CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
http://doi.org/10.5281/zenodo.4071258

Available online at: http://www.iajps.com *Review Article*

A REVIEW ON BETA LACTAM ANTIBIOTICS

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Article Received: August 2020 **Accepted:** September 2020 **Published:** October 2020

Abstract
The β-lactam antibiotics are a large class of diverse compounds used clinically in both the oral and parenteral forms. The β-lactam antibiotic agents have become the most widely used therapeutic class of antimicrobials because of their broad antibacterial spectrum and excellent safety profile. Reports of drug–drug interactions with the β-lactam antimicrobials are a relatively rare phenomenon, and when interactions do occur, they are generally minor. β-lactam antibiotics act by inhibiting the bacterial cell wall biosynthesis; they are the most available antibiotics which treat a number of bacterial infections. For having a global positive impact on health by treating bacterial infections, penicillin and other β-lactam antibiotics are arguably considered the most important drugs ever.
Key words *- Resistance to β-lactam activity*

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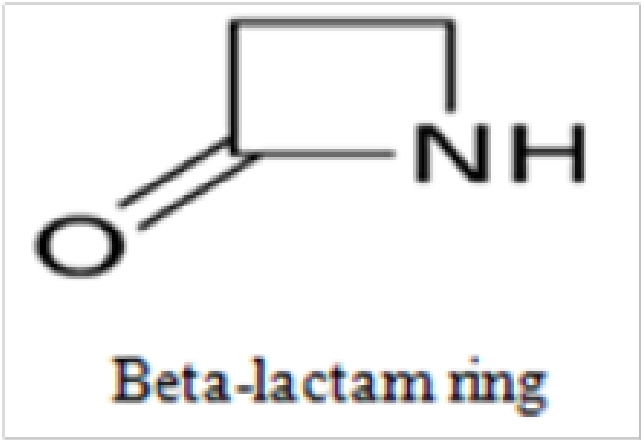
Please cite this article in press Nishad V M et al, ***A Review On Beta Lactam Antibiotics.,*** *Indo Am. J. P. Sci, 2020; 07(10).*

INTRODUCTION:

The concept that involves the use of chemicals to alleviate disease date back to the ancient Egypt One of the major significant advances in medicine is the development of antibiotics. Antibiotics have saved many lives and continue to be the main therapy for infections related to bacteria. Penicillin G was the first of beta-lactam developed which lead the search for the synthesis of additional derivatives. The quest gave result to the beta-lactam antibiotics in clinical application today. the class of broad-spectrum antibiotics that consist of all antibiotic agents with beta-lactam ring in their structures is called β-lactam antibiotics. It includes penicillin derivatives, monobactams, cephalosporin and carbapenems[1,]

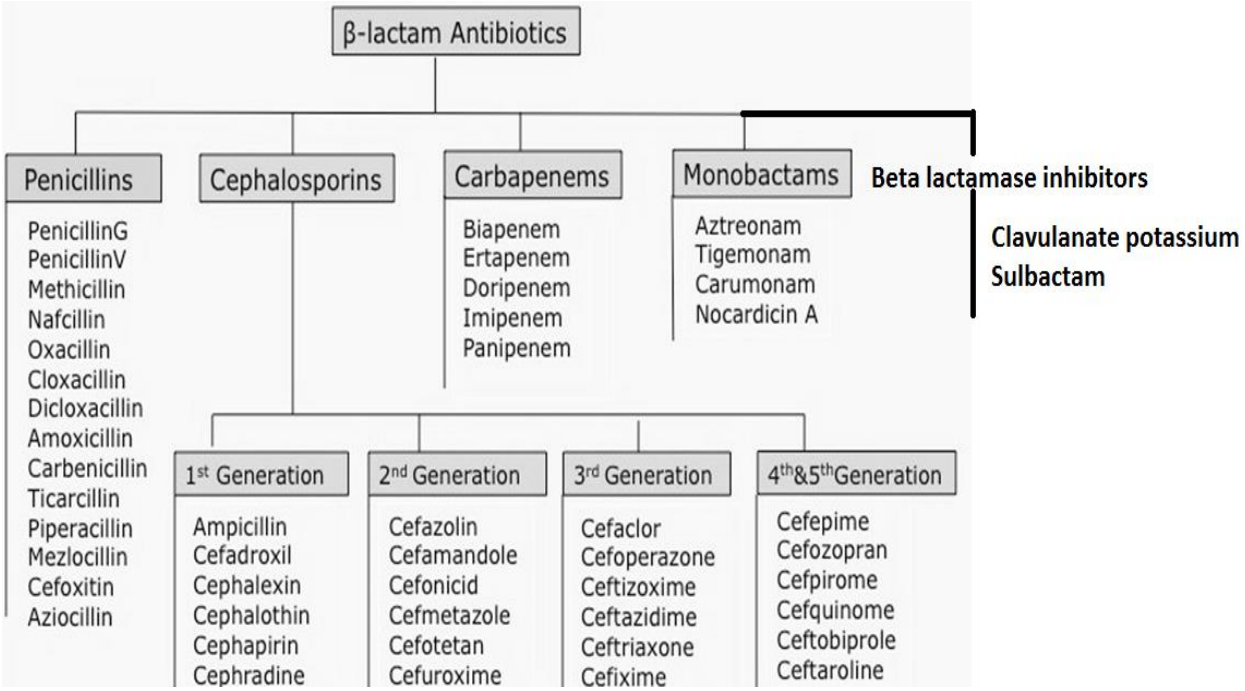
β-lactam antibiotics act by inhibiting the bacterial cell wall biosynthesis; they are the most available antibiotics which treat a number of bacterial infections. For having a global positive impact on health by treating bacterial infections, penicillin and other β-lactam antibiotics are arguably considered the most important drugs ever. A broad spectrum of bacteria can be killed by β-lactams and its toxicity to humans is very low this implies that, the resistance to β-lactam antibiotics is severe threat, bacteria and other infection causing microbes are remarkably developed several ways to become resistant to antibiotics and other antimicrobial drugs. This is as a result mainly of increase use and misuse of the antibiotics in different medical illnesses. nowadays, about. It was reported that 70% of the bacteria causing infections in hospitals are resistant to at one or more of the commonly used drugs, some bacteria are found to be resistant to almost all antibiotics that are approved and can be treated only by some drugs that are potentially toxic. There have been reports which are documented about the alarming increase in bacterial antibiotic resistance which cause community acquired infections, examples include the *staphylococci* and *pneumococci* which are major causes of disease and mortality.High prevalence of bacterial resistance to various pathogens such as *Acinetobacter*, *Proteus*, *E.coli*, *Klebsiella* and *Pseudomonas*.

β-lactam antibiotic resistance however has become a major health care issue. The reactions that involve the cleavage of the β-lactam ring of the antibiotic by β-lactamases of bacteria is the primary mechanism of β-lactam resistance.11 the cell wall of bacteria consists of Peptidoglycan which is a giant polymer of repeated chains of disaccharides joined by peptide bridges. The joining results from a transpeptidation reaction catalysed by enzymes which are inhibited by β-lactams. The enzymes responsible for the assembly of peptidoglycan are known as PBPs2 or penicillin-binding proteins. They consist of penicillin-binding domain which generally catalyses the transpeptidation reaction, but can also act as a endopeptidase or carboxypeptidase in some cases[3,4]



Beta-lactam ring

Classification



PENICILLINS

Natural penicillins [Penicillin G (IV), Penicillin V (PO)] are used to treat selected gram-positive and gram-negative infections:

Penicillin susceptible *Streptococcus pneumonia* and meningitis Streptococcal pharyngitis Endocarditis

Skin and soft tissue infections

Neisseria meningitides infections

Syphilis

PENICILLINASE RESISTANT PENICILLINS

These agents [oxacillin (IV), nafcillin (IV), dicloxacillin (PO)] are active against gram-positive organisms. Despite the occurrence of widespread resistance among staphylococci, they remain antibiotics of choice in managing methicillinsusceptible staphylococci (MSSA):

Skin and soft tissue infections (MSSA)

Serious infections due to MSSA

AMINOPENICILLINS

These antibiotics have activity against gram-positive and gram-negative bacteria (e.g., many *Enterobacteriaceae*) anaerobic organisms.

They are commonly used together with beta-lactamase inhibitors. Amoxicillin (PO), ampicillin (PO/IV):

Upper respiratory tract infections (sinusitis, pharyngitis, otitis media) *Enterococcus faecalis* infections Listeria infections Aminopenicillins/beta-lactamase inhibitors: amoxicillin/clavulanate (PO), ampicillin-sulbactam (IV)

Upper respiratory tract infections (sinusitis, otitis media) Intra-abdominal infections

CARBOXYPENICILLINS AND UREIDOPENICILLINS

Ticarcillin (carboxypenicillin) and piperacillin (ureidopenicillin) have activity against aminopenicillin-resistant gram-negative bacilli (*Pseudomonas aeruginosa*).

Are commonly combined with beta-lactamase inhibitors

CEPHALOSPORINS

First-generation cephalosporins

Cefazolin (IV), cephalexin (PO), cefadroxil (PO)

Skin and soft tissue infections serious infections due to MSSA

Perioperative surgical prophylaxis

Second-generation cephalosporins

Cefuroxime (IV/PO), cefoxitin (IV), cefotetan (IV), cefaclor (PO) cefprozil (PO)

Upper respiratory tract infections (sinusitis, otitis media)

Cefoxitin, cefotetan-gynecologic infections, perioperative

surgical prophylaxis

Third-generation cephalosporins

Cefotaxime (IV), ceftriaxone (IV), cefpodoxime (PO), cefixime (PO), cefdinir (PO), cefditoren (PO),

ceftibuten (PO) Community-acquired pneumonia, meningitis Urinary tract infections Streptococcal endocarditis Gonorrhea Severe Lyme disease. [5,6]

Anti-pseudomonal Cephalosporins
Ceftazidime (IV), ceftolozone/tazobactam (IV), ceftazidime/avibactam (IV), cefepime (IV) Nosocomial infections-pneumonia Meningitis Urinary tract infections Intra-abdominal infections (with metronidazole)

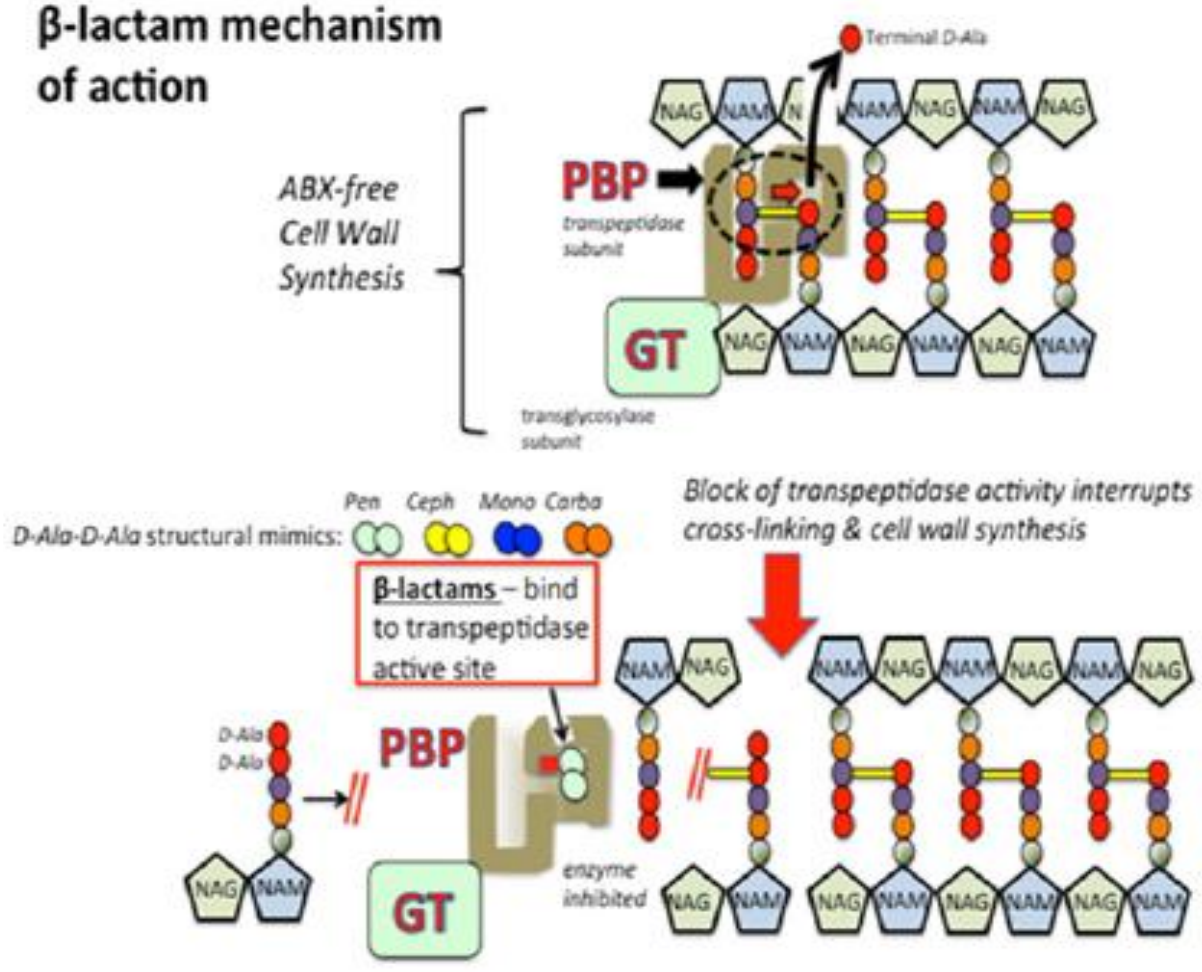
Anti-MRSA cephalosporins- Ceftaroline (IV) Community-acquired pneumonia Skin and soft tissue infection

CARBAPENEMS
Imipenem/cilastatin (IV), meropenem (IV), doripenem (IV)
Nosocomial infections-pneumonia, intra-abdominal infections, urinary tract infections Meningitis (especially meropenem) Ertapenem (IV) Community-acquired infections Nosocomial infections.

MONOBACTAMS
Aztreonam (IV). It is effective against aerobic gram-negative organisms but shows no activity against gram-positive bacteria or anaerobes. Nosocomial infections, e.g., pneumonia Urinary tract infections.

Because the emergence of antimicrobial resistance has become a progressively great concern, new beta-lactam, and betalactamase inhibitor combinations (ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, imipenem/cilastatin/relebactam, aztreonam/avibactam), siderophore cephalosporins (cefiderocol) have been developed and represent options for the management of complicated infections, especially in intensive care unit

Mechanism of action



The mechanism of action of beta-lactam antibiotics is usually by inhibiting the enzyme responsible for the bacterial cell wall synthesis.The stability of cell wall is essential for the shape and protection of the cell in hostile and hypertonic environment the cell wall is comprised of two alternating units which are the N-acetylmuramic acid (NAM) and N-acetyl glucosamine (NAG), these two units are linked together by enzyme transglycosidase. Pentapeptide is attached to each NAM unit which includes D-alaine-D-alanine. The cross-link between the two Dalanine of two NAM is catalysed by PBP. The cross-linked between the adjacent glycans gives the rigidity of the cell wall.The ring of beta-lactams antibiotics is similar to the pentapeptide's D-alaine-D-alanine of N-acetylmuramic acid, because of this similarity the penicillin binding proteins uses beta-lactam as building blocks for the synthesis of cell wall instead of NAM Pentapeptide.This result in the acylation of the enzyme PBP subsequently rendering the enzyme incapable of catalyzing further transpeptidation reactions.17 when this reaction comes to a halt, Peptidoglycans autolysis commence which result to the compromises of the integrity of the cell wall and increase its permeability .thus the beta-lactam mediated activity (inhibition) causes the lyses of the cell and the death of the bacteria.[7,8]

Resistance to β-lactam activity

There are four major ways bacteria avoid the bactericidal effect of beta-lactams

Altered Penicillin-binding proteins that exhibit relatively lowaffinity toward beta-lactam antibiotics some examples are the PBP 2_(PBP2a) of Staphylococcus aureus and PBP 2x of *Streptococcus pneumoniae*.53 penicillins are unable to inactivate these PBPs because they are relatively resistant to it and they can assume the functions of other PBPs after their deactivation. Diminished or completely lack of expression of outer membrane proteins (OMP) in gram-negative bacteria. In order to acquire access to PBPs, beta-lactam have move through porin channels in the outer membrane, decrease expression of OMPs limits the of certain beta-lactams from entry into the periplasmic space of gram-negative bacteria, therefore restrict its access to PBPs on the inner membrane. Resistance to Imipenem in *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* can arise from the loss of OmpK36 and OMP D2, respectively.54–56 It was reported that the resistance to meropenem and Imipenem in some isolate of multidrug resistant *Acinetobacter* baumannii to is associated with the loss of the CarO OMP. insertion of some sequence to porin encoding genes or its mutation can lead to the production of proteins with reduce functions and subsequently decrease the diffusion of beta-lactam into the cell.59 it is believed that the destruction of porin alone is not sufficient enough for acquiring resistance phenotype. This mechanism is usually coupled with the expression of beta-lactamases.

Efflux pumps it is a part of intrinsic resistance or acquired resistance phenotype. Efflux pumps have the capability to export various substrates from the periplasmic part of the cell to the surrounding environment.61 these pumps are the determinant of multidrug resistance in various Gram-negative bacteria especially *P. aeruginosa*. The decrease in the organism outer membrane permeability in combination with the upregulation of the mexA-mexB-OprD can contribute to decreased susceptibility to various beta-lactam antibiotics including Cephalosporin, penicillin, tetracycline, quinolones and Chloramphenicol[9,10]

Beta-lactamases Production Bacteria produce enzymes known as Beta-lactamases that hydrolyze the beta-lactam ring subsequently the beta-lactam antibiotic is rendered inactive before it get to the PBP target. because of the structural relation that beta-lactamases shares with PBP, it bind, acylate and also use water molecules to hydrolyze and inactivate beta-lactam share with PBPs allows these enzymes to bind, acylate, and use a strategically located water molecule to hydrolyze and thereby inactivate the beta-lactam.66 in gram-negative bacteria the most important resistance mechanism is the inactivation of beta-lactams by beta-lactamases. It has been reported that there are over 530 beta-lactamase enzymes (K. Bush, 9th International Congress on beta-Lactamases, Leonessa, Italy). beta-lactamases contains either serine residue or metal ion In their active site, betalactamases with a serine residue (Ambler classes A, C, D) and metal ion Zn^{2+} (Ambler class B) that attack beta-lactam ring and break the amide bond in the ring.

Serine β-lactamases have serine as an active-site which is used to hydrolyze the ring of β-lactam in β-lactam antibiotics. The serine β-lactamases are classified based on sequence similarity into three classes, A, C, and D.which are all related to the DD peptidases.

Amber class A

This class was first observed in *E.coli* in 1963 and was termed TEM; it was named after the person from whom it was isolated. This class of enzyme exhibit a level of susceptibility to many commercially available β-lactamase inhibitors like

Clavulante, Sulbactam and Tazobactam.74,75 other members of this class including VH5, PER and SHV were also reported.76 SHV-1 and TEM-1 have almost 68% sequence homology and can be found in *E.coli*, K. Pneumoniae and other pathogens responsible for various infections. TEM-t and SHV-1 confers resistance to Ampicillin and Piperacillin.

Ambler class B

These enzymes contain an enzyme a small number Zn2+ this class one of the atoms of Zinc in inactivation cephalosporins and penicillins of are MBLs that use one of two zinc (Zn2+) atoms for inactivating penicillins and cephalosporins. However, their activity can be inhibited by chelating agents (EDTA) but not by sulfones or clavulanic acid. IMP-1 was the first to be discovered in this class form *P. aeruginosa*. Varieties of genetic element such as plasmid, integron were found to have the bla genes encoding

Ambler class C

Enzymes in this class are active against cephalosporins, therefore sometimes called cephalosporinases.79 their genes are encoded in the chromosome and are mostly synthesized by Gram-negative bacteria. The sequences of these enzymes that are known are highly conserved.80 The cephalosporin-hydrolyzing chromosomal β-lactamase of his class in *P. aeruginosa* are encoded by ampC (PA4110), which was cloned and sequenced.

Amber class D

The enzymes in this class are capable of degrading isoxazolyl β-lactams like methnicillin and oxacillin. Thus they are also called oxacillinases.82 however their activity is inhibited by clavulanic acid.

Overcoming β-lactamases

There are basically two ways to overcome the effect of hydrolytic activity of beta-lactamases. The first principle involves getting molecules that inactivate or inhibit beta-lactamases. Sulbactam, clavulanic acid and tazobactam-lactamase are the three inhibitors that are used in the clinical application. All of these three compounds share similar structures with penicillin. Some of the features of these compounds include high affinity for β-lactamases, each of these compounds occupies the active site relatively longer than β-lactams and undergoes different reaction chemistry and they are also poorly hydrolyzed by the enzyme.84–86 therefore, β-lactamase inhibitors are also called "suicide inhibitors" because they get trapped by the beta-lactamase. This phenomenon has been the subject of research by academic laboratories and some pharmaceutical companies.87–93 synthesis of compounds by substituted sulfones, cephem and penem gives optimism that new inhibitors of β-lactamase will be found.94 The Recent research studies that are being carried out to elucidate the mechanistic details of beta-lactamase inhibition of deacylation-deficient beta-lactamases will surely advance the knowledge of the chemistry of inactivation.[11,12,13]

The second principle involves getting a new beta-lactam antibiotic that possesses great affinity for the β-lactamases and cannot behydrolyzed by the PBP, or poorly hydrolyzed by it. This has been the original rationale behind extended-spectrum carbapenems or cephalosporins. Common example of this principle is the development of compounds such as doripenem and ceftobiprol**.** Ceftobiprole is an "anti-MRSA cephalosporin" which demonstrates very high affinity for PBP2, it is active against gram-negative bacteria possessing betalactamases and resistant to penicillinase of *S. aureus* and is.96 Doripenem is a modified carbapenem with sulfamoylaminomethyl substituted pyrrolidylthio group at the C2 position and 1-beta-methyl group, which shows very high activity against *Acinetobacter* spp, *P. aeruginosa* and Burkholderia cepacia.

Sulbactam

Sulbactam known as a semi synthetic substance capable of inactivating β-lactamases though it is not as potent as Clavulanic acid it shows high activity against class ii-iv and displays relatively low action against class1β-lactamase. The combination of sulbactam with some antibiotics tends to increase their activity against antibiotic resistant bacteria for example; the antibacterial activity of ampicillin will be extended and becomes more effective when it is combining with sulbactam. A compound was developed containing sulbactam-ampicillin known as sultamicillin was found clinically effective in treatment of various infections such as those of skin and soft tissues as well as many other infections. it was also reported that a single dose of ampicillin-sulbactam administered intra-muscularly with probenecid had therapeutic effect against infections of neisseria gonorrhae which is an ampicillin resistant.

Tazobactam

Piperacillin combined with tazobactam was first prepared in 1993 in the United state. piperacillin is known to have antibiotic activity against gram-negative and gram-positive as well as aerobes and anaerobes. piperacillin-tazobactam combination act as a good β-lactamase inhibitor with broad spectrum of antibacterial activity in both gram-negative and

gram-positive bacteria. But such combination has no inhibition effect against isolates of gram-negative bacillus having AmpC β-lactamase. Piperacillin-tazobactam combination is reported to be effective for treatment of various infections including intra-abdominal infections.

Clavulanic acid

Ticarcillin-clavulanate was the first combination β-lactam β-lactamase inhibitor developed in 1985 for parenteral administration. It increases the inhibitory activity against -lactamase-producing *staphylococci*, *Proteus* spp, H. influenzae, *Pseudomonas* spp, *Klebsiella* spp *Providencia*, and *E. coli*.101 the combination of amoxicillin to clavulanic acid increases the organism susceptibility to amoxicillin like amoxicillin resistant *Haemoehilus influenza* and *Neisseria gonorrhea*.[14.15.16]

Adverse Effects

Compared to other classes, beta-lactam agents are usually safe and well-tolerated. The most frequent side effects are allergic reactions that vary from 0.7% to 10%. These reactions are mostly maculopapular rashes, whereas reports of anaphylaxis appear in 0.004 to 0.015% of patients.

Penicillins

A hypersensitivity reaction is the most common adverse effect ranging from a maculopapular rash to angioedema,
serum sickness, and anaphylaxis.
It may occur with any dosage form of penicillin.
Other side effects include bone marrow depression, granulocytopenia, and hepatitis.

Cephalosporins

A hypersensitivity reaction is the most common. Nephrotoxicity, diarrhea, and biliary pseudolithiasis can occur with
some cephalosporins.

Carbapenems

Nausea, vomiting, seizures, especially with imipenem at high doses.

Monobactams

Hepatotoxicity, especially in infants and young children.

CONCLUSION:

The mechanism of action of beta-lactam antibiotics is usually by inhibiting the enzyme responsible for the bacterial cell wall synthesis subsequently resulting in the lysis and death of the bacteria. Unfortunately, bacteria have developed resistance to β-lactam antibiotics through a defense mechanisms to protect themselves against the effect of the antibiotics by Altered Penicillin-binding proteins that exhibit relatively low affinity toward beta-lactam antibiotics, diminished or completely lack of expressionof outer membrane proteins (OMP) in gram-negative bacteria, Efflux pumps it is a part of intrinsic resistance or acquired resistance phenotype and by beta-lactamases Production which plays the major role in resistance mechanism by hydrolyzing the beta-lactam ring subsequently the beta-lactam antibiotic is rendered inactive before it get to the PBP target. Betalactams may be common, but their effective use still requires an interprofessional team approach for optimal patient outcomes.

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