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Anitibiotics –Beta Lactums: A Review

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Abstract:

Antibiotics are medicines that help stop infections caused by bacteria. They do this by killing the bacteria or by keeping them from copying themselves or reproducing. The word antibiotic means against life. Any drug that kills germs in your body is technically an antibiotic.

Antibiotics are classified into one of the following classes: penicillins, fluoroquinolones, cephalosporins, macrolides, beta-lactams with increased activity (e.g. amoxicillin-clavulanate), tetracyclines, trimethoprim-sulfamethoxazole, lincosamides (e.g. clindamycin), urinary anti-infectives, and other antibiotics

Beta lactum antibiotics (Penicillins, Cephalosporins, Monobactams, and Carbapenems) mainly act by interrupting bacterial cell wall formation as a result of covalent binding to essential penicillin-binding proteins (PBPs), enzymes that are involved in the terminal steps of peptidoglycan cross-linking in both Gram-negative and Gram-positive bacteria.

Key Words: Antibiotics, penicillins, fluoroquinolones, cephalosporins, macrolides, beta-lactams.

INTRODUCTION

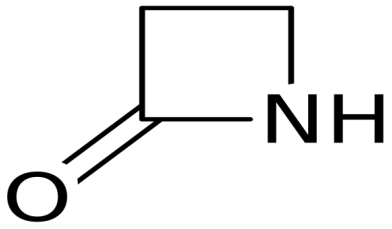
The ongoing battle against infectious diseases is widely acknowledged. The discovery of antibiotics sparked hope that infections could be managed and prevented. However, infections continue to be the primary cause of death in the developing world. This is attributed to the rise of new diseases, resurgence of previously controlled illnesses, and particularly the emergence of antimicrobial resistance. It seems inevitable that antimicrobial resistance will develop with nearly every new drug, posing a significant challenge in treating microbial infections both in medical facilities and communities. This review aims to explore the mechanisms of action and the development of resistance in commonly used antimicrobials. To achieve this, it is essential to understand the fundamental structure of bacterial cells, the categorization of antibiotics based on their mode of action, the mechanisms underlying antibiotic resistance, and the individual antibiotics alongside their typical resistance mechanisms.(1)

Antibiotics, fundamental to modern medicine, face a growing threat from antimicrobial resistance, jeopardizing global health. A seminal 2019 analysis of bacterial antimicrobial resistance underscored this,

linking 1.27 million deaths directly to resistant bacteria, with a further 4.9 million deaths associated with them.(2) Despite this urgent need for new antibiotics, the development of novel chemotypes or classes capable of overcoming existing resistance mechanisms has been impeded by the failure of the healthcare system marketplace to adequately recognize and compensate for such products.(3-5) Moreover, since 2001, branded antibiotic prices have decreased, exacerbating economic challenges.(6)

BETA LACTUM ANTIBIOTICS:

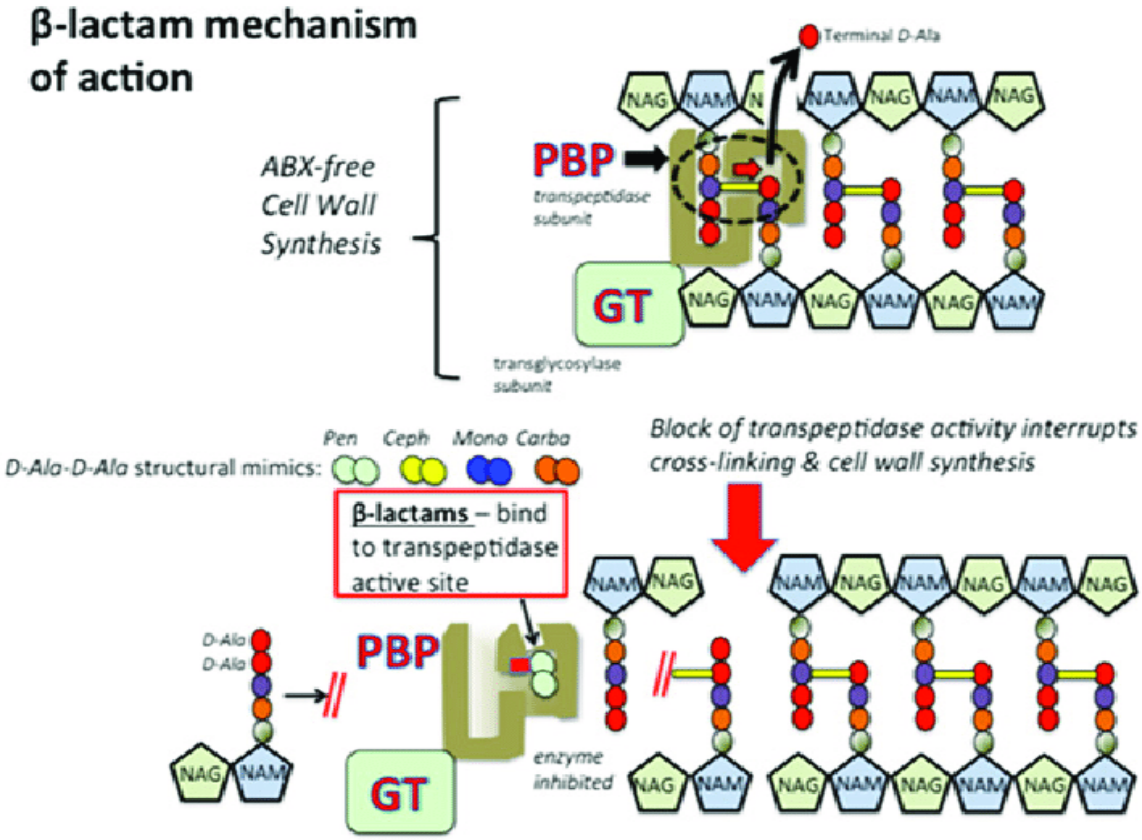
Members of this class of antibiotics contain a 3-carbon and 1-nitrogen ring that is highly reactive (Figures 1 and 2). They interfere with proteins essential for synthesis of bacterial cell wall, and in the process either kills or inhibits their growth. More succinctly, certain bacterial enzymes termed penicillin-binding protein (PBP) are responsible for cross-linking peptide units during synthesis of peptidoglycan. Members of beta-lactam antibiotics are able to bind themselves to these PBP enzymes, and in the process, they interfere with the synthesis of peptidoglycan resulting in lysis and cell death (Heesemann, 1993). The most prominent representatives of the beta-lactam class include Penicillins, Cephalosporins, Monobactams, and Carbapenems.(7)



β-lactam antibiotics (BLAs) are widely recommended and utilized for combating various infectious diseases [8]. They are characterized by either a bicyclic or monocyclic structure, both containing a four-term β-lactam nucleus, which represents their vulnerable point. Indeed, the β-lactam amide group can be enzymatically hydrolyzed by β-lactamase enzymes (BLEs), rendering the compounds devoid of antibacterial activity [9]. Stemming from natural penicillin, numerous penicillin derivatives have been developed over the past century, forming different classes of β-lactam compounds. These developments aimed to enhance potency, broaden the spectrum of activity, improve pharmacokinetic and safety profiles, and address the emergence of bacterial resistance(8) .Presently, the primary classes of β-lactams in clinical use encompass molecules characterized by a bicyclic nucleus, such as penicillin-like BLAs, cephalosporins, and carbapenems, as well as monocyclic systems like the monobactams. Notably, within the group of narrow and broad-spectrum penicillin-like BLAs, comprising 39.7% of prescriptions in the United States (USA), the four-membered β-lactam ring is fused to a thiazolidine ring .In cephalosporins (accounting for 47.5% of prescriptions in the USA), a six-membered dihydrothiazine ring is fused with the β-lactam one .while in carbapenems (making up 11.2% of prescriptions in the USA), the bicyclic system is completed by a five-membered pyrroline(8-10). Conversely, in the monocyclic monobactams, representing only 1.66% of prescriptions in the USA, the β-lactam nucleus features a sulfonic acid group attached to the nitrogen atom of the cyclic amide .(10)

MECHANISM:

SBLs and MBLs catalyze the irreversible hydrolysis of the β-lactam ring through substantially different reaction mechanisms .SBLs utilize an essential Ser residue for catalysis evolving from the mechanism of action of PBPs .An activated hydroxyl group from this residue initiates a nucleophilic attack on the amide bond of the β-lactam. This step forms a reaction intermediate called the tetrahedral intermediate, characterized by the sp3 hybridization of the carbon atom derived from the β-lactam. This species involves a covalent bond between the former carbonyl carbon of the β-lactam and the oxygen of the active site Ser residue .The tetrahedral intermediate, with a negative charge, is stabilized by interactions with a positively charged cleft on the active site, termed the oxyanion hole. Subsequently, the cleavage of the amide bond leads to the formation of a covalent acyl-enzyme intermediate .The final step involves the protonation and cleavage of the covalent bond that binds the hydrolyzed product to the enzyme. This deacylation event represents the rate-limiting step of the mechanism.(11)



SUB GROUPS OF BETA LACTUM ANTIBIOTICS:

Penicillins: Divided into four subtypes:

a. Natural penicillins, also known as penicillinase-sensitive penicillins, such as Penicillin G and Penicillin V.

b. Antistaphylococcal or penicillinase-resistant penicillins, like nafcillin, oxacillin, methicillin, and dicloxacillin. This group of penicillins possesses bulky R-group side chains .

c. Aminopenicillins, characterized by amino side chains, with examples including ampicillin and amoxicillin.

d. Extended-spectrum (antipseudomonal) penicillins, such as piperacillin and ticarcillin.

Cephalosporins: Categorized into five generations of antibiotics:

a. 1st Generation cephalosporins feature large R1 side chains, providing protection against beta-lactamases. Examples include cefazolin, cephalexin, cephalothin, and cefadroxil.

b. 2nd Generation cephalosporins have different side groups that enhance the antibiotic's potency. Examples are cefotetan, cefoxitin, cefuroxime, and cefaclor.

c. 3rd Generation cephalosporins exhibit better penetration into body tissues. Examples include cefotaxime, ceftazidime, and ceftriaxone.

d. 4th Generation cephalosporins are effective against bacteria resistant to 3rd Generation antibiotics . An example is cefepime.

e. 5th Generation cephalosporins have increased affinity for penicillin-binding protein 2a (PBP2a), which mediates methicillin resistance in Staphylococci.

Monobactams: These antibiotics possess a monocyclic β-lactam ring and selectively bind to penicillin-binding protein 3 (PBP3) . An example is aztreonam.

Carbapenems are primarily used to treat bacteria with multidrug resistance (MDR). They are considered the last line of treatment against stubborn bacterial infections as they bind to PBPs of most bacterial species and are known to be resistant to beta-lactamases. Examples include imipenem, meropenem, doripenem, and ertapenem(12)

SIGNIFICANCE OF BETA LACTUM ANTIBIOTICS:

Beta-lactam antibiotics have been the preferred first-line therapy for treating bacterial infections since they became widely available in the 1940s. Remarkably, ongoing discoveries about the mode of action of beta-lactams persist as our understanding of bacterial outer membrane biogenesis deepens. This includes the recent revelation that beta-lactams induce a futile cycle of peptidoglycan (PG) synthesis and degradation as a fundamental aspect of their lethal effect on bacteria. In this study, we employed a metabolomics approach to identify disruptions induced by the beta-lactam antibiotic mecillinam in the Gram-negative bacterial pathogen Escherichia coli. Inhibition of PBP2 by mecillinam leads to broad metabolic shifts affecting multiple anabolic and catabolic processes, including changes to PG and protein biosynthesis. Alongside these alterations, we observed changes in glycolytic activity and ATP utilization, as well as a widespread dysregulation of the cellular redox environment. Importantly, scavenging reactive metabolic by-products attenuates drug-induced lethality. This study connects the target-proximal effects of PG dysregulation with downstream metabolic events, including redox dysregulation, which collectively contribute to bacterial cell death.(13)

ANTIBACTERIAL EFFICACY OF BETA LACTUMS:

While determining the optimal antibiotic strategy for patient care involves considering numerous factors, a primary criterion is the susceptibility of the infectious bacterial strain. Utilizing The Sanford Guide to Antimicrobial Therapy (Gilbert et al., 2020), a "heat map" depicting susceptibility trends for β-lactam coverage by organism ultrastructure and metabolism was generated . Upon examining the fractional activity against general classes of pathogenic bacteria, several specific patterns emerge. None of the β-lactams demonstrate particularly high effectiveness against cell wall-deficient microbes, primarily consisting of intracellular pathogens such as mycoplasma and Chlamydia trachomatis.

However, for infections typically caused by Gram-negative and Gram-positive bacteria, β-lactams offer numerous options for effective empiric or specific coverage. When comparing the spectrum of activity versus h-Woodward values, a weak but noticeable correlation emerges. Beta-lactams with higher values generally exhibit broader spectra of activity within and across groups of microbes compared to those with lower h-Woodward values. Notably, the monobactam aztreonam possesses the lowest h-Woodward value and a very narrow spectrum of activity. Nevertheless, there are several exceptions, notably the relatively narrow spectrum of activity exhibited by nafcillin and oxacillin. As mentioned previously, this is attributable to various factors influencing microbial killing, including site accumulation (particularly relevant in Gram-negative pathogens) and target affinity.(14)

ADVERSE EFFECTS OF BETA LACTUM:

Common adverse reactions associated with β-lactam antibiotics encompass diarrhea, nausea, rash, urticaria, and superinfection (including candidiasis). Less frequent adverse effects encompass fever, vomiting, erythema, dermatitis, angioedema, and pseudomembranous colitis. Pain and inflammation at the injection site are also typical for parenterally administered β-lactam antibiotics. Immunologically mediated adverse reactions to any β-lactam antibiotic may manifest in up to 10% of patients receiving the agent, with a small proportion being truly IgE-mediated allergic reactions (refer to amoxicillin rash). Anaphylaxis is a rare occurrence, affecting approximately 0.01% of patients. While there may be a 5%-10% cross-sensitivity between penicillin derivatives, cephalosporins, and carbapenems, the validity of this figure has been disputed by various researchers. Nonetheless, the risk of cross-reactivity is substantial enough to warrant the contraindication of all β-lactam antibiotics in patients with a history of severe allergic reactions (such as urticaria, anaphylaxis, or interstitial nephritis) to any β-lactam antibiotic. Furthermore, a Jarisch–Herxheimer reaction may ensue after initial treatment of a spirochetal infection, such as syphilis, with a β-lactam antibiotic(15).

CLINICAL IMPLEMENTATIONS:

The clinical introduction of new β-lactam antibiotics is swiftly followed by the identification of β-lactamases capable of degrading them. This pattern has recurred over recent decades and is anticipated to persist for future β-lactams. The diversity of β-lactamases poses a critical challenge, given the specificities of known enzymes for substrates and their capacity to evolve and alter these specificities. Even if a β-lactam is not readily susceptible to β-lactamase-mediated degradation, bacteria have other resistance mechanisms at their disposal, such as efflux pumps.

While only a few new β-lactams have entered clinical practice in recent years, significant strides have been made in β-lactamase inhibitors(16). Novel inhibitors like avibactam, based on diazabicyclooctane, and vaborbactam, based on boronate scaffolds, have demonstrated effectiveness and gained clinical approval(17,18). Other inhibitors in the antibiotic development pipeline exhibit promising characteristics, such as taniborbactam, which inhibits both SBLs and MBLs(19).

Despite extensive research on β-lactams, PBPs, and SBLs, there is still much to uncover. The revelation that β-lactam antibiotics target Ldts is relatively recent(20), and some β-lactams exhibit activity against additional enzyme groups, such as bacterial signal peptidases and viral proteases(21-24). The multitude of β-lactam antibiotics, target proteins, and resistance

mechanisms introduces a high degree of complexity concerning inhibition and catalysis. Modern experimental techniques, such as cryogenic electron microscopy, have opened up new avenues for investigating the structures and functions of these proteins(25), while our understanding of peptidoglycan synthesis and cell wall remodeling continues to advance(26-27)

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