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Ceftazidime-Avibactam: A Salvage Therapy in the Treatment of Drug-Resistant Gram-Negative Bacterial Infections

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ABSTRACT

Drug-resistant Gram-negative bacterial infections are increasing at an alarming rate and treatment options for these types of infections are still a challenge in the modern world. Complicated urinary tract infections, complicated intra-abdominal infections, hospital-acquired pneumonia (including ventilator-acquired pneumonia), sepsis, and skin and soft tissue infections are the most commonly encountered gram-negative infections. Over the last decade, an increase in carbapenem-resistant isolates has resulted in the widespread use of colistin as a 'last resort' of antimicrobial agents. However, an increase in colistin resistance is a major concern that leads to the spectre of untreatable Gram-negative infections with difficult antibiotic therapy. To overcome the resistance against gram-negative bacterial infections, an agent called ceftazidime-avibactam was introduced. The drug is mainly active against multi-resistant gram-negative organisms such as *Enterobacteriaceae (E.coli, Klebsiella pneumonia)* and *Pseudomonas aeruginosa*, including those expressing certain types of Class A, Class C, and Class D enzymes. Dosage regimen for ceftazidime-avibactam can be expressed as total grams of combination product and its typical dosing is 2.5g administered every 8 hours by intravenous infusion over 2 hours in adults. It is a well-tolerated drug with no nephrotoxicity compared to colistin. Dose adjustment is needed according to the variation in creatinine clearance of the patient.

Keywords: Ceftazidime-avibactam, *Enterobacteriaceae*, Gram-negative, *Klebsiella Pneumonia*, Nephrotoxicity, *Pseudomonas aeruginosa*

INTRODUCTION

Gram-negative bacterial infections are becoming more prevalent and have become a serious threat to public health worldwide because of their difficulty in treatment.[1] These infections are associated with high morbidity and mortality rates. [2].Gram-negative bacterial infections represent one of the most significant and microbiologically documented infections causing a wide range of Infections in the world.[3]This global spike in the number of gram-negative bacterial infections that have occurred in recent years is more prevalent than gram-positive infections in many settings.[4] The common sites of these infections include the lungs, urinary tract, bloodstream, nervous system, and soft tissues. Surgical wounds can also become infected with gram-negative bacteria. The predominant gram-negative bacteria associated with gram-negative bacterial Infections are *Escherichia coli (E.coli), Pseudomonas aeruginosa, Klebsiella pneumonia, Acinetobacter baumannii,* and *Enterobacteriaceae.*[5] These microorganisms are the common causes of intra-abdominal infections (IAIs), urinary tract infections (UTIs), ventilator-associated pneumonia (VAP), and bacteremia.[6] *Escherichia coli, K. pneumoniae,* and *P. aeruginosa*, in particular, are the important pathogens in a hospital environment and it accounts for about 27% of all pathogens and 70% of all gram-negative pathogens causing hospital-associated infections. [3]

E. coli is the most common causative agent of community and hospital urinary tract infections and the main aerobic component in intra-abdominal infections. *P. aeruginosa, Klebsiella pneumonia*, and *Enterobacter* are the major cause of nosocomial pneumonia, especially in patients with a prolonged hospital stays.[7]Increased severity of illness, greater hospital, and antibiotic costs -and prolonged hospital and ICU stays are correlated with gram-negative infections. [8,9] According to a study conducted by the U.S National safety

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Network, gram-negative bacteria is the major cause for more than 30% of hospital-acquired Infections and they predominate in cases of ventilator-associated pneumonia (47%) and urinary tract infections (45%) [2].Prevalence of gram-negative Infections - *Acinetobacter baumannii* (20.9%), *Klebsiella pneumonia* (19.7%), *Escherichia coli* (18.3%), and *Pseudomonas aeruginosa* (14.0%). [10]

ESCHERICHIA COLI

In 1885 the scientist Theodor Escherich introduced and identified the reliance on the segregation and characterization of an organism. It is a slender short rod in shape and obtained from infant stool, later the scientist called it Bacterium Coli commune.[11] The eminent scientist Alphonse Lesage proposed that this organism contains harmless strains as well as variants with different pathogenic potentials.[12] *E Coli* comes under the bacterial family of *Enterobacteriaceae*.[13] It is a rod-shaped bacteria having immobile or mobile with uniformly distributed flagella which can live in both aerobic and anaerobic conditions at a temperature of 37°C. [14] The organism lives in the gastrointestinal tract of human and warm-blooded animals.[13] The consumption of contaminated food products (undercooked meat, contaminated fresh products like salad leaves, drinking water contaminated with animals, through person to person from poor hygiene.[15] Out of gram-negative bacteria, *E Coli* is an utmost and common human pathogen that can cause bloodstream infections and UTI. The acridity factors such as Adhesins, toxins, iron-acquisition systems, polysaccharide coats, and invasions which are not existing in the symbiotic and intestinal infectious strains. [16,17] Vaginal or endocervical colonization, inflammations in conceiving women caused due to presence of the organism in the genital tract of women. [18] The *E Coli* can be classified into O (determined by Cell wall Lipopolysaccharide) and H(due to Flagella Protein), A, B1, B2, D, E with Shigella fabricate distinct groups are the phylogenetic classification of the organism. [19] The 3 main clinical subsets of E Coli are commensal, ExPEC, diarrheagenic. [20] *Enterohemorrhagic E Coli, Enterotoxigenic E Coli, Enteropathogenic E Coli*, *enteroaggregative E Coli* are the sub pathotype classification.[21] The organism dominates discrete coherent elements which help to colonize the small intestine and urethra. Mainly Fimbriae (pili) or Fibrialle helps for the adhesion, along with (intimin of *UroPathogenic Escherichia coli (UPEC) and Enterohemorrhagic Escherichia coli(EHEC) proteins* or other non-fimbrial proteins are present on the outer membrane of E Coli. The congregation of subcellular messengers like cyclic AMP, cyclic GMP, and Ca2+ can be enlarged, later the oozing of toxins, as a result of the activity of heat-labile enterotoxin (LT), heat-stable enterotoxin a, and heat-stable enterotoxin b, lead to ion discharge. The ribosomal RNA is divided by Shiga toxin (Stx) of EHEC thereby derange protein synthesis and killing the inebriate epithelial or endothelial cells.[22]

Clinical manifestations include abdominal pain, tenesmus, meager stools with blood and slime, and desiccation, nausea, vomiting, abdominal pain, mild liquid diarrhea, tiredness, restlessness, pyrexia, and malnutrition are evolved in the initial phase of the disease.[23]Preventive Measures include-Intake of safe water, the decrease the chance of food contamination, sanitation procedures, public teaching and vaccination, correct storage and cooking temperatures, Food irradiation technology are the methods adopted for the eradication of the spread of E Coli. [24]

KLEBSIELLA PNEUMONIA

Klebsiella pneumonia is a Gram-negative, rod-shaped, non-motile, encapsulated, facultatively anaerobic,/ lactose fermenting pathogenic bacterium.[25] Genus' 'Klebsiella' is a member of the Enterobacteriaceae family which comprises the other familiar pathogens like *Escherichia Coli, Salmonella Species, Yersinia Species*, and *Shigella Species*.[26] The Klebsiella species is an opportunistic pathogen, which is a natural inhabitant of the gastrointestinal ecosystem, which widely colonizes in the mucosal layers of the mouth, skin, and intestines of healthy humans and mammals. [27] It is also a hospital-associated opportunistic pathogen that is widely present in hospital equipment and medical devices. Klebsiella pneumonia colonies are further found in the urinary tract, respiratory tract, and blood. [25] The species is found everywhere in nature and is prevalent in the natural environment (i.e. water and soil). [27]

After infecting the host, Pneumonia colonizes mostly the mucosal surfaces in humans such as the GI tract and nasopharynx. The colonization rate of *K. pneumonia* varies between body sites as well as between community and hospital-acquired infections. The nasopharynx colonization is mostly associated with alcohol consumption and gastrointestinal colonization is associated with hospitalized patients. With regards to the risk of transmission and infection, GI colonization is the most common and significant reservoir. [28,29] There are several potential sources of K. Pneumonia transmission in a hospital environment and one such source is the direct transmission due to person-to-person contact between healthcare workers and patients, where the healthcare worker's hands are a major source of infectious bacteria. Another identified source of transmission is through contaminated surfaces and instrumentations of hospital equipment. [30,31]

The opportunistic *K. Pneumonia* typically affects hospitalized or immunocompromised individuals with compromised immune systems or those affected with other underlying diseases such as cancer, diabetes mellitus, alcoholism which can

affect the host's innate immunity. [32,33] *K. Pneumonia* forms colonies generally before the development of nosocomial infections. [34] Despite identifying various infection progression risk factors the exact mechanism of progression from colonization to infection has not yet been identified. The risk of bacteremia infection is five times more in patients who underwent allogeneic hematopoietic stem cell transplantation. For procedures like endoscopy, repeated use of scopes or medical devices or implants with openings facilitates *K. Pneumonia* entry resulting in increased chances of endogenous infections. Endotracheal intubation has an increased risk of causing Ventilator-associated Pneumonia [VAP] due to the microaspiration of the pooled oropharyngeal secretions from the folds of the inflated cuffs into the trachea acts as a substrate for the bacterial growth as well as the formation of biofilms on the inner side of the tracheal tube. [35] Infections in hospitalized patients are significantly associated with Intestinal colonization, fluid and electrolyte disorders, neurologic disorders, and prior hospital admissions. [34]

About one-third of all Gram-Negative Infections are caused by *K. Pneumonia*, [36,37]which includes hospital and community-acquired serious extraintestinal infections but not limited to pneumonia, UTI, meningitis, cystitis, and soft tissue infections [38,39]. The classical strains of *K. Pneumonia* are responsible for primary infections such as Pneumonia and /or UTI, which may also sometimes lead to serious infections such as bacteremia which may be primary, or secondary bacteremia that arises as a secondary infection from the primary site of infection. [40,41,42] *Klebsiella pneumonia* is also involved in life-threatening infections such as septicemia and endocarditis as well as serious community-onset infections such as necrotizing pneumonia, pyogenic liver abscess, and endogenous endophthalmitis.[27] Pneumonia plays a major role in less common but serious systemic infections such as pyogenic liver abscesses that can lead to bacteremia and extrahepatic abscesses [43] and invasive syndrome, septic arthritis, and generalized pustulosis.[44] The hypervirulent strains of Pneumonia are more likely to cause community-acquired as well as systemic infections when compared to the classical strain of Pneumonia.[45] Pneumonia is a triggering factor in the initiation and development of ankylosing spondylitis and Crohn's disease. [31]

Pneumonia is divided into two types: Hospital-acquired pneumonia [HAPs] and Community-acquired pneumonia [CAPs]. Pneumonia CAPs are less prevalent when compared to Pneumonia HAPs. [45] The clinical signs and symptoms of Pneumonia HAPs are similar to other nosocomial pneumonia with respiratory symptoms like cough and unilateral pulmonary infiltrates as well as systemic symptoms like fever and leukocytosis. Pneumonia HAPs are seen both in ventilated as well as non-ventilated patients. [46] Meanwhile, the clinical signs and symptoms of Pneumonia CAPs are the classical signs of acute pneumonia, including cough, fever, leukocytosis, and chest pain. It also displays the characteristic Pneumonia symptom "currant jelly sputum," which is the production of thick blood-tinged mucous due to high levels of inflammation and necrosis in the lungs. [47,48] Among the gram-negative bacteria, Pneumonia is the second leading cause of bloodstream infections (BSI). Cancer is one of the primary diseases associated with hospital-acquired bloodstream infections and the primary diseases associated with community-acquired bloodstream infections are liver diseases and diabetes mellitus. In situations when BSI is a primary infection, there is no identifiable source but whereas in the case of BSI being a secondary infection it results from dissemination into the bloodstream from a known source. The common sites of secondary BSI are the urinary tract, gastrointestinal tract, intravenous or urinary catheters, and respiratory sites.

The most common site of Klebsiella-associated infections is the urinary tract and Klebsiella-associated UTI is mostly linked with diabetes mellitus. Pneumonia causes Catheter-associated infections by forming biofilms and adhering to these catheters. Klebsiella is also accountable for wound/surgical site infections too. As a result, *Klebsiella Pneumonia* has become a substantial healthcare burden.[38,39]

PSEUDOMONAS AERUGINOSA

The recent emergence and widespread of so-called high-risk clones of multidrug resistance or extensive drug resistance towards bacteria are becoming major threats to public health. Multidrug resistance infections are very associated with high mortality, long hospital stay, and increased costs due to narrow therapeutic options for infected patients. [49,50] *Pseudomonas aeruginosa* is one of the most important bacteria with reported resistance to antimicrobial classes including aminoglycosides, carbapenems, beta-lactams, fluoroquinolones, and polymyxins. [51] It is one of the central asymptomatic, chronic pathogens causing a diversity of healthcare-associated infections including urinary tract infections, sepsis, pneumonia, and soft tissue infections .[52] These kinds of infections make a major impact on healthy individuals infrequently only but cause high mortality and morbidity in immunocompromised individuals and cystic fibrosis (CF) patients. [53]

The gram-negative bacterium *pseudomonas aeruginosa* normally inhibits the soil and surfaces in aqueous environments and colonizes the animate surface of plants, animals, and humans. [54]. It is a gram-negative, encapsulated, heterogenous, rod-shaped bacteria that are capable of causing a variety of life-threatening gram-negative infections [55]. *Pseudomonas aeruginosa* carries a single flagellum that is capable of their motility and helps in surface correlations. [56] A type IV surface pili are present in aeruginosa which helps in attachment to some surfaces and cell membranes.

Pseudomonas aeruginosa causes various diseases. Pneumonia is identified in chronic lung disease and immunosuppressive patients. Fever, chills, cyanosis, productive cough, and confusion are the major symptoms of Pneumonia. Bacteraemia is another type and its occurrence depends upon the primary site of infection. Endocarditis infection is another type that presents with fever and malaise as the starting symptoms followed by more specific symptoms depending on which cardiac valve is involved. *Pseudomonas aeruginosa* can cause meningitis and brain abscess with symptoms like fever, headache, and confusion. Also, pseudomonas is the common cause of chronic otitis media with symptoms of continuous pain, oedema, and sensitiveness of soft tissues of the ear. Bacterial keratitis and endophthalmitis in adults and conjunctivitis in children are pseudomonas infections affecting the eye. Its symptoms include pain, blushing, swelling, and reduced vision. Instrumentation, catheterization, and surgery give rise to other infections such as Pseudomonas urinary tract infections (UTI) are normally acquired from the hospital. Pseudomonas also affects the skin causing green nail syndrome, tinea pedis, folliculitis, ecthyma gangrenosum, etc.[57]

Pseudomonas aeruginosa infections can be treated only with limited classof antibiotics due to their increased multiple microbial resistance. Many of the antibiotics are ineffective because Aeruginosa shows resistance towards them.[56] Intrinsic acquired, and adaptive are the major three mechanisms of *Pseudomonas aeruginosa* that can be used to reverse the antibiotic attack. The intrinsic resistance includes low membrane permeability, the ability of efflux pumps that expel antibiotics out of the cell, and the synthesizing antibiotic inactivating enzymes. Through the exchange of genetic material across genera or by mutational changes the acquired resistance can be obtained.[58] Formation of biofilm in the lungs of infected patients is the method of obtaining adaptive resistance where the biofilm acts as a barrier to limit antibiotic entry to the bacterial cells. [59]

The major infections caused by *pseudomonas aeruginosa* bacteria are community-acquired infections and infections acquired through the hospital. Community-acquired infections include keratitis, otitis externa, and skin and soft tissue infections. Hospitalized patients may acquire *pseudomonas aeruginosa* infections during their hospital stay and they can be confined within the hospital itself [60] Bloodstream infections, pneumonia, urinary tract infections(UTIs), surgical site infections, and skin infections in the setting of burn injuries are the nosocomial infections caused by *P. Aeruginosa.*[61] *Pseudomonas aeruginosa* is particularly responsible as a cause of nosocomial infections, and many infections in immunocompromised patients. *Pseudomonas aeruginosa* reveals several acrimony factors, also antibacterial resistance mechanisms that have given increased antibacterial resistance in recent years, thus becoming difficult to treat.

HOW ARE CARBAPENEMS EFFECTIVE IN THE TREATMENT OF GRAM-NEGATIVE BACTERIAL INFECTIONS

As we know that beta-lactam antibiotics include penicillin, cephalosporins, monobactam, and carbapenems. Among these, carbapenem exhibit a wide spectrum of antibacterial activity against gram-negative bacterial infections.[62] is considered as standard treatment for this type of infection.[63] Carbapenems entered into gram-negative organism via porins(outer membrane proteins)and then reached the periplasmic space where its bind to penicillin-binding proteins(PBPs) and inhibit peptidoglycan cross-linking during cell wall synthesis.[64] It covers a wide range of in vitro spectrum of activity when compared to penicillin, cephalosporins, and other beta-lactam antibiotics [65] Carbapenems include meropenem, imipenem, ertapenem, doripenem, panipenem, biapenem [66]. Among these, meropenem, ertapenem and doripenem are considered to be active against severe gram-negative bacterial infections.[67] Ertapenem is not much effective as meropenem or imipenem in case of infection caused by *Pseudomonas aeruginosa* Meropenem is not much effective as imipenem or doripenem in case of infections caused by *Acinetobacter baumannii.*[68]

Minimum inhibitory concentration(MIC) of doripenem is lower than imipenem and meropenem against *Pseudomonas aeruginosa Acinetobacter baumannii.*[69] A Combination of meropenem with clavulanic acid is effective against MDR Mycobacterium tuberculosis. [70] Combination therapy of carbapenem with other antibiotics is used to treat gram-negative bacterial infections especially if a patient is infected with MDR(multidrug-resistant) pathogens.[71] Sometimes it also resulted in unexpected side effects due to the high resistance of any one of the drugs used in combination. The oral bioavailability of carbapenems is very low thus it is effective when given intravenously. Imipenem-cilastatin and ertapenem can be also administered intramuscularly. [65,67] Carbapenems are excreted via the renal route. These drugs are generally used to treat complicated bacterial infections. Apart from gram-negative bacterial infection, the combination of carbapenem with other antibiotics can be used as an empirical treatment in the case of gram-positive infections. The commonly reported side effects with carbapenems are nephrotoxicity, neurotoxicity abs immunomodulation.[72]

RESISTANCE MECHANISM OF CARBAPENEMS

The drug is considered to be safer with fewer adverse effects. Therefore carbapenem resistance towards gram-negative bacterial infections is still a challenge in the modern world. This resistance is mainly due to the following reasons:

a) Intrinsic: Resistance occurs due to gene mutations through horizontal transfer. However, this pattern of resistance is not clinically significant.[73]

b) Some gram-negative organisms block the entry of carbapenems in the initial step itself (that is binding to penicillin-binding proteins) by destroying the permeability of the outer membrane which leads to the carbapenem remaining being ineffective.[74]
c) After the entry of carbapenem into the periplasmic space, resistance is due to the ejection of carbapenems with the help of tripartite efflux pump systems into the periplasmic space.[75]
d) Another mechanism by which the drug exhibits resistance is by overproduction of beta-lactamase enzymes, which results in the hydrolysis of the beta-lactam ring, and the drug remains inactive.[76] This is considered the most clinically significant resistance mechanism offered by carbapenems.

CARBAPENEM RESISTANT ENTEROBACTERIACEAE

Enterobacteriaceae are the principal pathogen responsible for serious infections like Hospital-acquired pneumonia, bloodstream infections, Urinary tract infections, Intra-abdominal infections within the family, UTIs are mainly caused by *Escherichia coli,* and *Pneumonia* are caused by *Klebsiella* and *Enterobacter species*. Overproduction of extended-spectrum beta-lactamases (ESBL) enzymes, an utterance of efflux pumps, porin loss, modification in PBPs which can lead to resistance towards this organism.[77] Phenotypic observations of carbapenemase producers are identified by using the modified Hodge test. It is not widely used because of sensitivity and specificity. In contrast with format-disk diffusion or broth dilution or E test, the carbapenem (eg-Meropenem) or Cephalosporin (eg-Ceftazidime) amalgam with EDTA and Phenanthroline (inhibitors of MBL) and also with Phenylboronic acid (inhibitor of KPC).In some cases, the temocillin disk integrates with avibactam used whenever there is no particular inhibitor used in class D carbapenemase. Recognition of KPC Carbapenemase (in 45minutes) or MBL (in 150 minutes) by using Mass Spectrometry (MALDI -TOF).The identification of carbapenemase genes in the clinical laboratory by using real-time PCR, hybridization test, simple or multiple PCR. This test can resolve the susceptibility and explicitness problems with phenotypic tests.[80]

CARBAPENEM RESISTANT PSEUDOMONAS SPECIES

OprD is the outermost membrane porin present in *Pseudomonas species*, it acts as a pathway for the entry of carbapenem where penicillin-binding protein(PBPs) is located. However, carbapenem resistance in this type is mainly due to the leakage, loss, or mutation in the porin membrane. As a result, the binding of carbapenem to PBPs does not take place.[74]

CEFTAZIDIME-AVIBACTAM

It is an intravenously administered fixed drug combination of ceftazidime, a third-generation cephalosporin, and avibactam, a non-beta lactam beta-lactamase inhibitor. The drug was approved by U.S Food and drug administration (FDA) in February 2015.[81]for the treatment of adults with complicated urinary tract infections(UTI), complicated intra-abdominal infections(cIAI), and hospital-acquired pneumonia(HAP)[81]. In the EU, it is also approved for the treatment of serious infections caused by aerobic gram-negative organisms with limited or no other treatment options.[81]

HOW DOES CEFTAZIDIME-AVIBACTAM OVERCOME THE RESISTANCE?

Like all other cephalosporins, Ceftazidime binds to penicillin-binding protein PBPs and inhibiting peptidoglycan cross-linking during cell wall synthesis results in bacterial cell lysis and cell death. But due to the overproduction of the beta-lactamases enzyme, the beta-lactam ring gets hydrolyzed and renders the antibiotic ineffective. To overcome this difficulty, avibactam a non-beta lactam beta-lactamase is added to ceftazidime which helps in preventing the hydrolysis of beta-lactam ring and increases the spectrum of activity of ceftazidime.[82] It is effective againstmany multi-resistant gram-negative organisms such as *Enterobacteriaceae (E.coli, Klebsiella pneumonia)* and *Pseudomonas aeruginosa*, including those expressing certain types of ESBLs(*extended-spectrum beta-lactamases*) and KPC(*Klebsiella pneumoniae carbapenemase*) (Class A enzymes), extended-spectrum *cephalosporinases* (Class C enzymes)) and also carbapenemase produced from the OXA gene (Class D enzymes) [83]. (Table 2) (Figure 1)

Pharmacokinetics and Pharmacodynamics

The pharmacokinetic properties exhibited by this combination drug are the same as those administered alone. Only a small portion of the drug is bound to plasma hence it provides a wide volume of distribution. 80- 90% of the drug is eliminated as an unchanged drug and there is no metabolism of avibactam in liver cells of humans. The main route of elimination is via the kidney.

EFFECTIVENESS OF CEFTAZIDIME-AVIBACTAM AGAINST ENTEROBACTERIACEAE

Ceftazidime-avibactam is a new drug accepted by the US Food and Drug Administration. It is a beta-lactam or beta-lactamase inhibitor used for the therapy of complicated intra-abdominal infection, complicated urinary tract infections, and in vitro activity against Carbapenem-Resistant Enterobacteriaceae which

generate Klebsiella Pneumoniae Carbapenemase (KPC) and no activity against New Delhi (MBL), Verona -integron-encoded MBL (VIM),imipenemase. The drug is administered 2.5 mg intravenously (IV) every 8 hours and the dose should be adjusted in renal impairment patients.

In April 2015 and February 2016 a retrospective study was conducted in patients having CRE infection who were treated with ceftazidime-avibactam at the University of Pittsburgh Medical Center. Thirty-seven consecutive patients were evaluated and treated for 3 days or more. The drug was given as monotherapy or in an amalgamation of regimens in 70% (26/37) and 30% (11/37) of patients, respectively. The meld agents (intravenous or inhaled gentamicin, intravenous or intrathecal colistin, and tigecycline)were started along with ceftazidime-avibactam and given for 72 hours or more.

The 30-day durability rate was 76% (28/37) and the durability rate for 90-day was 62% (23/37). Clinical success was achieved in 59% (22/37) and did not differ for patients receiving monotherapy (58% [15/26]) or combination therapy (64% [7/11]). The success rates will not be on the basis of baseline creatinine clearance (<30, 31–50, or >50 mL/min (100% [2/2], 67% [6/9], and 65% [13/20]. Microbiologic failures occurred in 27% (10/37) of patients due to recurrent infections within 30 and 90 days and urinary colonization with Carbapenem-Resistant Enterobacteriaceae. [84] (Table 3)

EFFECTIVENESS OF CEFTAZIDIME-AVIBACTAM AGAINST PSEUDOMONAS AERUGINOSA

Complicated intra-abdominal infections, complicated urinary tract infections (cUTIs), and nosocomial pneumonia are mostly caused by *pseudomonas aeruginosa* species. Its resistance towards antibiotics is a major problem thus leads to limited treatment options for those infections.

Ceftazidime- avibactam is a combinational drug approved by the US FDA for the treatment of serious gram-negative infections and has completed trials in cIAI, cUTI, and ventilator-associated pneumonia patients.

Study analysis of evaluation of the clinical activity of ceftazidime-avibactam against *MDR Enterobacteriaceae* and *Pseudomonas aeruginosa* was conducted in 2018. The isolates were pooled from clinical trials in patients with complicated intra-abdominal infections, complicated urinary tract infections, and nosocomial pneumonia including ventilator-associated pneumonia where .95 patients with MDR *P.aeruginosa*isolates were identified. Clinical and microbiological responses were assessed at the test-of-cure (TOC) visit. It showed a clinically cured response rate of 85.4% for ceftazidime-avibactam and 87.9% for comparators. A higher susceptibility rate was reported for *pseudomonas aeruginosa* isolates.(Table 4)

In conclusion, the ceftazidime-avibactam clinical trial program successfully demonstrated it is a suitable drug for gram-negative infections. [85]

DISCUSSION

The article serves to provide clinical information regarding a novel antibiotic combination Ceftazidime-Avibactam for the treatment of drug-resistant gram-negative bacterial infections, which is mainly active against *Klebsiella pneumoniae, Pseudomonas aeruginosa, and E Coli. The* Majority of studies showed that this combination is predominantly active against *Klebsiella pneumoniae* for abdominal infection, urinary tract infection as well as pneumonia. The drug showed resistance patterns towards carbapenem-resistant Enterobacteriaceaepossessing NDM-1enzyme (class B Metallo beta-lactamases), which is mostly overcome by combining Ceftazidime-Avibactam with aztreonam. Moreover, Ceftazidime-Avibactam has superior efficacy as well as limited adverse drug reaction than colistin therapy especially in the case of renal impaired patients. It is also observed that Ceftazidime-Avibactam can be also used as an alternative therapy when colistin could not be used with worsening renal function.

CONCLUSION

The drug is effective in the case of Enterobacteriaceae and P. aeruginosa but has no activity against A. baumannii. Ceftazidime-avibactam is incompetent to inhibit metallo-b-lactamases (IMP or NDM).The drug can cause serious infections in CRE patients due to a lack of clinical trials. As a result of the higher rate of SAEs compared with carbapenems, safety should also need to be assessed. In minority patients having a chance of developing resistance after the continuous use of the drug over 10 days, which later leads to treatment failures and death, so to avoid this need more drugs to be active against CRE. Dose adjustment is not done in CRRT patients.

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Table 1: Dosage regimen of ceftazidime-avibactam

Indication	Dose	Frequency	Treatment duration
cIAI	2 g/0.5 g	Every 8 hours	5-14 days
cUTI	2 g/0.5 g	Every 8 hours	5-10 days
Hospital-acquired pneumonia	2 g/0.5 g	Every 8 hours	7-14 days SS

Ambler classification of beta-lactamases enzymes (table 2)[77-79]

Table 2: Classification of beta-lactamases enzymes

Classes	Groups
Class A	serine beta-lactamases [77]
Class B	metallo-b-lactamases [78]
Class C	AmpC beta-lactamases
Class D	OXA beta-lactamases [79]

Table 3: Success Rate of Ceftazidime-Avibactam for Carbapenem-Resistant Enterobacteriaceae in various diseases.

Underlying Disease	Success Rate
Pyelonephritis	100%
Primary bacteremia	70%
Pneumonia	50%
Skin/Soft tissue infections	50%
Intra Abdominal infections	50%
Other infections	33%

Table 4: Microbiological and clinical response data

Pathogen	Number of Patients	MIC50 (mg/L)	MIC90(mg/L)	Susceptibility
Enterobacteriaceae	509	0.12	1	99.2
Pseudomonas aeruginosa	56	8	64	66.1

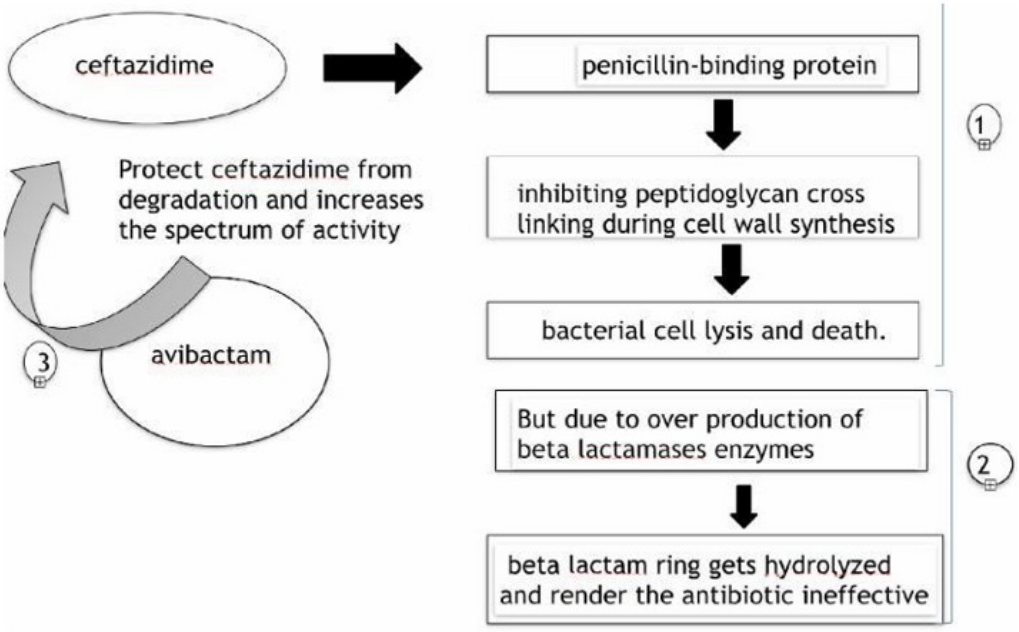

Figure 1: Mechanism of action of ceftazidime-avibactam (83).