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SUCCESSFUL TREATMENT OF CARBAPENEM RESISTANT KLEBSIELLA PNEUMONIAE WITH COMBINATION OF MEROPENEM & COLISTIN-A CASE REPORT

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ABSTRACT

One of the most serious problems in global public health today is the increasing incidence of antibiotic resistant bacterial infections, which increases mortality, morbidity, length of the hospital stay and cost of the treatment. Among the *enterobacteria* harboring Carbapenemase-encoding genes, *Klebsiella Pneumoniae* is the most common, rapidly become endemic in many hospital settings around the world. Of particular concern, emergence of *Enterobacteriaceae* that are resistant to Carbapenemes, the class of antibiotics considered being a serious threat which is seen in this case and limited treatment options associated with these organisms. In this we report a case of Carbapenem resistant *K.Pneumoniae* in a patient diagnosed with Subdural hemorrhage and right lower lobe Pneumonia (Hospital acquired) and who was successfully treated with antimicrobial combination of Meropenem and Colistin.

KEYWORDS: Antibiotic resistant, bacterial infection, *K. pneumoniae*, Meropenem, Colistin.

INTRODUCTION

K. pneumoniae is one of the most common pathogens in clinical infections, such as pneumonia, urinary tract infections, sepsis, wound infections, meningitis and other diseases. Multi-drug resistant *K. pneumoniae* strains are becoming a severe problem worldwide, and it usually carries one or more Extended-Spectrum –Beta Lactamases (ESBLs) that confers the resistance to expanded-spectrum cephalosporin's [1]. The emergence of Carbapenem Resistant *Enterobacteriaceae* (CRE) in recent times has become a serious threat to public health due to

the high mortality, potential dissemination rates and limited treatment options associated with these organisms [2]. In the United States, Carbapenem-resistant *Klebsiella pneumoniae* constitutes 92% of all Carbapenem-resistant Enterobacteriaceae and carbapenemase production mediated by *bla*KPC is the most prevalent mechanism conferring resistance to Carbapenemes [3]. Carbapenem antibiotics are considered as a drug of choice for the treatment of extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae and other multidrug resistant bacteria. The emergence of bacterial strains that produce carbapenemases further limits the therapeutic options available to clinician [4]. Meropenem is a Carbapenem antibiotic approved by the US food and drug administration for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and pediatric bacterial meningitis [5]. Treatment for patients infected with Carbapenem resistant *Enterobacteriacae* is challenging due to limited treatment options. Such isolates also show resistance to all β-lactam antibiotics and very often carry on the same transposon the genes responsible for resistance to Trimethoprim-Sulfamethoxazole, Aminoglycosides and Fluoroquinolones. Only Tigecycline, Colistin and Fosfomycin can be effective but these also have limitations. Tigecycline has limited use in urine and primary blood-stream infection despite *in vitro* susceptibility. In other clinical scenarios, better results were obtained when Tigecycline was used in combination. Colistin is being reused in the era of antibiotic resistance to treat multidrug resistant strains as either monotherapy or preferably as part of combination therapy. In addition, *Enterobacteriaceae* resistant to Colistin have been recently described. Fosfomycin, not widely available, shows excellent activity *in vitro* against strains resistant to both colistin and Tigecycline [4].

Case Report

A 28 yrs old, healthy male patient brought to our hospital casuality with an accidental fall while working at home. No history of seizure episode at the time of fall. His CT brain shows fracture in frontal bone in left side involving the roof of left orbit, scalp Hematoma (1×2cm abrasion) in left parietal region. The patient does not have any infection at the time of admission but the WBC count shows 15.2 cells/mm^3, PCT- 0.5ng/ml which is elevated hence the patient was treated with Cefaperazone Sulbactam and Amikacin for 3 days as an empirical treatment. The patient is a known case of Hypertension and Diabetes mellitus who was on regular treatment with drugs like Nebivolol 5mg, Prazosin 2mg, Metformin 500mg. On hospital day 4, due to patient's ongoing fever (102°F), bronchial aspirate was sent which showed Acinetobacter baumanii growth and radiographic evidence shows ® lower lobe

Pneumonia was consistent with hospital acquired pneumonia. Then the patient antimicrobial therapy was switched to Meropenem 1gm Q8H which is the recommended therapy for Pneumonia. On 10th day of the hospital stay, the patient's urine, wound swab cultures were sent, culture showed >1, 00,000 colony-forming units (CFU) per mL of a highly resistant, KPC-producing *K. pneumonia* strain. The bacterial isolates, sensitivity and susceptibility report was shown in table. Then the patient was treated with combination of Meropenem 1gm Q8H and Colistin 2 units BD. During the hospital stay, the patient developed a seizure (2 times) which is suspected as a known adverse event due to Meropenem. Hence the dose adjustment was done for those drugs by the physician upon suggestion by the clinical pharmacist. Seizures were treated symptomatically with Fosolin (Fosphenytoin) 1ml. After treatment with Fosphenytoin and dose reduction of Meropenem from 1000mg to 500mg Q8H, then the Seizures subsided completely. Thus it is confirmed to be an adverse event of Meropenem. On the 17th day of hospital stay patient blood and wound swab culture was sent, where blood culture showed no growth and wound swab culture showed 50,000 colony forming units of K. Pneumonia, WBC count 12.2 cells/mm^3 for which treatment was continued with the same drugs as the patient responded to the treatment. After 7 days of antibiotic therapy, his culture report showed no growth, WBC count- 10,000cells/mm^3 and PCT level was 0.15ng/ml which indicates the infection was subsided and antimicrobial therapy was stopped, which showed rational.

Table: Showing the Bacterial Isolates, Sensitivity and Susceptibility during the Hospital Stay.

Day	Specimen	Isolated organism	Drugs		
			Resistant to	Sensitive to	Moderately sensitive to
1	Bronchial Aspirate	Acinetobacter baumanii	Chloramphenicol, Tetracyclines, Ofloxacin, Amikacin, Ampicillin, Amoxycalv, Ceftriaxone, Cefaperazone sulbactum, Cefuroxime, Piperacillin/Tazobactum, Gentamycin10mcg Netillin.	Meropenem, Ertapenem, Colistin, Doxycycline, Imipenem, Tigecycline, Polymixin-B	Levofloxacin

2	Blood culture	K.Pneumoniae	Amikacin Doxycycline Gentamycin Piperacillin/tazobactum, Levofloxacin, Ofloxacin.	Meropenem, Colistin, Tigecycline, Polymixin-B	Linezolide
3	Wound swab Urine culture (1,00,000 CFU)	K.Pneumoniae	Above drugs + Meropenem, Imepenem,	Colistin Tigecycline *Polymyxin B*	Linezolide
4	Urine culture (50,000 CFU) Bronchial aspirate	K.Pneumoniae	Meropenem, Imepenem, Etrapenem	Colistin, Tigecycline Polymyxin B	-

DISCUSSION

Resistance to antimicrobial agents in several bacteria is on increasing because of the irrational and rampant use of antimicrobial drugs [6]. Carbapenems are β-lactam antibiotics, presently considered as the most potent agents for treating multidrug resistant Gram-negative infections due to the stability of these agents against the majority of β-lactamases and their high rate of permeation through bacterial outer membranes [7]. Currently, the spread of Carbapenem-resistant bacteria has caused grave concern due to the limited choice in antibiotics for treating infections caused by them [8]. Resistance to Carbapenems is due to the poor binding of carbapenems to penicillin-binding proteins present in the bacteria, the over-expression of multidrug efflux pumps by the bacteria or lack of porins present in the bacterial cell membrane [2]. These bacteria have the potential to spread rapidly within the hospital environment and also across continents. Mechanism of carbapenem resistance is mainly due to production of Carbapenem hydrolyzing enzymes called carbapenemases coded by *bla*KPC, *bla*VIM and *bla*IMP. These belong to Class B of β-lactamases. *Klebsiella pneumonia* carbapenemase (KPC) was first identified in 2000 among the isolates of *K. pneumoniae* in the United States of America; this mechanism has been identified in many countries and has spread across the globe [9]. Salvage therapy with systemic Colistin provided a moderate degree of efficacy against multidrug-resistant *P.aeruginosa*, Carbapenem resistance *K. pneumonia*[10].

The case presented above illustrates the complexities associated with nosocomially acquired Pneumonia due to multidrug resistant bacteria. The patient had been treated with multiple broad spectrum antimicrobial agents, had numerous invasive devices, and had a prolonged stay in an intensive care unit. All are recognized risk factors for colonization and subsequent

infection with resistant bacteria, especially CRKP. Meropenem was chosen for parenteral therapy because its activity is slightly greater than that of Imipenem. However, it was considered insufficient as an single form of therapy because of the potential for Carbapenem resistance related to loss of an outer membrane protein among strains of CRKP [11]. . Although the strains are resistant to Meropenem, a combination treatment of Meropenem and Colistin is recommended due to synergistic or additive effect might be influenced by the ability of Colistin to disrupt the bacterial outer membrane and increase its permeability for Carbapenems and therefore stop the cross linking of the newly synthesized polymers. [11]

Colistin is being used in case of antibiotic resistance to treat multidrug resistant strains as either monotherapy or preferably as part of combination therapy but Monotherapy is not recommended because emergence of bacterial resistance will occur within short period. [11]

CONCLUSION

The management of hospital-acquired bacterial infections is becoming a significant challenge for the health care providers because of the increased prevalence of multi-drug resistant bacteria like *Acinetobacter baumanii*, *K. pneumonia*, carbapenemase-producing *Enterobacteriaceae* and extended-spectrum β-lactamase (ESBL) *Enterobacteriaceae*, which will causes increase in mortality, morbidity and treatment cost. Antimicrobial stewardship program along with clinical pharmacist Intervention and Infectious Disease consultant physician is highly recommended to optimize the use of antimicrobials, and to decrease antimicrobial resistance in hospitalized patients which in turn reduces mortality and treatment cost. The study shows the effectiveness of combination therapy with Meropenem and Colistin in a patient infected with Carbapenem resistant K.pneumoniae.

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