A DISSERTATION ON

A Study on Susceptibility of Ceftazidime Avibactam in Carbapenem Resistant *Enterobacteriaceae* causing UTI at a Tertiary Care Superspeciality Institute in North India.

SUBMITTED TO

DEPARTMENT OF MICROBIOLOGY

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BY

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M.Sc. MICROBIOLOGY

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Integral University, Lucknow.

UNDER THE SUPERVISION OF

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DECLARATION

I, Reeti Sharma, declare that this submission is my own work under the supervision of Dr. Manodeep Sen (Professor), Department of Microbiology, Dr. RMLIMS, Lucknow. I have taken four month of training at the Microbiology Lab with the supervisor at the center.

I further declare that to the best of my knowledge the project report is original and it does not contain any part of any work and has not been submitted in part or full to any other institute or university for award or any kind of degree without proper citation.

Date: June 15, 2022

Place: Lucknow **REETI SHARMA**

ACKNOWLEDGMENT

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KEYWORDS.

Ceftazidim- avibactam (CAZ- AVI) (AVYCAZ)

Antibiotic susceptibility test (AST)

Urinary tract infection (UTI)

Urine culture and sensitivity (UC/s)

Carbapenem

Enterobacteriaceae

Cephalosporin

Metallo beta- Lactamase (MBL)

CRITICAL TERMS

Antimicrobials

Agent that destroys or inhibits microorganisms; capable of destroying or inhibiting their growth" (CLSI). Antibiotics are a type of antimicrobial.

Antibiotic

Drugs produced by a microorganism that inhibit growth or destroy micro-organisms. Antibiotics are used to treat infectious disease in humans, animals, or plants.

Antimicrobial Resistance

Ability of a microorganism to multiply under conditions that would inhibit other members of the strain (Anonymous, 2006). Refers to failure of a given antimicrobial treatment.

Multi – Drug Resistant

For this study, MDR is defined as resistance to 5 or more antimicrobial agents.

Enterobacteriaceae

Enterobacteriaceae are a large family of Gram-negative bacteria that includes a number of pathogens similar as *Klebsiella, Enterobacter, Citrobacter, Salmonella, Escherichia coli, Shigella, Proteus, Serratia* and other species. These pathogens are present in the intestinal tract and are a normal part of the gut foliage. They're a common cause of urinary tract infections(UTIs).

INTRODUCTION

° **Urinary Tract Infection (UTI)** – A Urinary tract infection is an infection of the urinary system. This type of infection can involve your urethra (a condition called urethritis), kidneys (a condition called pyelonephritis) or bladder, (a condition called cystitis). Urine typically doesn't contain bacteria . Urine is a byproduct of our filteration system the kidneys. When waste products and excess water is removed from blood by the kidneys, Urine is created. Normally , Urine moves through your urinary system without any contamination . However, bacteria can get into the urinary system from outside of the body , causing problems like infection and inflammation. This is a urinary tract infection (UTI). Most UTIs can be treated with an antibiotic.

- **Origin of MDR in UTI -** Urinary tract infections (UTIs) are among the most frequent infectious diseases affecting humans, and represent an important public health problem with a substantial economic burden. Due to the high empiric use of antibiotics for the treatment of UTI, antibacterial resistance of *Enterobacteriaceae*, specifically the main uropathogens Escherichia coli and *Klebsiella pneumoniae,* has significantly increased worldwide. The increased prevalence of MDR *Enterobacteriaceae*, limiting available treatment options for infections caused by these organisms, and the lack of new antibiotics provide good rationale for using older antibiotics, such as fosfomycin, that have been shown to retain some activity against MDR bacteria.
- Ceftazidime – Avibactam has good activity against Gram – negative bacteria, especially *Enterobacteriaceae*. In recent times, the rapid-fire spread of considerably medicine- resistant(XDR) and multidrug- resistant(MDR) Gram-negative bacteria have seriously hovered global public health. β- Lactams and carbapenems are effective medicines against Gram-negative bacteria.

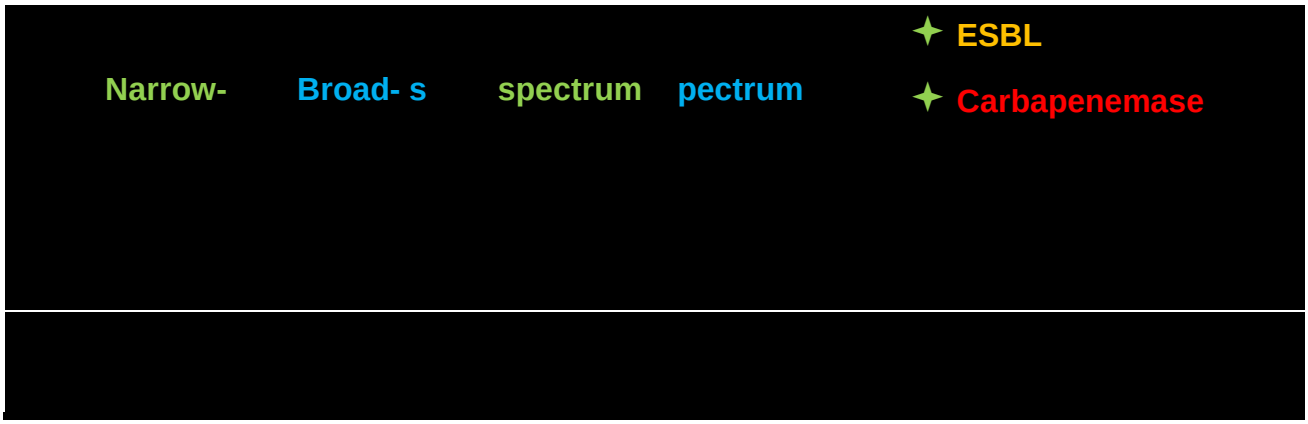
  Their effectiveness has been dropped due to β- lactamase production, efflux pumps and target variations. According to Ambler's classification, β- lactamases are subdivided into four molecular classes A, B, C and D. *Klebsiella pneumoniae* carbapenemases(KPCs, class A), New Delhi metallo- β- lactamases(NDMs,

class B), and oxacillinase-48-like(OXA48-like, class D) carbapenemase are generally reported around the world. Still, the diapason of exertion for classic β-lactamase impediments, including clavulanic acid, sulbactam and tazobactam, is substantially confined to class A and some class C β- lactamases. Also, the overexpression and structural revision in AmpC lead to the resistance to tazobactam. also, decades of clinical use have increased the resistance of pathogens. New β- lactamase impediments, vaborbactam and relebactam, substantially inhibit class A and class C β- lactamases. As a synthetic andnon-β-lactam (diazabicyclooctane) β- lactamase asset, avibactam(AVI) can reversibly acylate the class A(extended- diapason β- lactamases(ESBLs), KPCs), class C(AmpC), and class D (OXA- 48) β- lactamase and others .

Ambler Classification –

Beta-lactamase in Enterobacteriaceae -

Ambler class A Penicillinases	Ambler class C	Ambler class B	Ambler Class D
TEM	VIM	Ampc	OXA-48
SHV	IMP		OXA-23
CTX- M	NDM		
KPC	GIM		
GES			
IMI			
NMC-A			



Avibactam has several unique advantages, similar as a long half- life, low molecular weight, opposition and commerce with important catalytic remainders near the active spots of β- lactamases. AVI can expand the antibacterial exertion of CAZ, especially against AmpC-, ESBL-, and carbapenemase- producing strains, similar as Enterobacteriaceae andP. aaeruginos.

As a third- generation cephalosporin, ceftazidime(CAZ) has broad-spectrum of action and inhibits cell wall conflation by binding to penicillin- binding proteins(PBPs) of Gramnegative bacilli.

CAZ- AVI was approved for marketing by the US Food and Drug Administration(FDA) in February 2015 for the treatment of complicated urinary tract and intraabdominal infections caused by MDR or XDR Gram-negative bacteria. According to the CAZ- AVI package insert(Avycaz, Astra

Zeneca) and the results of a global surveillance program(INFORM), the antibacterial exertion of CAZ- AVI extends to the following susceptible Gram-negative microorganisms:-

Escherichia coli, K. pneumoniae, Proteus mirabilis, Enterobacter cloacae, Klebsiella oxytoca ,Citrobacter freundii complex P. aeruginosa .

REVIEW OF LITERATURE

Background -

Bacteria retain a cell wall comprising a glycopeptide polymer generally known as peptidoglycan, which is synthesized and remake through the action of a family of enzymes known as" penicillin- binding proteins"(PBPs).1 β- lactam antibiotics, including cephalosporins, are PBP impediments that, through inhibition of essential PBPs, affect in impaired cell wall homeostasis, loss of cell integrity, and ultimately bacterial cell death.

Ceftazidime is a third- generation cephalosporin with broad- spectrum antibacterial exertion, including against some treatment- resistant bacteria analogous as *Pseudomonas aeruginosa*. Cephalosporins are beta- lactam antimicrobials used to manage a wide range of infections from Gram-positive and Gram-negative bacteria. The five generations of cephalosporins are useful against skin infection, resistant bacteria, meningitis, and other infection This exertion describes the suggestions, contraindication, and possible adverse goods of cephalosporins and will punctuate the medium of action, adverse event profile, monitoring, route of administration. (Yosra Ahmad Modafer) 2019.

Ceftazidime was approved by the FDA on July 19, 1985.First

Gram-negative antibiotic approved in the U.S. to treat Hospital

Acquired Bacterial Pneumonia and Ventilator Associated Bacterial Pneumonia.Ceftazidime is in a class of specifics called cephalosporin antibiotics. It is a third generation cephalosporin. It works by killing bacteria. Avibactam is in a class of specifics called beta- lactamase impediments. It works by precluding bacteria from breaking down ceftazidime, and is presently available also alone or in combination with the non- β- lactam β- lactamase asset avibactam to treat a variety of bacterial (Philippe Lagace – Wiens , Andrew Walkty, James A Karlowsky) (24 January 2014).

Ceftazidime and avibactam is being concertedly developed with Pfizer. Allergan holds the rights to manipulate ceftazidime and avibactam in North America under the brand name AVYCAZ, while Pfizer holds the rights to manipulate the combination in the rest of the world under the brand name ZAVICEFTA . To reduce the development of medicine-resistant bacteria and maintain the effectiveness of AVYCAZ and other antibacterial

medicines, AVYCAZ should be used to treat only indicated infections that are proven or explosively suspected to be caused by susceptible bacteria.

Ceftazidime avibactam is used for treatment of :-

Ceftazidime avibactam, sold under the brand name Avycaz among others, is a fixed- cure combination medicine composed of ceftazidime, a cephalosporin antibiotic, and avibactam, a B- lactamase asset. It's used to treat complicated intra- abdominal infections, urinary tract infections, and pneumonia. It's only recommended when other options are not applicable. It's given by injection into a to a vein.

Indications:

1. Complicated intra- abdominal infections caused by the following susceptible gram-negative microorganisms *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter cloacae, Klebsiella oxytoca, Citrobacter freundii complex, and Pseudomonas aeruginosa*.
2. Complicated urinary tract infections(UTI) including pyelonephritis caused by the following susceptible microorganisms *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Citrobacter freundii complex, Proteus mirabilis, and Pseudomonas aeruginosa*.
3. Hospital acquired Pneumonia/ Ventilator associated bacterial pneumonia (HABP/ VABP) caused by the following susceptible Gram negative microorganisms *Klebsiella pneumoniae, Enterobacter cloacae, Escherichia coli,*
   Serratia marcescens, Proteus mirabilis, Pseudomonas aeruginosa, and Haemophilus influenzae in cases aged ≥ 18 times.

The combination of ceftazidime and avibactam injection is used with metronidazole(flagyl) to treat abdominal(stomach area) infection. It's also used to treat pneumonia that developed in people who are on ventilators or who were in a sanitorium, and order, urinary infection. Antibiotics analogous as ceftazidime and avibactam will not work for flu or other viral infections. Misuse of antibiotics is a major cause for increasing antimicrobial resistance patterns.

Dosage and administration-

Dosage of AVYCAZ in Adult patients with Creatinine Clearance (CrCl) greater than 50mL/min(2.1)

Infection	Dose	Frequency/Influence time
cIAI, cUTI including Pyelonephritis	AVYCAZ 2.5 grams(CAZ2grm AVI0.5grm)	Every 8 hrs/ 2hrs
HABP/VABP		

Mechanism of action –

The bacterial cell wall, which is located at the fringe of Gram-positive bacteria and within the periplasm of Gram-negative bacteria, comprises a glycopeptide polymer synthesized through cross-linking of glycans to peptide stems on interspersing saccharides, which is known generally as peptidoglycan. Cell wall conformation, recycling, and remodelling bear multitudinous enzymes, including a family of enzymes with analogous active point character despite distinct and occasionally lapping places as carboxypeptidases, endopeptidases, transpeptidases, and transglycosylases, known as" penicillin- binding proteins"(PBPs). The number of PBPs differs between bacteria, in which some are considered essential and others spare. In general, inhibition of one or further essential PBPs results in disabled cell wall homeostasis, loss of cell integrity, and is eventually bactericidal.

Ceftazidime is a semisynthetic third- generation cephalosporin with broad exertion against multitudinous Gram-negative and some Gram-positive bacteria. Like other β-lactam antibiotics, ceftazidime exhibits its bactericidal effect primarily through direct inhibition of specific PBPs in susceptible bacteria. In vitro trials in

Gram-negative bacteria similar as *Escherichia coli, Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae* suggest that ceftazidime primarily binds to PBP3, with weaker binding to PBP1a/ 1b and PBP2 as well; although binding to

other PBPs, similar as PBP4, is sensible, the attention needed are much lesser than those achieved clinically also, (Michele B.
2016) .

Resistance- No cross – resistance with other classes of antimicrobials has been identified. Some isolates resistant to other cephalosporin (including ceftazidime) and to carbapenems may be susceptible to Avycaz.

Avycaz FDA Approval History-

FDA Approved : February 25, 2015

Brand name :. Avycaz

Generic name: avibactam and ceftazidime

Dosage form :. Injection

Company : Actavis Pharma,Inc .

Treatment for :. Intraabdominal infection, Urinary Tract Infection, Pneumonia.

Development Timeline for Avycaz –

Date	Article
March 18, 2019	Allergan Announces FDA Approval of Avycaz (Ceftazidime and Avibactam) for Pediatric Patients.
February 1,2018	FDA Approves Avycaz for the treatment of Patients with Hospital- Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia.
February 25, 2015.	FDA Approves Avycaz for Complicated Abdominal and Urinary Tract Infections.

CLINICAL PHARMACOLOGY :-

The first element of Avycaz is ceftazidime, a third- generation cephalosporin with a great advantage over common antibiotics in that it has the broadest extended-spectrum beta-lactamase(ESBL) profile in its class. Whereas some third- and fourth- generation

cephalosporins are considerably hydrolyzed by ESBL, ceftazidime is not, which makes it a better treatment option against multidrug- resistant bacteria. The alternate element, avibactam, is a new beta- lactamase asset that adds a defensive factor to ceftazidime. Avibactam inactivates the beta- lactamases that would ultimately lead to the declination of ceftazidime, which gives ceftazidime a broader ESBL profile. Avycaz sets itself piecemeal by being the first cephalosporin – beta- lactam combination with exertion against carbapenemases (Juan F.Mosley , Lillian L. Smith, Lydia V. Gibbs) .

WARNINGS AND PRECAUTIONS

- Decreased efficacy in adult cIAI patients with baseline CrCl of 30 to less than or equal to 50 mL/ min: Monitor CrCl atnging renal function and adjust the dose of AVYCAZ accordingly.
- Hypersensitivity reactions: Includes anaphylaxis and serious skin reactions. Cross-hypersensitivity may occur in patients with a history of penicillin allergy. If an allergic reaction occurs, discontinue AVYCAZ.
- Clostridium difficile-associated diarrhea (CDAD): CDAD has been reported with nearly all systemic antibacterial agents, including AVYCAZ. Evaluate if diarrhea occurs.
- Central Nervous System Reactions: Seizures and other neurologic events may occur, especially in patients with renal impairment. Adjust dose in patients with renal impairment.

URINARY TRACT INFECTION :-

A UTI develops when microbes enter the urinary tract and beget infection. Bacteria are the most common cause of UTIs, although fungi infrequently can also infect the urinary tract. E. coli bacteria, which live in the bowel, beget utmost UTIs. Shorter urethra and closer proximity to sources of bacteria from the anus and vagina makes women more susceptible to UTI compared to men. Sexual exertion can move bacteria to the urethral opening.

Symptoms:-

- Strong and frequent urge to urinate.
- Bloody or dark urine with strong smell.
- Burning sensation while urinating.
- Pain in bladder region.
- Nausea.
- Fever

ESBLs producing organisms are clinically important and remain a major cause of treatment failure with Cephalosporin's and other classes of antibiotics in the world.

Third generation of Cephalosporin's was introduced in1980, which brought a relief in the fight against beta- lactamase resistance to antibiotics. Cephalosporin's were introduced due to increased resistance by beta- lactamases produced by different Gramnegative bacteria similar *Klebsiella pneumoniae,E.coli, Pseudomonas aeruginosa, Proteusspp.* and may circulate new host, for illustration, produced by Neisseria gonorrhea and Hemophillus influenza.

CARBAPENEM:-

Carbapenems are a class of beta- lactam antibiotic that are active against numerous aerobic and anaerobic Gram-positive and Gram-negative organisms. Thienamycin was the first carbapenem to be discovered in 1976. Carbapenems are a class of beta- lactam antibiotics that are suitable of killing most bacteria by inhibiting the conflation of one of their cell wall layers. The carbapenems were developed to overcome antibiotic resistance intermediated by bacterial beta- lactamase enzymes. still, the blaNDM- 1 gene produces NDM- 1, which is a carbapenemase beta- lactamase- an enzyme that hydrolyzes and inactivates these carbapenem antibiotics. Carbapenems are a class of antibiotics called beta- lactam antibiotics(that have a chemical structure called a beta- lactam ring). They bind to and block a type of enzyme called penicillin- binding proteins, which is responsible for peptidoglycancross- linking during the conflation of the bacterial cell wall. Whenever

a bacterial cell tries to synthesize a new cell wall to grow and divide, they intrude with their capability to form cell walls, inhibit the bacterial cell wall conflation, render the cell vulnerable to bibulous disturbance, and ultimately kill them. It used to treat a wide variety of bacterial infections(including Escherichia coli, Klebsiella pneumoniae, and Enterobacter cloaca) of the skin, lungs, stomach, pelvis, urinary tract, and feathers. They're also used for the treatment of complicated intra- abdominal infections, complicated urinary tract infections including pyelonephritis(a bacterial infection causing inflammation of the feathers), gynecological, bone and common infections, skin and skin structure infections, and endocarditis(a life- hanging inflammation of the inner filling of the heart's chambers and gates.

METALLO – BETA-LACTAMASE (MBL) :-

Metallo- β- lactamases(MBLs) are arising as the most notable resistance determinants in Enterobacteriaceae. The inhibition of bacterial growth and β- lactam hydrolysis caused by MBL impediments(IMBL) also were estimated. The isolates were tested for MBL product by both a Double Disc Diffusion Test(DDDT) and a Combined Disc Diffusion Test(CDT) using imipenem and ceftazidime as substrates in combination with distinct IMBL.

Detection of NDM-1 gene depends upon the phenotypic determination of the enzyme activity. These enzymes are zinc dependent and therefore termed as metallo-beta-lactamase. Indian studies have been done which demonstrate their dependency on zinc and the ability of zinc chelating agents like EDTA to decrease their activity. The Modified Hodge Test and the ReModified Hodge Test were developed for phenotypical detection on a routine basis in resource limited laboratories. Other tests for phenotypic detection are: -

- Double disk synergy testing (DDST)
- Vitek detection (Automated system)
- E-test (E-Strip)

MATERIALS AND METHODS

STUDY DESIGN :-

In the study conducted a total of 15 bacteria isolates obtained from the urine samples received from patients with urinary tract infections bacterial culture in the Microbiology Laboratory of Dr. Ram Manohar Lohia Institute of Medical

Sciences were included from 15 february 2022 to 15 june 2022. Patients demographic characteristics such as Sex, age, etc were noted.

Types of samples received & proceed:-

Urine samples were received and processed in microbiology laboratory.

1. **Bacterial culture:-**

   A bacterial culture is a test to confirm a bacterial infection. The test can also identify what type of bacteria caused the infection which help guide treatment decisions. For a bacterial culture test takes a sample of blood, stool, urine, mucus and spinal fluid.

   Specimen is collected and sent to a microbiology laboratory where it is examined microscopically and plated on appropriate culture media. It is incubated overnight at 37 degrees and then the bacteria is studies for further details.

Bacterial culture test:-

Bacteria can be sampled from various area of our body or substances inside our body, depending on the type of infection suspected. The different types are –

1. **Urine culture**- A urine culture tests helps in diagnosis of infection in the urinary tract, including the kidneys.

   Clean catched midstream urine is collected in a universal container. If the patient is catheterized urine is collected from the catheter port after cleaning it with povidone-iodine.

Materials used in the bacterial culture :-

- Wire loop
- Disposable plastic loop
- Inoculation poop
- Agar medium (HiCrome Agar in a petri dish)
- The samples to be observed (urine samples)
- Bunsen burner

Test Procedure:-

1. Take a HiCrome agar petri plate and labelled it with patients name .
2. Flame the loop and shift in a bunsen burner until they are bright orange. Let the loop cool near the flame for about 10 seconds.
3. Mix the urine sample properly steriliser the wire loop.
4. Now with the help of loop place urine over HiCrome agr in zig zag manner and place the culture in to incubator at 37° c for 24 hrs.
5. HiCrome agar is a differential medium for presumptive identification and confirmation of microorganism- mainy causing UTI.
6. After 24 hrs bacteria grow over the culture plate with the help of stick place the bacteria over peptone water or sterilize normal saline for 24 hrs at 37°c for bacterial growth.

Antibiotic sensitivity test :-

An antibiotic sensitivity test is used to help find the best treatment for a bacterial infection. It may also be used to find out which treatment will work best on certain fungal infections.

Materials :-

- Actively growing broth or streaked plate of a single organisms (pure culture)
- Mueller Hinton Agar (MHA) plate
- Sterile saline
- Sterile test tube
- Sterile swab
- Disk dispenser
- Antibiotic disc – these disc are commersiely available and have to be stored in the refrigerator. They have to be brought to room temperature atlist 1 hrs before use.

- Antibiotic disk cartridges

  - Ampicillin (AM-10)
  - Piperacillin – Tazobactam
  - Cefazolin
  - Cefepime
  - Aztreonam
  - Doripenem
  - Ertapenem
  - Imipenem
  - Meropenem
  - Gentamicin
  - Tobramicin
  - Amikacin
  - Tetracycline
  - Doxycycline
  - Ciprofloxacin
  - Levofloxacin

° Norfloxacin

° Trimethoprim- sulfamethoxazole

° Fosfomycin

° Nitrofurantoin

° Netilmicin

° Ceftazidim avibactam (30/20)

°Cefoxitin

Procedure:-

1. Take a sterile cotton swab and dip into the inoculum press the cotton swab against side of the test tube to remove axis inoculum.
2. The swab is then streak on an agar plate and allowed to dry at room temperature for few minutes with the lid on.
3. With the help of a sterile forceps or a needle , an antibiotic disc is picked an placed gently on the media. It is make sure that the disc is in contact with the media. The disc should not be removed.
4. Within 30 the plates are placed in an incubator at 35°c for 16-18hrs.
5. Reports the values as-

- **Resistant –** Indicates that clinical efficacy has not been reliable in treatment studies.
- **Intermediate-** implies clinical applicability in body sites where the drug is physiologically concentrated or when a high dosage of the drug can be used.
- **Susceptible-** implies that an infection due to the organism may be treated with the concentration of antimicrobial agent used, unless otherwise contraindicated.

Detection of Resistance:-

Resistance among microorganisms can generally be detected either phenotypically or genotypically. The phenotypic approach is the usual system when testing bacteria for clinical purposes. The Clinical Laboratory norms Institute(CLSI). has outlined standard vulnerability testing guidelines.

Disk Diffusion Zone Diameter Chart –

The size of the zone of inhibition is generally related to the position of antimicrobial exertion present in the sample or product – a larger zone of inhibition generally means that the antimicrobial is further potent.Measure from the center of the fragment to the edge of area with zero growth. Take your dimension in millimeters. This measures the compass of the zone of inhibition. Multiply that by two in order to get the periphery.

Table 1. Antimicrobials agents used in susceptibility testing against Enterobacteriaceae and interpretive criteria of MIC.

ANTIBIOTIC	CODE	ZONE DIAMETER(mm)		
		RESISTANT	INTERMEDIATE	SUSCEPTIBLE
AMPICILLIN-SULBACTAM	A/S	≤11	12-14	≥15
PIPERCILLIN-TAZOBACTUM	PIT	≤17	18-20	≥21
CEFAZOLIN	CZ	≤19	20-22	≥23
CEFEPIME	CPM	≤14		≥15
CEFTOXITINE	CX	≤14	15-17	≥18
AZTREONAM	AT	≤17	18-20	≥21
DORIPENEM	DOR	≤19	20-22	≥23
ERTAPENEM	ETP	≤18	19-21	≥22
IMIPENEM	IPM	≤19	20-22	≥23
MEROPENEM	MRP	≤19	20-22	≥23
GENTAMICIN	GEN	≤12	13-14	≥15
TOBRAMICIN	TOB	≤12	13-14	≥15
AMIKACIN	AK	≤14	15-16	≥17
TETRACYCLINE	TE	≤11	12-14	≥15
DOXYCYLINE	DO	≤10		≥14
CIPROFLOXACIN	CIP	≤21		≥26
LEVOFLOXACINE	LE	≤16		≥21

NORFLOXACIN	NOR	≤12	11-13 22-25 17-20 13-16	≥17
TRIMETHOPRIM-SULFAMETHOXAZOLE	TMP	≤10	11-15	≥16
FOSFOMYCIN	FO	≤12	13-15	≥16
NITROFURANTOIN	NIT	≤14	15-16	≥17
NETILMICIN	NET	≤12	13-14	≥15
CEFTAZIDINE AVIBACTAM	CAZAVI	≤20		≥21
PENICILLIN-G	P	≤14		≥15

RESULT

Table 2 - Samples are assessing ceftazidime with the combination of avibactam for gram-negative bacterial infection.

SR.NO.	CR.NO.	AGE/SEX	TEST	CLINICAL DIAGNOSIS	ORGANISM	CAZ-AVI
1.	003701	67/F	UC/S	Enterobacteriaceae (MBL+)	E . coli	Resistant
2.	110230	82/M	UC/S	Enterobacteriaceae (MBL+)	E.coli	Resistant
3	006732	42/F	UC/S	Enterobacteriaceae (MBL+)	E.coli	Resistant
4	112853	57/F	UC/S	Enterobacteriaceae (MBL+)	K.pneumoniae	Susceptible
5.	008929	59/M	UC/S	Enterobacteriaceae (MBL+)	E.coli	Resistant
6.	008898	56/M	UC/S	Enterobacteriaceae (MBL+)	E.coli	Resistant
7.	009349	27/F	UC/S	Enterobacteriaceae (MBL+)	E.coli	Susceptible
8.	112795	51/M	UC/S	Enterobacteriaceae (MBL+)	K.pneumoniae	Resistant
9.	019011	39/M	UC/S	Enterobacteriaceae (MBL+)	E.coli	Susceptible
10.	001824	55/M	UC/S	Enterobacteriaceae (MBL+)	E.coli	Resistant
11.	001149	62/M	UC/S	Enterobacteriaceae (MBL+)	E.coli	Resistant

	08		S	MBL+)	niae	nt
13.	145322	53/F	UC/S	Enterobacteriaceae(MBL+)	E.coli	Resistant
14.	010653	69/M	UC/S	Enterobacteriaceae(MBL+)	E.coli	Resistant
15.	004046	34/M	UC/S	Enterobacteriaceae(MBL+)	E.coli	Resistant

✞ A total of 15 E.coli or K.pnemoniae strains were isolates from patients. The isolates were from patients at Dr. Ram Manohar Lohia hospital .The studied strains were isolated from the urology ward . Antimicrobials drug resistance pattern of 15 E.coli and K.pneumoniae isolates are shown in table 2 .

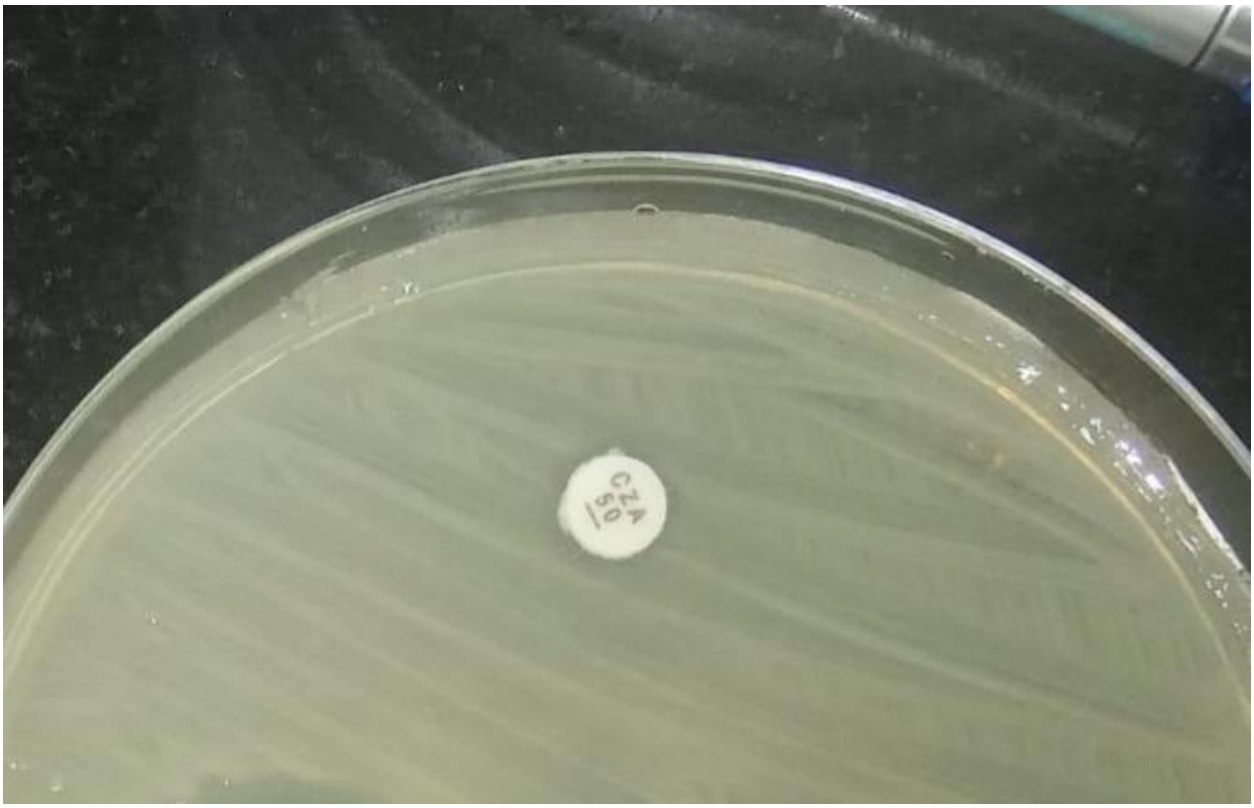


Figure 2. Ceftazidim- avibactam resistance.(≤20mm).

Figure 3. Ceftazidime- avibactam sensitivity.(≥20mm).

DISCUSSION

Samples from the study came from a larger study designed to assess the UTI and other gram – negative infections, this study examined the pattern of antimicrobials resistance for *E.coli*. While ceftazidime is an aged third- generation cephalosporin, avibactam is a new diazabicyclooctane beta- lactamase asset. Avibactam is a non-beta- lactamase asset. It contains a five- membered cyclic urea rather of the fourmembered beta- lactamring. Avibactam covalently and reversibly binds to serine beta- lactamases; thus, it has potent exertion against KPC and AmpC beta- lactamases but doesn't have exertion against MBL carbapenemases). Avibactam is most potent against Class A and Class C beta- lactamases, but has weaker inhibition against Class D beta- lactamases. The medium of action of avibactam differs from other betalactamase impediments in that it doesn't serve as the enzyme substrate and bind irreversibly, but rather reversibly binds to the enzyme causing a slowed deacylation and ring check. This allows avibactam to recapture exertion and beget inhibition to other enzymes. This regression is most probably due to the lower natural strain of a fivemembered ring than a four- membered ring.

Rested on limited available data, the eventuality for the selection of resistance to ceftazidime- avibactam appears to be fairly low. The most common medium of acquired resistance to ceftazidime- avibactam in clinically important Gram-negative pathogens is the product of β- lactamases that are refractory to inhibition by avibactam(e.g. class B enzymes(metallo- β- lactamases) and numerous class D enzymes).

Ceftazidime- avibactam resistance has also been observed in strains with mutations in AmpC or carbapenemase enzymes. Some cases of ceftazidime- avibactam resistance have been linked to mutations in plasmid- borne KPC- 3 Interestingly, it was set up that some KPC- 3 mutations that conferred ceftazidime- avibactam resistance were associated with diminishments in the

MICs for carbapenems and other β- lactam antibiotics. Avycaz was estimated in four active- controlled clinical trials in cases with cIAI or cUTI, including pyelonephritis. These trials included two phase 2 trials, one in cIAI and one in cUTI, as well as two phase 3 trials, one in cIAI and one in cIAI or cUTI due to ceftazidime- resistant pathogens. The four clinical trials included a total of 862 adult cases treated with Avycaz and 866 cases treated with comparators.8 Data from the two most recent trials(phase 3 for cIAI and phase 2 for cUTI) follow.

CONCLUSION

A aggregate of 15 cases were tested for susceptibility to ceftazidime avibactam for verified CRE infection. And 3 cases out of 15 cases had CREs sensitive to ceftazidime - avibactam, and 22 of cases hab ceftazidime avibactam resistance.

ceftazidime- avibactam is the only medicine showing exertion against OXA-48-like directors. Hence, it's being decreasingly used in India to treat infections caused by carbapenem- resistant

Enterobacteriaceae(CRE), especially as a colistin- sparing agent.

The addition of avibactam to ceftazidime improves its activity against Enterobacteriaceae and P.

aeruginosa because avibactam inhibits isolates with serine ß- lactamases, including ESBL, AmpC, and KPC enzymes. still, avibac tam doesn't ameliorate the exertion of ceftazidime against Acinetobacter spp., Burkholderiaspp., or most anaerobic Gramnegative rods. Pharmacodynamic data indicate that ceftazidime- avibactam is bactericidal at attention attainable in mortal serum.

Beast studies demonstrate that ceftazidime- avibactam is effective in ceftazidime-resistant Gram-negative septicemia, meningitis, pyelonephritis, and pneumonia. The limited clinical trials published to date have reported that ceftazidime- avibactam is as effective as remedy with a carbapenem in complicated urinary tract infection and complicated intra-abdominal infection(com bined with metronidazole), including infection caused by cephalosporin- resistant Gram-negative isolates. Safety and tolerability of ceftazidime- avibactam in clinical trials has been excellent, with many serious medicine-related adverse events and reported; published data suggest that no fresh consider ations

need to be taken when dosing ceftazidime avibactam compared to ceftazidime alone. Given the abundant clinical experience with ceftazidime and the significant enhancement that avibactam provides in its exertion against contemporary B- lactamase- producing Gram-negative pathogens, it's likely this new combination agent will play a part in the empiric monotherapy of complicated urinary tract infection caused or suspected to be caused by antimicrobial- resistant pathogens(eg, ESBL-, AmpC-, or KPC- producing Enterobacteriaceae and multidrug- resistantP. aeruginosa), and in combination with metronidazole for polymicrobialintra-abdominal infec tions. Ceftazidime- avibactam may also represent salvage remedy after treatment failure with a third- generation cepha losporin or for proved infections due to Gram-negative bacilli producing ESBL, KPC, and/ or AmpC enzymes. In addition, because of its increased exertion versusP. aerugi nosa, it may prove useful in the treatment of suspected and provedP. aeruginosa infections. Implicit unborn uses may include sanitarium- acquired pneumonia(in combination with antistaphylococcal andanti-pneumococcal agents) or treatment of skin and soft towel infections caused by antimi crobial- resistant Gram-negative pathogens(eg, diabetic bottom infections), but further clinical trials are needed.

Avycaz, a combination of ceftazidime and avibactam, is the fifth anti bacterial medicine to be designated as a QIDP. It's FDA approved for the treatment of complicatedintraabdominal infections and urinary tract infections, including pyelonephritis. The combination of the cephalosporin and non – beta- lactam beta-lactamase asset increases the half- life of ceftazidime, which equates to a longer duration of action in the body. With its effectiveness against numerous medicine- resistant, gram-negative bacteria and its unique action against carbapenemases, Avycaz is putatively

an applicable choice for the last- line treatment of life- hanging infections. New carbapenemase- asset combinations(ceftazidime/ avibactam and imipenem/ relebactam) parade the stylish exertion against KPC- producing CRE. The polymyxins, amikacin, and tigecycline parade the stylish exertion against VIM- producing CRE. Meropenem in combination with polymyxin B is bactericidal and synergistic when the meropenem MIC is ≤ 32 mg/ L, and meropenem should noway be administered after polymyxinB. Meropenem and amikacin is bactericidal and synergistic when the amikacin MIC is ≤ 16 mg/L. Etest strips shouldn't be used for characterizing polymyxin B or colistin exertion. Clinicians should be apprehensive that automated testing systems may produce poisoned vulnerability results relative to the gold standard system, broth microdilution, which may impact interpretation of in vitro results.

REFERENCES

1. Munoz-Price LS, Poirel L, Bonomo RA, et al. Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. Lancet Infect Dis. 2013;13(9):785-796.

doi:10.1016/S1473 3099(13)70190-7

2. Bush K. Alarming B-lactamase-mediated resistance in multidrug-resistant Enterobacteriaceae. CurrCurr Opin Microbiol.

2010;13(5):558-564. doi:10.1016/j.mib.2010.09.006

3. Martinez RM, Wolk DM. Bloodstream Infections. In: Diagnostic

Microbiology of the Immunocompromised Host, Second Edition.

Vol 4. American Society of Microbiology; 2016:653-689.

doi:10.1128/microbiolspec.DMIH2-0031-2016

4. Iwashyna TJ, Cooke CR, Wunsch H, Kahn JM. Population burden of long-term survivorship after severe sepsis in older

Americans. J Am Geriatr Soc. 2012;60(6):1070-1077.

doi:10.1111/j.15325415.2012.03989.x

5. Stevenson M, Pandor A, James MM-S, et al. Background and definition of the decision problem. 2016.
https://www.ncbi.nlm.nih.gov/books/NBK368614/. Accessed
January 19, 2019.

6. Prescott HC, Langa KM, Liu V, Escobar GJ, Iwashyna TJ.
Increased 1-Year Healthcare Use in Survivors of Severe Sepsis.
Am J Respir Crit Care Med. 2014;190(1):62-69.
doi:10.1164/rccm.201403 04710C

7. Tacconelli E, Carrara E, Savoldi A, Kattula D, Burkert F. Global
Priority List of Antibiotic-Resistent Bacteria to Guide Research,
Discovery and Development of New Antibiotics.; 2017.
https://www.who.int/medicines/publications/WHO-PPL-Short Summary_25Feb
ET_NM_WHO.pdf?ua=1. Accessed January 19,
2019.

8. Neuner EA, Yeh J-Y, Hall GS, et al. Treatment and outcomes in carbapenem-resistant Klebsiella pneumoniae bloodstream infections. Diagn Microbiol Infect Dis. 2011;69(4):357-362.

doi:10.1016/j.diagmicrobio.2010.10.013

9. Boucher HW, Talbot GH, Benjamin DK, et al. 10 x '20

Progress--Development of New Drugs Active Against GramNegative Bacilli: An Update From the Infectious Diseases Society of America. Clin Infect Dis. 2013;56(12):1685-1694. doi:10.1093/cid/cit152

10. van Duin D, Lok JJ, Earley M, et al. Colistin Versus

Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae. Clin Infect Dis.

2017;66(2):163-171. doi:10.1093/cid/cix783

11.Rao G, Li J, Garonzik S, Nation R, Forrest A. Assessment and modelling of antibacterial combination regimens. Clinical

Microbiology and Infection. 2018;24(7):689-696. doidoi:10.1016/j.cmi.2017.12.004.

12. Allergan G. AVYCAZ Highlights of Prescribing Information.;

2018.

6. 2019. Avycaz (ceftazidime/avibactam) [prescribing information]. Irvine, CA: Allergan USA Inc; March 2019.

7. Abraham, E.P., Chain, E., 1940. An Enzyme from Bacteria

Able to Destroy Penicillin. Nature 946.

8. American Society for Microbiology. Antimicrobial Resistance: An Ecological Perspective. 2000. Website http://www.asm.org/academy/index.asp?bid=2167.

Access April, 2007. Animal Health Institute (AHI), 2000.

Survey Indicates most Antibiotics used in

9. Anonymous. Antimicrobial Resistance: Implications for the Food System. An Expert Report: July 2006, Funded by the IFT Foundation Comprehensive Reviews in Food

Science and Food Safety 5 (3), 71-137.

10. Berge, A.C.B., Atwill, E.R., Sischo, W.M., 2005. Animal and farm influences on the

11. dynamics of antibiotic resistance in faccal Escherichia coli in young dairy calves.

12. Preventive Veterinary Medicine. 69, 25-38.CDC, 1999.

Four Pediatric Deaths from Community-Acquired

Methicillin-Resistant Staphylococcus Aureus - Minnesota
and North Dakota, 1997-1999. MMWR, 707 CDC, 2002.

Inventory of Projects - DRAFT Progress Report: Implementation of "A Public Health Action Plan to Combat

Antimicrobial Resistance - Part I: Domestic Issues".

13. CLSI, 2006a. Performance Standards for Antimicrobial Susceptibility Testing: Sixteenth Informational

Supplement. CLSI document M100-S16.

14. CLSI, 2006b. Methods for Dilution Antimicrobial

Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard--Seventh Edition. CLSI document M7-

A7.

15. Cripps, C.J., Warnick, L.D., Ray, K.A., Nydam, D.L., McDonough, P.L., Grohn, Y.T., Reed, K.E., 2006. Incidence of Clinical Salmonellosis in Northeastern USA

Dairy Herds. The Eleventh Annual International.
Symposium on Veterinary Epidemiology and Economics,

Cairns, Australia.

16. Davis, M. A., Hancock, D. D., Besser, T. E., Rice, D. H., Gay, J. M., Gay, C., Gearhart, L. and DiGiacomo, R. 1999. Changes in antimicrobial resistance among