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Chemistry, mode of action, bacterial resistance, classification and adverse effects of beta-lactam antibiotics: A review

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Abstract
Beta-lactam antibiotics are heterocyclic compounds which contains saturated β-lactam ring (monobactam) or a bicyclic ring, in which a β-lactam ring fused to saturated or unsaturated five membered rings and unsaturated six membered ring. β-lactam antibiotics are a broad class of antibiotics, consisting of cephalosporins, penicillin derivatives, monobactams and carbapenems. Most β-lactam antibiotics have been used for treatment of bacterial infections by inhibiting cell wall biosynthesis in the bacterial organism and are the most widely used group of antibiotics. This review is aimed to discuss the chemistry, adverse effect, classification and activities of various classes of the beta lactam antibiotics.

Keywords: Antibiotics, beta-lactam, carbapenems, cephalosporins, penicillins

Introduction
Antibiotics are defined as chemical substances produced by microorganism species that possess bactericidal or bacteriostatic properties. The term antibiotic is more comprehensive and includes also semi-synthetic drugs [1]. The first researchers to ever recognize the clinical potential of microorganisms and their products as therapeutic agents were Pasteur and Joubert in 1877. They observed that the anthrax bacillus grew rapidly when inoculated into sterile urine but failed to multiply. They also immediately died if ordinary bacteria from the air were simultaneously inoculated into the urine. Similar results were achieved through the same kind of experiences in animals. They then stated that life destroys life much more among inferior beings than among superior ones and arrived to the conclusion that anthrax bacillus could be massively administered in animals without causing any kind of wound as long as "ordinary bacteria" were also inoculated in the animal at the same time. They realized that this remark could be highly promising for therapeutics development [2].
In 1928, Alexander Fleming, then Director of Inoculation at St Mary Hospital in Paddington, London, observed that some Staphylococcus-inoculated Petri dishes forgotten on the lab counter early-summer were accidently infected by a fungus called Penicillium notatum. He also noticed a transparent halo around the contaminating mold which indicated lysis and a reduced growth rate of the Staphylococcus colonies. This seemed to indicate that the fungus could produce some bactericidal compound. In 1932, Fleming published the complete results of his work on identifying a new antimicrobial agent from Penicillium notatum's metabolites. He named the new antibacterial as penicillin in reference to the penicillium gender. At first, Fleming findings didn't sparkle interests and there was no intent of using them therapeutically until the Second World War unfolded [3, 4].
β-lactam antibiotics (beta-lactam antibiotics) are a class of broad-spectrum antibiotics, consisting of all antibiotic agents that contain a beta-lactam ring in their molecular structures. This includes penicillin derivatives (Penams), cephalosporins (Cephems), monobactams, and carbapenems. Most β-lactam antibiotics work by inhibiting cell wall biosynthesis in the bacterial organism and are the most widely used group of antibiotics. Until 2003, when measured by sales, more than half of all commercially available antibiotics in use were β-lactam compounds [5].

Bacteria often develop resistance to β-lactam antibiotics by synthesizing a β-lactamase, an enzyme that attacks the β-lactam ring. To overcome this resistance, β-lactam antibiotics are often given with β-lactamase inhibitors such as clavulanic acid.

Mode of Action of β - Lactam Antibiotics

Penicillin and most other β-lactam antibiotics act by inhibiting penicillin-binding proteins, which normally catalyze cross-linking of bacterial cell walls. In the absence of β-lactam antibiotics, the bacterial cell wall plays an important role in bacterial reproduction. Adding β-lactam antibiotics to the cell medium while bacteria are dividing will cause them to shed their cell walls and fail to divide, forming large, fragile spheroplasts. β-lactam antibiotics are bactericidal, and act by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls. The peptidoglycan layer is important for cell wall structural integrity, especially in Gram-positive organisms, being the outermost and primary component of the wall. The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by DD-transpeptidases which are penicillin binding proteins (PBPs). PBPs vary in their affinity for binding penicillin or other β-lactam antibiotics. The amount of PBPs varies among bacterial species [6].

β-lactam antibiotics are analogues of d-alanyl-d-alanine-the terminal amino acid residues on the precursor N-acetylmuramic acid/N-acetylglucosamine (NAM/NAG)-peptide subunits of the nascent peptidoglycan layer. The structural similarity between β-lactam antibiotics and d-alanyl-d-alanine facilitates their binding to the active site of PBPs. The β-lactam nucleus of the molecule irreversibly binds to (acylates) the Ser_{403} residue of the PBP active site. This irreversible inhibition of the PBPs prevents the final crosslinking (transpeptidation) of the nascent peptidoglycan layer, disrupting cell wall synthesis [6].

β-lactam antibiotics block not only the division of bacteria, including cyanobacteria, but also the division of cyanelles, the photosynthetic organelles of the glaucophytes, and the division of chloroplasts of bryophytes. In contrast, they have no effect on the plastids of the highly developed vascular plants. This is supporting the endosymbiotic theory and indicates an evolution of plastid division in land plants [7]. Under normal circumstances, peptidoglycan precursors signal a reorganisation of the bacterial cell wall and, as a consequence, trigger the activation of autolytic cell wall hydrolases. Inhibition of cross-linkage by β-lactams causes a build-up of peptidoglycan precursors, which triggers the digestion of existing peptidoglycan by autolytic hydrolases without the production of new peptidoglycan. As a result, the bactericidal action of β-lactam antibiotics is further enhanced.

Modes of Resistance of β - Lactam Antibiotics

By definition, all β-lactam antibiotics have a β-lactam ring in their structure. The effectiveness of these antibiotics relies on their ability to reach the PBP intact and their ability to bind to the PBP. Hence, there are two main modes of bacterial resistance to β-lactams:

a. Enzymatic hydrolysis of the β-lactam ring

If the bacterium produces the enzyme β-lactamase or the enzyme penicillinase, the enzyme will hydrolyse the β-lactam ring of the antibiotic, rendering the antibiotic ineffective. (An example of such an enzyme is New Delhi metallo-beta-lactamase 1, discovered in 2009.) The genes encoding these enzymes may be inherently present on the bacterial chromosome or may be acquired via plasmid transfer (plasmid-mediated resistance), and β-lactamase gene expression may be induced by exposure to β-lactams.

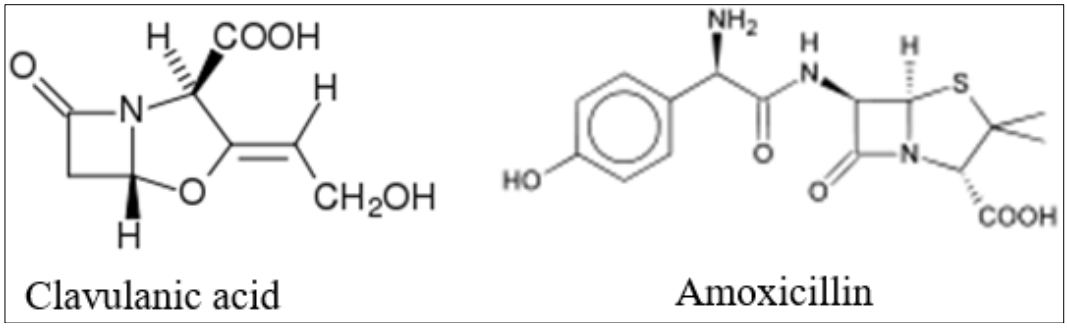

Fig 1: Structures of Clavulanic acid and Amoxicillin

The production of a β-lactamase by a bacterium does not necessarily rule out all treatment options with β-lactam antibiotics. In some instances, β-lactam antibiotics may be co-administered with a β-lactamase inhibitor. For example, Augmentin (FGP) is made of amoxicillin (a β-lactam antibiotic) and clavulanic acid (a β-lactamase inhibitor). The clavulanic acid is designed to overwhelm all β-lactamase enzymes, and effectively serve as an antagonist so that the amoxicillin is not affected by the β-lactamase enzymes [8].

Other β-Lactamase inhibitors such as boronic acids are being studied in which they irreversibly bind to the active site of β-lactamases. This is a benefit over clavulanic acid and similar beta-lactam competitors, because they cannot be hydrolyzed, and therefore rendered useless. Extensive research is currently being done to develop tailored boronic acids to target different isozymes of beta-lactamases [8]. However, in all cases where infection with β-lactamase-producing bacteria is suspected, the choice of a suitable β-lactam antibiotic should be carefully considered prior to treatment. In particular, choosing appropriate β-lactam antibiotic therapy is of utmost importance against organisms which harbor some level of β-lactamase expression. In this case, failure to use the most appropriate β-lactam antibiotic therapy at the onset of treatment could result in selection for bacteria with higher levels of β-lactamase expression, thereby making further efforts with other β-lactam antibiotics more difficult [8].

b. Possession of altered penicillin-binding proteins

As a response to increased efficacy of β-lactams, some bacteria have changed the proteins to which β-lactam antibiotics bind. β-lactams cannot bind as effectively to these altered PBPs, and, as a result, the β-lactams are less effective at disrupting cell wall synthesis. Notable examples of this mode of resistance include methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae*. Altered PBPs do not necessarily rule out all treatment options with β-lactam antibiotics [8].

Classification of β -Lactam Antibiotics

a. Cephalosporins

Cephalosporins are β-lactam antibiotics differ from the penicillins in such that the ring is a 6 membered dihydrothiazine ring (Figure 2). Variations among the cephalosporins are made on either the acyl side chain at the 7-position to change antibacterial activity or at the 3-position to alter the pharmacokinetic profile. The cephalosporins inhibit bacterial cell wall synthesis by blocking the transpeptidases [9]. Cephalosporins are classified into five generations.

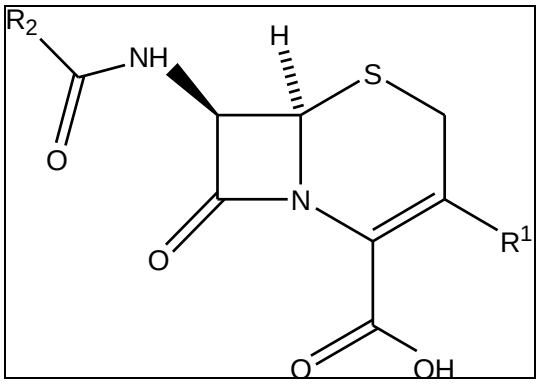

Fig 2: Structure of Cephalosporin

i. First-generation

These are most active against *aerobic* gram-positive cocci and include cefazolin, cephalexin, and cefadroxil and they are often used for skin infections caused by *S. aureus* and *Streptococcus*. They have activity against *E. coli* and some activity against *H. influenzae* and *Klebsiella* species, but because of the limited gram-negative coverage, they are not first-line agents for infections that are likely to be caused by gram-negative bacteria [10].

ii. Second-generation

These are more active against gram-negative organisms, such as *Moraxella*, *Neisseria*, *Salmonella*, and *Shigella*. Cefoxitin and cefotetan, also have more coverage against *anaerobic* bacteria. The true cephalosporins that are also part of this class are cefprozil, cefuroxime, cefaclor, cefoxitin, and cefotetan. These drugs are used primarily for respiratory tract infections because they are better against some strains of beta-lactamase producing *H. influenza* [10].

iii. Third-generation

These have the most activity against gram-negative organisms, including *Neisseria* species, *M. catarrhalis*, and *Klebsiella*, while ceftazidime is active against *P. aeruginosa*. These agents have less coverage of the gram-positive cocci, notably methicillin-sensitive *S. aureus*. In addition to the agent with antipseudomonas coverage, this class includes cefdinir, cefditoren, cefixime, cefotaxime, cefpodoxime, ceftibuten, and ceftriaxone. These drugs are useful for more severe community-acquired respiratory tract infections, resistant infections, and nosocomial infections (because of the high incidence of resistant organisms) [10].

iv. Fourth-generation

Cefepime is involved in this class because it has good activity against both gram-positive and gram-negative bacteria, including *P. aeruginosa* and many Enterobacteriaceae. The gram-negative and anaerobic coverage makes cefepime useful for intra-abdominal infections, respiratory tract infections, and skin infections [10].

v. Fifth-generation

Ceftaroline fosamil is the only advanced generation cephalosporin; it has enhanced activity against many both gram-negative and positive bacteria. It is active against community-acquired pneumonia infections caused by *E. coli*, *H. influenzae*, *Klebsiella*, *S. aureus* (methicillin-susceptible isolates only), and *S. pneumoniae* and safe for treating skin infections caused by multidrug-resistant *S. aureus* [11].

Activity of Cephalosporins

In general, the first generation oral cephalosporins have more gram-positive coverage, while the second which includes, cefamandole, cefonicid, ceforanide, and cefuroxime. Cefaclor and cefuroxime axetil are the only orally available second-generation cephalosporins. These antibiotics are usually active against the same organisms, but they have more activity against certain *aerobic* gram-negative bacteria and *H. influenzae*. Cefaclor is generally less active against gram-negative bacteria than the other agents. *In vitro*, cefmetazole and cefotetan have been shown to be slightly less active than cefoxitin against *Bacteroides* species, Third generation oral cephalosporins have broad spectrum gram-negative coverage. The only orally available third-generation cephalosporin is cefixime. Ceftizoxime and cefotaxime exhibit some activity against *B. fragilis* and other *anaerobes* [12].

b. Penicillin

These are natural or synthetic antibacterial agents derived from fungi. All penicillins share three basic chemical components: A thiazoldine ring, an attached beta-lactam ring and a side chain (Figure 3). Penicillin colonies inhibited the growth of *staphylococci* on agar plates [13]. Penicillin is classified into;

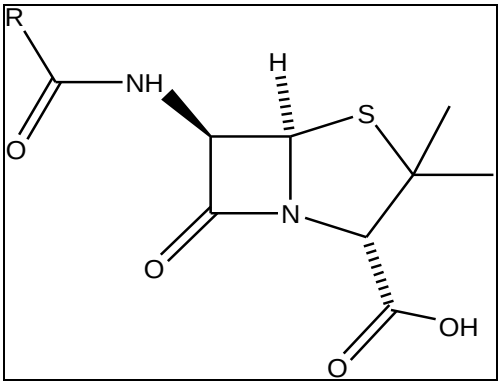

Fig 3: Structure of Penicillin

i. Natural penicillins

Penicillin G (Benzylpenicillin) for parenteral use and penicillin V (Phenoxymethylpenicillin) for oral use have the narrowest spectrum of activity. These were the first drugs introduced into clinical use. It is highly effective against susceptible organisms and achieves excellent tissue penetration, which is available in both oral and parenteral form, while penicillin V, the other natural penicillin is stable in gastric secretions, making it the drug of choice when oral administration of natural penicillin is desirable and should be used only in mild, localized infections caused by susceptible organisms. Penicillin V is still considered the drug of choice for *streptococcal pharyngitis* [13].

ii. Penicillinase Resistant Penicillins

This group of drugs achieves their effectiveness by the addition of a large side chain to the penicillin molecule, which prevents penicillinase produced by *staphylococcus* from entering the penicillin molecule and cleaving the beta-lactam ring. Methicillin is the prototype for these drugs and nafcillin is available only for intravenous use. Also, cloxacillin and dicloxacillin are only available as oral agents, these drugs makes them useful in the treatment of mild infections of the skin and soft tissue, especially when penicillinase-producing staphylococci are the presumed or known causative agents. They may also be useful for hemolytic streptococcal pharyngitis and in pneumonia when penicillin sensitive staphylococcal infections are proven or suspected. However, dicloxacillin is particularly effective against penicillinase-producing staphylococci and is the treatment of choice for mastitis because oral administration achieves relatively high bioavailability in comparison to other drugs [14].

iii. Amino-penicillins

These penicillins have activity against gram-negative bacteria. Amoxicillin is better absorbed when administered orally than is ampicillin. However, amoxicillin achieves higher serum levels and has a longer half-life [14]. So, amoxicillin has replaced by ampicillin for oral administration. Moreover, ampicillin is the only amino-penicillin available in both parenteral and oral formulations. Also; bacampicillin has no therapeutic advantage over either ampicillin or amoxicillin and is more expensive than both. Its only advantage is seen in dosing intervals [14]. Ampicillin is optimally dosed at least every 6 hours. Both ampicillin and amoxicillin are used for prophylaxis against bacterial endocarditis and for prophylaxis prior to gastrointestinal and genitourinary procedures.

iv. Extended Spectrum Penicillins

The carboxypenicillin group includes carbenicillin and ticarcillin is used for the treatment of *P. aeruginosa* infections. However, piperacillin and the ureidopenicillins have the widest spectrums of antibacterial activity and have enhanced anti-pseudomonas activity and also useful in the treatment of nosocomial [14].

v. Amino-penicillin/beta lactamase inhibitor combinations

They are ineffective against beta-lactamase producing organisms. The addition of beta-lactamase inhibitors to the amino-penicillins was a critical step in improving their spectrums of activity. The beta lactamase inhibitors have no intrinsic antimicrobial activity [14].

Activity of Penicillins

The natural penicillins are primarily effective against aerobic, gram-positive organisms such as *streptococci*, *enterococci* and some *staphylococci* that do not produce beta lactamase. Synthetic penicillins such as the aminopenicillins and extended spectrum penicillins have increased this spectrum to include activity against some gram-negative organisms such as *H influenza*, *N. gonorrhoeae*, and *E coli* that have not developed resistance. The addition of beta lactamase inhibitors to some aminopenicillins further increases the activity making the penicillin family one of the broadest spectrum class of antibiotics [14].

c. Carbapenems

Carbapenem is considered to be the most potent and to have the widest spectrum of antimicrobial activity. Carbapenems are rapidly bactericidal. Their spectrum of antimicrobial activity includes gram-positive and gram-negative aerobic and anaerobic pathogens [15].

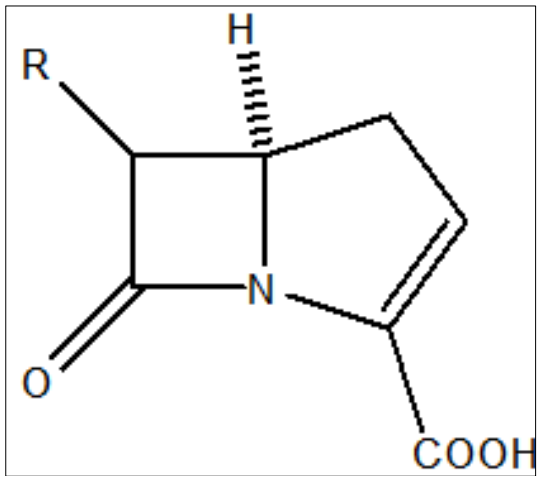

Fig 4: Structure of Carbapenems

Activity of Carbapenems

Carbapenems are active against many clinically important pathogens and are particularly stable to a wide variety of β-lactamases. They retain activity against a wide variety of multiply resistant pathogens, especially cephalosporin resistant gram-negative bacteria. However, imipenem, meropenem and ertapenem are considered to be equally active against most gram-negative and gram-positive pathogens. Imipenem and ertapenem have a wide antimicrobial spectrum with excellent activity against *anaerobic* bacteria, including *bacteroides* species. They also cover many gram-positive *cocci*, such as Enterococcus and Streptococcus, as well as many gram-negative bacteria [16]. Moreover, meropenem has somewhat greater activity against gram-negative bacteria, which are not affected by most beta-lactamases, while doripenem has good activity against *Pseudomonas aeruginosa*. Also, imipenem and ertapenem are indicated by the U.S. Meropenem is approved by the FDA for treatment of intra-abdominal infections, skin and skin structure infections, and meningitis in patients older than 3 months of age.

d. Aztreonam

Aztreonam exhibits potent and specific activity *in vitro* against a wide spectrum of gram-negative *aerobic* pathogens including *P. aeruginosa*. The bactericidal action of aztreonam results from the inhibition of bacterial cell wall synthesis due to a high affinity of aztreonam for penicillin binding protein. Aztreonam, unlike the majority of betalactam antibiotics, does not induce beta-lactamase activity and its molecular structure confers a high degree of resistance to hydrolysis by beta-lactamases (i.e, penicillinases and cephalosporinases) produced by most gram-negative and gram-positive pathogens. It is active against many strains that are multiply-resistant to other antibiotics, such as certain cephalosporins, penicillin, and aminoglycosides. Aztreonam maintains its antimicrobial activity over a pH range of 6 to 8 *in vitro*, as well as in the presence of human serum and under anaerobic conditions [17].

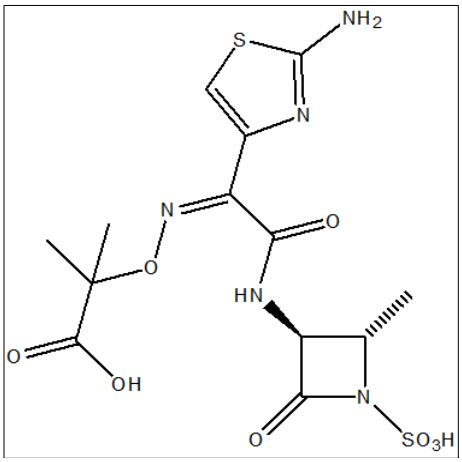

Fig 5: Structure of Aztreonam

Adverse Effects of β - Lactam Antibiotics

Common adverse drug reactions for the β-lactam antibiotics include diarrhea, nausea, rash, urticaria, superinfection (including candidiasis) [18]. Infrequent adverse effects include fever, vomiting, erythema, dermatitis, angioedema, pseudomembranous colitis. Pain and inflammation at the injection site is also common for parenterally administered β-lactam antibiotics [18]. Immunologically mediated adverse reactions to any β-lactam antibiotic may occur in up to 10% of patients receiving that agent (A small fraction of which are truly IgE-mediated allergic reactions, see amoxicillin rash). Anaphylaxis will occur in approximately 0.01% of patients [18]. There is perhaps a 5%-10% cross-sensitivity between penicillin-derivatives, cephalosporins, and carbapenems; but this figure has been challenged by various investigators. Nevertheless, the risk of cross-reactivity is sufficient to warrant the contraindication of all β-lactam antibiotics in patients with a history of severe allergic reactions (urticaria, anaphylaxis, interstitial nephritis) to any β-lactam antibiotic. A Jarisch–Herxheimer reaction may occur after initial treatment of a spirochetal infection such as syphilis with a β-lactam antibiotic [18].

Conclusion

Beta-lactam antibiotics have a bactericidal mechanism of action. They inhibit the growth of rapidly multiplying bacteria by inhibiting their cell wall synthesis; this occurs through inhibition of the enzymes responsible for cell wall biosynthesis located in the cell membrane, the most common enzyme being penicillin-binding proteins (PBPs). This binding interrupts the terminal transpeptidation process and induces, loss of viability and lysis, also through autolytic processes. Resistance to beta-lactams is an alarming and growing phenomenon. It concerns above all *Streptococcus pneumoniae* and individual gram-negative bacilli such as *Pseudomonas aeruginosa*.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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