Microbiological evidence suggested that imipenem have more potent activity against gram positive pathogens and less potent to gram negative pathogens as compared to meropenem. Both agents could be indicated in a variety of infections and nosocomial infections (hospital acquired).[10-13]. Both of these agents have a short half lives in-vitro. Heeding to structural consideration meropenem are stable to DHP-1 degradation for a reason that they have 1-beta methyl constituent on the nucleus of carbapenems while the imipenem lack it so undergoes DHP-1 degradation[14-17]..

Meropenem have superactivity against gram negative pathogens and *Pseudomonas aeroginosa* as compared with imipenem because it have pyrrolidinyl at position 2. Carbapenems is a beta-lactam

antibiotic so that it also produce its actions through penicillin binding protein (PBP) and have bactericidal activity.[18-20]. Imipenem prefer to binds with PBP2 (penicillin binding protein 2) followed by PBP1a and 1b but it has weak effects on PBP3. However, meropenem strongly binds with PBP2 followed by PBP3 but it also have strong type of affinity for PBP1a and PBP1b .The PBP3 (penicillin binding protein 3)is the primary taeget for aminopenecillins and cephalosporins generations while the carbapenems targets PBP 1a , 1b and PBP2 most commonly rather than PBP 3.[21-24]

In case of carbapenems less bacterial endotoxins released because it cause lysis of bacterial cell without filamentation as it happens in case of third generation cephalosporins. Carbapenems have one unique advantage that it can use against that pathogen which are resistant to beta lactamase enzyme even including AmpC beta lactamase and extend spectrum beta lactamase (ESBL).[25-28]*Pseudomonas aeroginosa*is very resistant isolate and it is even sensitive to carbapenems that shows versatile actions of carbapenems. Imipene/clistatin sodium and meropenem both could intravenously administer and both could easily penetrate in body fluids.[29-30]. Studies suggest that imipenem could also easily penetrate in tisssues compartment while meropenem readily and rapidly distributes in intestinal fluid and cerebrospinal fluid so that could be indicated in case of meningitis.[31-33] Both of the drugs imipenem and cilastatin have 10 hours half lives and 60-70% of drug is excreted unchanged in urine while meropenem is more stable and could administer as single entities.The clinically significant indications of imipenem/cilastatin included intra abdominal infections in comparison with cefipime , soft tissues and skin infection, nosocomial pneumonia (500mg four times a day) , in febrile neutropenia (1g of meropenem given tid) while 1g meropenem every 8 hour is beneficial in case of advance appendicitis. In case of acute pulmonary exacerbation in cystic fibrosis patients (40mg/kg upto2g every 8 hour) of meropenem administer with tobramycin. Meropenem is also used to treat febrile neutropenia with ceftazidime. It was concluded that imipenem/clistatin and meropenem both agents could be used in the treatment of variety of infections including UTI(urinary tract infection), meningitis ,nosocomial pneumonia and against a variety of polymicrobial infections.[34-35]

The adverse effects of imipenem/clistatin and meropenem mostly include local irritation on injected site , nausea,rash, diarrhea, vomiting and pruritis[36]. The use of these drugs could alter different laboratory reports like they may increase the level of several hepatic enzymes e:g. Alanine aminotransferase, lactate dehydrogenase and alkaline phosphatase. They may increase the creatinine and urea levels in blood and severe thrombocytopenia and eosinophilia also reported.[37] The very major risk factor of imipenem/clistatin is seizure development because of renal impairment functions while on the other hand meropenem have less chances to develop seizures. If probenecid is given with imipenem/clistatin could decrease imipenem renal clearance 30% while it increase plasma half life of meropenem 33%.[38].

The objective of this retrospective studies is to evaluate comparitive efficacy of carbapenems in terms of patients safety and efficacy of patient with immunocompromised system because of infectious diseases creates an emergence against life saving antimicrobials.

MATERIAL AND METHODS

Bacterial strains

Basically Study designed on retrospective announcement of yesterday two years from Intensive Care Units of nation and unknown Health Care Sector of Critically Ill patients. For that end Sensitivity and Resistance pattern and behaviour of most omnipresent Microorganisms, greater than 6000 isolates were obtained from Antibiograms of hospitals. Isolates obtained were sometimes hospitals acquired mutually and little are population acquired. Duplicate isolate approach the elimination criteria and Non Duplicate isolates antibiogram were interpreted on results.

Organism identification:

All pathogens were identified at the participating center via routine methods for that empirical and were absolute at the coordinating Laboratory.*klebsiela, pseudomonas, staphylococcus , proteus* species and e.coli ex were the most frequent identified micro-organisms.

Susceptibility testing:

Methods of Sensitivity suspect performed by participating hospital was based on: Disk Diffusion Method of Kirby-Bauer; VITEK (biomerieux vitek, Hazlwood MO); by the whole of micro broth dilution of cation adjusted Muller-Hinton broth (CAMHB) and colonies suspended on them were comparable to a 0.5 McFarland Standard. The resulting antibiograms interpretated through CLSI recommendation standard. clinical and laboratories standard institutes (CLSI, formaly NCLSS) refrence disk diffusion(Kirby-bauer) method (bauer et al,1996;CLSI,2011).

Antimicrobial agents:

Antimicrobials confidential to pathogens were figure it to be on undeniable result relish on variety of antibiotics including Quinolones (levofloxacin, piperacillin, nalidixic acid etc), Cephalosporin (cefipime, ceftriaxone etc), Amino glycosides (neomycin , kanamycin etc), and Beta-lactamase inhibitors (penecilins etc) , Carbapenems (meropenem, imipenem, doripenem etc), Monobactams (aztrionam) , Anti-infective (ciprofloxacin etc), Macrolides (clarithromycin, azithromycin etc), and Colisthemetate.

ZONE term inhibition drop for explanation of Susceptibility and Resistance behaviour were based on hand operated casual disc of Piperacillin/tazobactam 100/10µg, Parenteral Cephalosporins 30µg (ceftazidime, cefepime), Aztreonam in a quantity of 30µg along with 10µg of Carbapenems, Colisthemetate amount was 10µg, Amikacin in a quantity of 30 µg, Gentamycin along with Tobramycin 10µg by all of Ciprofloxacin 5µg respectively by all of reference standard by CLSI of sector of fury and conflict measurement. clinical and laboratories standard institutes (CLSI, formaly NCLSS) refrence disk diffusion (Kirby-bauer) method [39].

Quality control:

Resulting outcomes were compared by all of ATCC standard strains. ATCC is a standard strains group in order to maintain high efficacy and quality of work in microbiology field and other susceptibility analysis from drugs. *Escherichia coli (Migula) Castellani and Chalmers (ATCC® 8739-MINI-PACK™), Enterobacter aerogenes Hormaeche and Edwards (ATCC® 13048™)* are the examples of some ATCC standards strains.

The data then extracted carefully for further studies and According to these carefull considerations meropenem are highly efficacious against *e.coli* (108%) and imipenem is highly efficacious against *coagulase negative staphylococci* (70%) while they are least effective against *streptococcal group D* meropenem (2%) and imipenem (1%). Both of these carbapenems have no activity against *micrococci* and several *gram negative bacilli.*

RESULTS

The ratio of various pathogens in out patients is shown in figure 1 and that of in patients shows as figure 2.

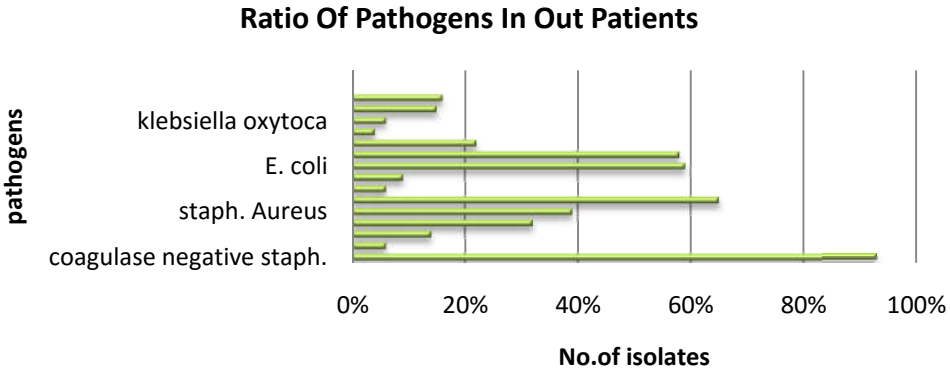

Figure 1: ratio of pathogens frequently found in out patients

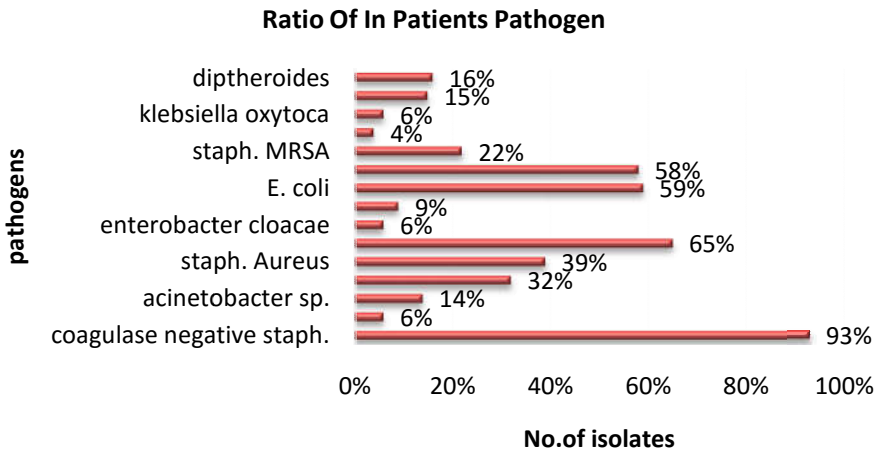

Figure 2: ratio of pathogens found in IP in patients:

The efficacy of meropenem vs imipenem efficacy against out patients pathogens is describe in figure 3 and that of in patients in figure 4.

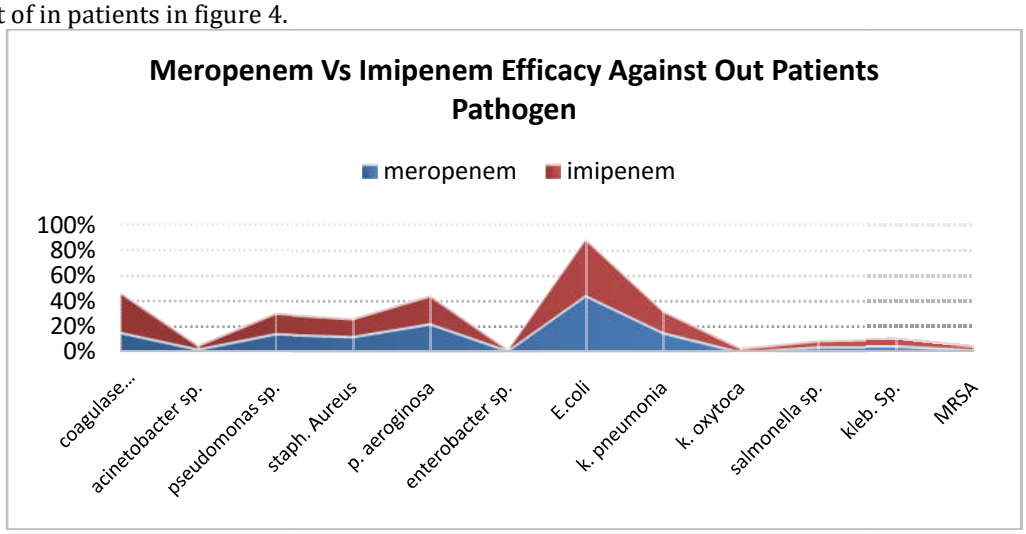

Figure 3: meropenem vs imipenem efficacy against out patients pathogens:

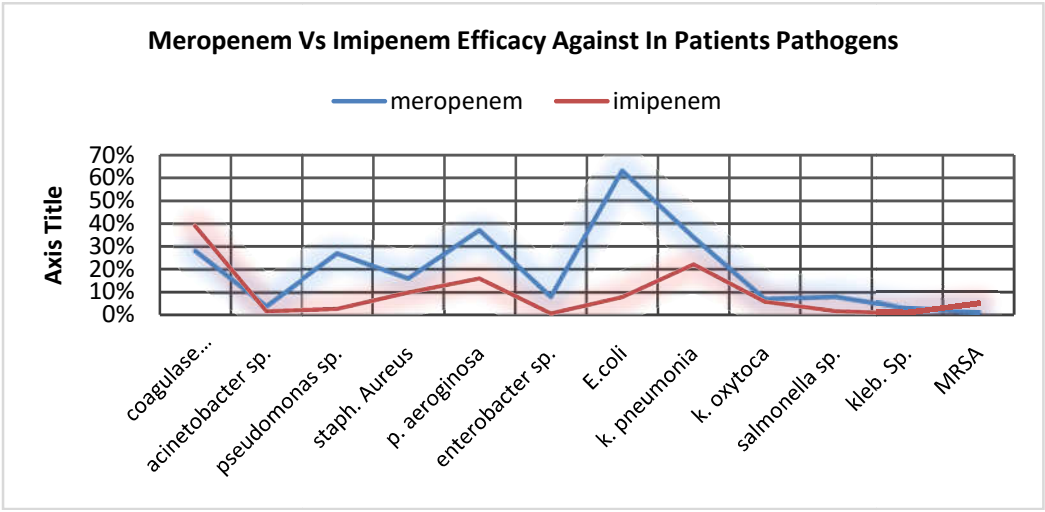

Figure 4: meropenem vs imipenem efficacy in in patient's pathogens:

The comparative efficacy of meropenem vs imipenem in out patient's vs in patients is shows as in figure 5.

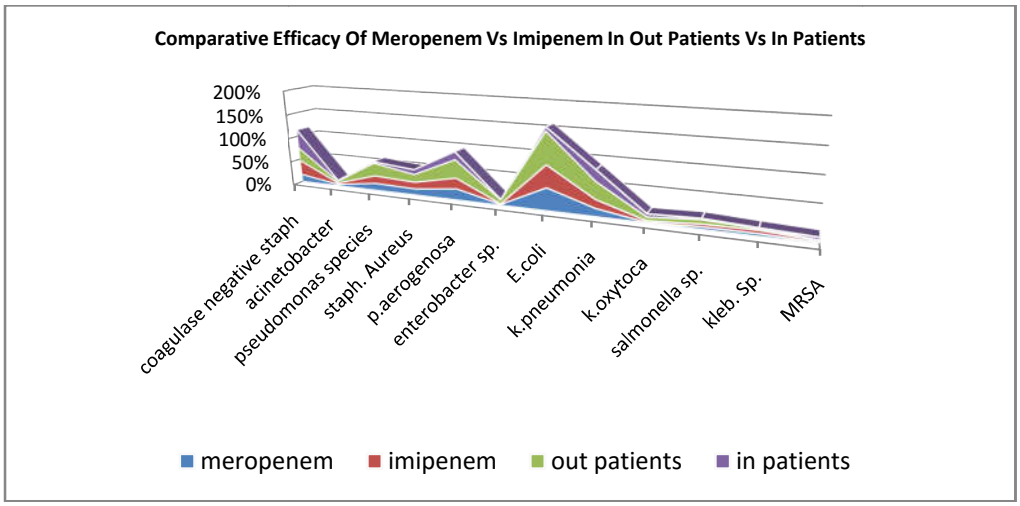

Figure 5: comparative efficacy of meropenem vs imipenem against out patients vs in patients pathogens:

Total isolates numbers and isolates found in out patients and in patients with comaparative efficacy between carbapenems shown in figure 6& 7.

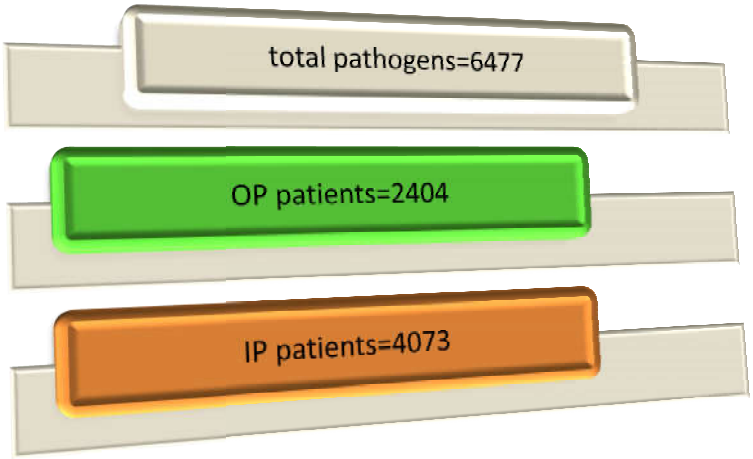

Figure 6: the number of total isolates and isolates found in out patients and in patients

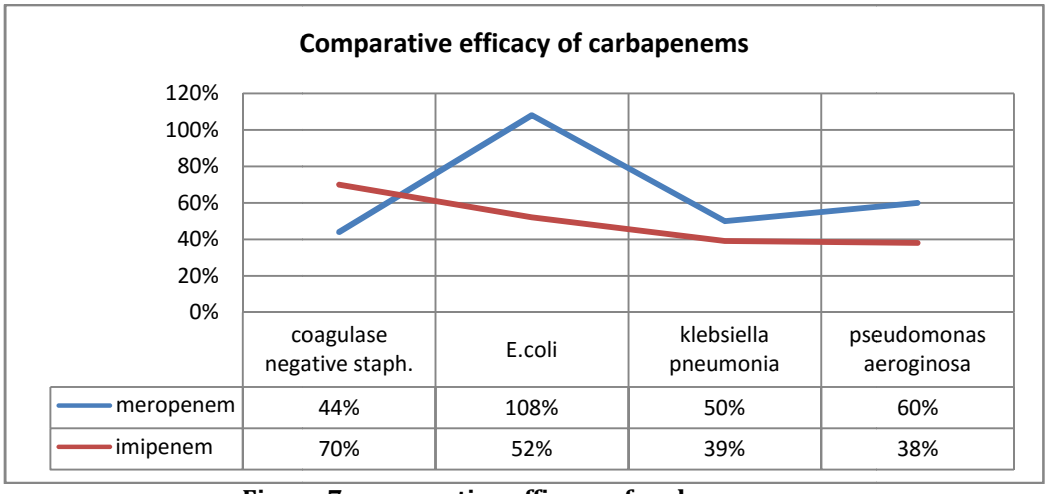

Figure 7 comparative efficacy of carbapenems

The common pathogens found in out patients and in patients and efficacy of meropenem vs imipenem against that pathogens is shows in table 1.

Table 1: Efficacy of meropenem vs imipenem against various pathogens of out patients and in patients:

Total pathogens 6477	Pathogens (%)	eropenem efficacy	Imipenem efficacy
OP patients 2404	*Coagulase negative staphylococci* (90%)	37%	31%
	Klebsiella pneumonia (23%)	16%	17%
	Pseudomonas species (27%)	15%	16%
	E.coli (50%)	45%	44%
	Pseudomonas aeroginosa (22%)	23%	22%
IP Patients 4073	*Coagulase negative staphylococci* (93%)	28%	39%
	E.coli (50%)	63%	8%
	Staphylococci aureus (39%)	16%	10%
	Klebsiella pneumonia (58%)	34%	22%
	Pseudomonas aeroginosa (65%)	37%	16%

Collection of different out patients and in patients' isolates through various samples is shows as in table 2.

Table 2: percentage of sources of isolates from in patients and out patients

SPECIMEN	OP	IP
Blood CS	90%	93%
urine CS	55%	59%
pus CS	35%	42%
ear swab CS	9%	12%
Nasal CS	0%	6%
left ear CS	1%	4%
Stool CS	0%	6%
catheter tipCS	0%	3%
Sputum CS	8%	8%
throat CS	1%	1%
Central line	1%	1%
skin scar	0%	2%
Right ear CS	6%	1%
right eye CS	0%	1%
buttock CS	0%	3%
tracheal section CS	0%	3%
Left foot CS	0%	1%
wrist wound CS	0%	2%
Pleural fluid CS	0%	1%
right arm CS	0%	1%
mouth Cs	0%	2%
right leg CS	1%	0%
right finger CS	1%	0%
Left chest CS	1%	0%
Abcesses	0%	1%
HVS /CS	0%	4%

The resistance and sensitivity pattern of imipenem against various disease causing pathogens in out patients and in patients is describe in table 3. And that of meropenem in table 4.

Table 3: the percentange of sensitivity and resistance of imipenem against various isolates of OP and IP

Isolates	Out patients resistance	Out patient sensitivity	In patients resistance	In patients sensitivity
Coagulase negative staph.	23%	31%	21%	39%
Citrobacter sp.	-	3%	-	4%
Acinetobacer sp.	4%	3%	9%	2%
Staph. aureus	-	14%	-	10%
p.aeroginosa	6%	22%	12%	16%
Enterobacter species	2%	1%	1%	-
Streptococcus group D	2%	2%	1%	-
Proteus vulgaris	1%	-	-	1%
E.coli	2%	44%	3%	8%
Klebsiella pneumonia	1%	17%	18%	22%
Staph. MRSA	5%	3%	6%	5%
Pseudomonas sp.	2%	16%	2%	2%
Klebsiella oxytoca	2%	-	1%	6%
Proteus mirabilus	2%	-	2%	1%
Salmonella species	-	5%	-	1%

Table 4: percentage of resistance and senstivity of meropenem against various isolates of OP and IP

isolates	Out patients resistance	Out patient sensitivity	In patients resistance	In patients sensitivity
Coagulase negative staph.	37%	16%	54%	28%
Citrobacter sp.	-	3%	-	-
Acinetobacer sp.	4%	3%	11%	4%
Staph. aureus	-	13%	4%	16%
p.aeroginosa	5%	23%	20%	37%
Enterobacter species	1%	2%	-	8%
Streptococcus group D	2%	3%	-	-
Proteus vulgaris	-	1%	-	1%
E.coli	1%	45%	24%	63%
Klebsiella pneumonia	2%	16%	20%	34%
Staph. MRSA	7%	2%	9%	1%
Pseudomonas sp.	4%	15%	6%	27%
Klebsiella oxytoca	1%	1%	-	7%
Proteus mirabilus	1%	1%	3%	1%
Salmonella species	-	5%	-	8%

DISCUSSION

Imipenem and meropenem are the most established and prominent members of the class carbapenems .These antibiotic globaly used against a variety of poly microbial and nosocomial infections. Generally all carbapenems antibiotics shows a broad spectrum activity against beta lactamases including AmpC beta lactamases and ESBL. According to the results imipenem is slight more active against gram positive organisms as compared to meropenem while on the other hand meropenem is slight more active against gram negative organisms as compared to imipenem. Hence, the class of beta lactams i:e. carbapenems could used to treat severe gram positive and negative spectrum disease conditions. The comparison between these two drugs shows a similar activity against bacteria and shows the same cure rate. However, in addition meroepenem could treat meningitis but imipenem not because it have tendency to develop seizures. But the current use of these two drugs is only against nosocomial and polymicrobial infections. Universaly gram positive isolates are considered to be the major cause of infections. The resistance against antibiotics is increase due to its illogical use and could create severe problems while originaly treat a disease by proper treatment therapy.

Klebsiella pneumonia is difficult to treat because very less antibiotics are active against these isolates but both of carbapenems imipenem and meropenem could effectively treat the diseases caused by *klebsiella pneumonia*.(50%), *Staphylococci* species are so commonly found isolates and both of these drugs efficaciously treat infections cause by *staphylococci*. While the *proteus* species which is commonly present on human skin, in intravenous solutions etc cannot very effectively treat by these drugs due to development of resistance or they are not active against this specie.

It has been concluded after a long carefull experimental and observational studies that meropenem is efficiently active against *coagulase negative staphylococci(44%), E.coli(108%), klebsiella pneumonia(50%), pseudomonas species(60%), staph. Aureus and pseudomonas aeroginosa (60%)*. While imipenem is more efficaciously treat the disease conditions of *coagulase negative staphylococci,(70%) klebsiella pneumonia,(39%) E.coli (52%), Staph MRSA(5%), p. aeroginosa(38%) and streptococcus viridans(8%).*

CONCLUSION

After all of these studies it was concluded that resistance against antibiotic is the major curse for humans and increasing day by day. No antibiotic should be used on the basis of just a clinical guess.the universal authorities like FDA, infection prevention society(IPS), world health organization (WHO), infection control society of Pakistan (ICSP) has been strongly prohibited the unjustified use of antibiotics. In the present aura theres a need to aware people heeding to the use of antibiotics as well as the responsible health care professionalists should always check the in-vitro vulnerability of antibiotics against a variety of isolates. To prepare the guidelines heeding to the use of antibiotics and not to use them empiricaly is very important to know for both health care professionalists and patients.

CONFLICT OF INTEREST

There is no conflict of interest reported regarding this publication.

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