**Beta lactam antibiotic**

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**Abstract**

βlactam antibiotics are a type of antibiotic that have a specific molecular structure called a β-lactam ring. This group includes well-known antibiotics like penicillins, cephalosporins, carbapenems, and monobactams. They work by interfering with the synthesis of the bacterial cell wall, causing the bacteria to burst and die.

However, over time, bacteria have developed ways to resist the effects of these antibiotics. One common resistance mechanism involves the production of enzymes called β-lactamases. These enzymes break down the β-lactam ring in the antibiotic molecules, rendering them ineffective against the bacteria.

To combat this resistance, scientists have developed combination therapies that include β-lactamase inhibitors along with the β-lactam antibiotics. These inhibitors work by blocking the action of β-lactamases, allowing the antibiotics to remain active and kill the bacteria effectively.

In summary, β-lactam antibiotics are widely used to treat bacterial infections by disrupting cell wall synthesis, but bacteria can develop resistance through β-lactamases. Combining β-lactam antibiotics with β-lactamase inhibitors helps overcome this resistance and enhances the effectiveness of the treatment.

**Introduction**

The idea of using chemicals to treat diseases goes back to ancient Egypt. One major breakthrough in medicine was the development of antibiotics, which have saved countless lives and remain the main treatment for bacterial infections. Penicillin G was the first β-lactam antibiotic developed, leading to the discovery of many more derivatives.

β-lactam antibiotics, including penicillin, cephalosporins, carbapenems, and monobactams, work by disrupting the synthesis of bacterial cell walls, effectively killing the bacteria. They are widely available and treat a variety of bacterial infections.

However, bacteria have developed resistance to these antibiotics due to overuse and misuse. This resistance poses a serious threat to public health, as some bacteria are now resistant to nearly all available antibiotics.

Resistance to β-lactam antibiotics often occurs through the action of enzymes called β-lactamases, which break down the β-lactam ring in the antibiotics, rendering them ineffective. These enzymes interfere with the assembly of the bacterial cell wall by inhibiting the action of penicillin-binding proteins (PBPs), which are essential for cell wall synthesis.

The prevalence of antibiotic-resistant bacteria, such as Staphylococcus and Pseudomonas, is a growing concern. Additionally, bacteria can transfer resistance genes between different strains and species, leading to the emergence of multiple drug-resistant organisms.

Examples of such organisms include Extended-spectrum beta-lactamases (ESBLs) and Penicillin-resistant Streptococcus pneumonia (PRSP). ESBLs can hydrolyze and inactivate a wide range of β-lactam antibiotics, while PRSP is resistant to penicillins.

In summary, β-lactam antibiotic resistance is a significant healthcare issue caused primarily by the action of β-lactamases, which break down the antibiotics' β-lactam ring. This resistance threatens the effectiveness of these life-saving drugs, underscoring the need for responsible antibiotic use and the development of alternative treatment strategies.

**Beta lactam antibiotics**

1. **Penicillins**:

 - Penicillins have a specific structure consisting of a thiazolidine ring connected to a beta-lactam ring, with various side chains.

 - They are derived from 6-Amino-penicillinic acid and are usually extracted from cultures of Penicillium fungi.

 - The prototype penicillin is penicillin G, which is effective against Gram-positive bacteria sensitive to penicillin but is pH-sensitive.

 - Semi-synthetic penicillins are produced by modifying the side chains of natural penicillins. These modifications can broaden their spectrum of activity and make them resistant to penicillinase, an enzyme that breaks down penicillins.

2. **Cephalosporin**:

 - Cephalosporins are a class of β-lactam antibiotics derived from the fungus Acremonium, formerly known as “Cephalosporium.”

 - They are structurally related to penicillins and also contain a beta-lactam ring.

 - Cephalosporins are relatively stable in dilute acid and highly resistant to penicillinase.

 - They are categorized into generations based on their spectrum of activity and resistance to bacteria.

 - First-generation cephalosporins have stronger effects against Gram-positive bacteria.

 - Second-generation cephalosporins have increased activity against Gram-negative bacteria.

 - Third-generation cephalosporins have broad activity against both Gram-positive and Gram-negative bacteria.

 - Fourth-generation cephalosporins are extended-spectrum agents with activity against a wide range of bacteria, including those resistant to earlier generations. They have greater resistance to β-lactamases compared to third-generation cephalosporins.

3. **Mechanism of Action**:

 - β-lactam antibiotics, including penicillins and cephalosporins, work by inhibiting the enzyme responsible for bacterial cell wall synthesis.

 - The bacterial cell wall is essential for maintaining the shape and protection of the cell.

 - The cell wall is composed of alternating units of N-acetylmuramic acid (NAM) and N-acetylglucosamine (NAG), linked together by enzymes.

 - Penicillin binding proteins (PBPs) catalyze the cross-linking of these units, providing rigidity to the cell wall.

 - β-lactam antibiotics mimic the structure of the pentapeptide D-alanine-D-alanine of NAM, so PBPs mistakenly use them instead of NAM.

 - This leads to the acylation of PBPs, rendering them unable to catalyze further cross-linking reactions.

 - Without proper cross-linking, the bacterial cell wall becomes weakened and more permeable, leading to cell lysis and bacterial death.

In summary, both penicillins and cephalosporins are important classes of antibiotics that disrupt bacterial cell wall synthesis, ultimately leading to the death of bacteria. Their structures and mechanisms of action are similar, making them effective against a wide range of bacterial infections.

**Different types of analyses conducted on the effects of β-lactam antibiotics:**

1. **Physiological Analysis**:

 - Researchers observed that when bacteria are treated with low concentrations of penicillin, they form filaments. This indicates that penicillin affects the bacteria’s ability to maintain their normal shape and division.

2. **Biochemical Analysis**:

 - Studies showed that after treatment with penicillin, bacteria accumulate specific peptides in their cytoplasm. These peptides are similar in composition to the building blocks of the bacterial cell wall, suggesting that penicillin interferes with cell wall synthesis.

3. **Biophysical Analysis**:

 - Radioactive penicillin was used to identify its specific binding site on the bacterial cell wall, known as the penicillin binding component (PBC). This complex, formed between penicillin and PBC, is crucial for the antibiotic’s action.

 - Further analysis using techniques like SDS-PAGE revealed that PBC is actually composed of proteins called penicillin binding proteins (PBPs), which vary in size and sensitivity to β-lactam antibiotics among different bacterial species.

4. **Genetic Analysis**:

 - Different PBPs have been identified, each with specific functions in bacterial cell wall synthesis and maintenance.

 - PBP1 is involved in elongating the cell wall, and its absence or inhibition leads to abnormal cell growth.

 - PBP2 is crucial for maintaining cell shape, and its inhibition by β-lactam antibiotics can disrupt cell division.

 - PBP3 is essential for cell division, as its absence halts cell division but not cell growth.

 - PBP4 is associated with specific enzymatic activities involved in cell wall remodeling.

 - PBP5 and PBP6 catalyze similar reactions but differ in their specific activities and effects on antibiotic sensitivity.

 - PBP7 and PBP8 are more recently characterized proteins associated with antibiotic resistance.

In summary, these analyses shed light on how β-lactam antibiotics interfere with bacterial cell wall synthesis and maintenance, ultimately leading to cell death. Understanding the specific interactions between antibiotics and bacterial proteins helps in the development of new treatments and strategies to combat antibiotic resistance.

**The ways to overcome the effects of hydrolytic activity of β-lactamases and the role of inhibitors:**

1**. β-lactamase Inhibitors**:

 - There are molecules designed to deactivate or inhibit β-lactamases, enzymes that render β-lactam antibiotics ineffective.

 - Examples include sulbactam, clavulanic acid, and tazobactam, which are structurally similar to penicillin.

 - These inhibitors have high affinity for β-lactamases and can occupy their active sites for longer periods compared to β-lactam antibiotics.

 - They are called “suicide inhibitors” because they get trapped by the β-lactamase enzyme.

 - Current research aims to synthesize new inhibitors using compounds like substituted sulfones, cephem, and penem.

2. **Development of New β-lactam Antibiotics:**

 - Another approach is to develop new β-lactam antibiotics that have high affinity for β-lactamases and cannot be easily hydrolyzed by them.

 - Extended-spectrum carbapenems and cephalosporins are examples of such antibiotics.

 - Doripenem and ceftobiprol are examples of antibiotics developed using this principle, showing high activity against various resistant bacteria.

**characteristics and clinical applications of specific β-lactamase inhibitors:**

1. **Sulbactam**:

 - Sulbactam is a semi-synthetic substance that can deactivate β-lactamases, although it’s not as potent as clavulanic acid.

 - It’s effective against certain classes of β-lactamases and is often combined with antibiotics like ampicillin to enhance their activity against resistant bacteria.

 - Combination drugs like sultamicillin, containing sulbactam and ampicillin, have been clinically effective in treating various infections.

2. **Tazobactam**:

 - Tazobactam is often combined with antibiotics like piperacillin to form a combination drug that inhibits a broad spectrum of β-lactamases.

 - This combination is effective against a wide range of gram-negative and gram-positive bacteria but may not be effective against certain types of β-lactamases.

3. **Clavulanic Acid:**

 - Clavulanic acid is commonly combined with antibiotics like amoxicillin to increase their effectiveness against β-lactamase-producing bacteria.

 - This combination is effective against various bacterial strains, including those resistant to amoxicillin alone.

In summary, β-lactamase inhibitors and the development of new β-lactam antibiotics are crucial strategies in overcoming antibiotic resistance, allowing for more effective treatment of bacterial infections.

**Conclusion**

Beta-lactam antibiotics have been widely used to treat bacterial infections for over 60 years. They work by stopping bacteria from building their cell walls, which ultimately kills them. However, bacteria have become smart and developed ways to resist these antibiotics. They do this by changing certain proteins in their cell walls, using pumps to flush out the antibiotics, or by producing enzymes called beta-lactamases, which break down the antibiotics before they can work.

Scientists have found ways to fight back against these resistant bacteria. One way is by using molecules that can stop the beta-lactamases from working, like sulbactam, clavulanic acid, and tazobactam. Another way is by creating new antibiotics that are better at avoiding being broken down by the beta-lactamases. These methods help us stay one step ahead in the fight against antibiotic-resistant bacteria.

**Reference**:

[1] Kong, K.F.; Schneper, L.; Mathee, K. Beta-lactam antibiotics: from antibiosis to resistance and bacteriology. .

[2] Kalant, H. The pharmacology of semisynthetic antibiotics.

[3] Kardos, N.; Demain, A.L. Penicillin: the medicine with the greatest impact on therapeutic outcomes.

[4] Davies, J.; Davies, D. Origins and evolution of antibiotic resistances.

[5] Abraham, E.P.; Newton, G.G. The structure of cephalesporin

[6] Aminov, R.I. A brief history of the antibiotic era: lessons learned and challenges for the future.

[7] Reading, C.; Cole, M. Clavulanic acid: a beta-lactamase-inhiting beta-lactam from Streptomyces clavuligerus.

[8] Maffioli, S. A chemist’s survey of different antibiotic classes. Wiley- VCH Verlag GmbH & Co. KGaA, Berlin, Germany;

[9] Abraham, E.P.; Newton, G.G.; Crawford, K.; Burton, H.S.; Hale, C.W. Cephalosporin N: a new type of penicillin.

[10] Brown, A.G.; Butterworth, D.; Cole, M.; Hanscomb, G.; Hood, J.D.; Reading, C.; Rolinson, G.N. Naturally-occurring beta-lactamase inhibitors with antibacterial activity. J. Antibiot.

[11] Pieren, M.; Tigges, M. Adjuvant strategies for potentiation of antibiotics to overcome antimicrobial resistance.

[12] Saudagar, P.S.; Survase, S.A.; Singhal, R.S. Clavulanic acid: a review.

[13] Akova, M. Sulbactam-containing beta-lactamase inhibitor combinations.

14. Goffin C, Ghuysen JM. Multimodular penicillin-binding proteins: an enigmatic family of orthologs and paralogs.

15. Sauvage E, Kerff FM, Terrak JA, et al. The penicillin-binding proteins: structure and role in peptidoglycan biosynthesis.

16. Zapun AC, Contreras M, Vernet T. Penicillin-binding proteins and beta-lactam resistance.

17. Fiher JF, Mobashery S. Three decades of the class a beta-lactamases acyl-enzyme. Curr Protein Pept Sci.

18. Bayles KW. The bactericidal action of penicillin: new clues to an unsolved mystery. Trends Microbiol.

19. Gardner AD. Morphological effects of penicillinon bacteria.

20. Duguid JP. The sensitivity of bacteria to the action of penicillin.

21. Park JT, Johnson MJ. Accumulation of labilephosphate in Staphylococcus aureus grown in the presence of penicillin. J Biol Chem.

22. Park JT. Uridine-5￠-pyrophosphate derivatives.III. Amino acid-containing derivatives. J Biol Chem. 1

23. Burdon-Sanderson J. Memoirs. The origin and distribution of microzymes (bacteria) in water, and the circumstances which determine their existence in the tissues and liquids of the living body.

24. Cooper PD, Rowley D. Investigations with radioactive penicillin. Nature.

25. Cooper PD, Rowley D, Dawson IM. Location of radioactive penicillin in Staphylococcus aureus after contact with the drug. Nature. 1

26. Maass EA, Johnson MJ. Penicillin uptake by bacterial cells. J Bacteriol.

27. Maass EA, Johnson MJ. The relations between bound penicillin and growth in Staphylococcus aureus. J Bacteriol.

28. Spratt BG, Pardee AB. Penicillin-binding proteins and cell shape in Escherichia coli. Nature.

29. Georgopapadakou NH, Liu FY. Penicillinbinding proteins in bacteria. Antimicrob Agents Chemother.

30. Spratt BG. Distinct penicillin binding proteins involved in the division, elongation, and shape of Escherichia coli K12. Proc Natl Acad Sci USA.

31. Spratt BG, Jobanputra V, Schwarz U. Mutants of Escherichia coli which lack a component of penicillin-binding protein 1 are viable

32. Suzuki H, Nishimura Y, Hirota Y. On the process of cellular division in Escherichia coli: a series of mutants of E. coli altered in the penicillin-binding proteins. Proc Natl Acad Sci USA.

33. Nakagawa J, Tamaki S, Tomioka S, et al. Functional biosynthesis of cell wall peptidoglycan by polymorphic bifunctional polypeptides. Penicillin-binding protein 1Bs of Escherichia coli with activities of transglycosylase and transpeptidase. J Biol Chem.

34. Tamura T, Suzuki H, Nishimura Y, et al. On the process of cellular division in Escherichia coli: isolation and characterization of penicillin-binding proteins 1a, 1b, and 3. Proc Natl Acad Sci USA.

35. Spratt BG, Pardee AB. Penicillin-binding proteins and cell shape in Escherichia coli.

[36] Mehta, A.; Prabhakar, M.; Kumar, P.; Deshmukh, R.; Sharma, P.L. Excitotoxicity: bridge to various Triggers in neurodegenerative disorders.

[37] McKenna, M.C. Glutamate pays its own way in Astrocytes. Front. Endocrinol.

[38] Danbolt, N.C. Glutamate uptake. Prog. Neurobiol.

[39] Rothstein, J.D.; Dykes-Hoberg, M.; Pardo, C.A.; Bristol, L.A.; Jin, L.; Kuncl, R.W.; Kanai, Y.Hediger, M.A.; Wang, Y.; Schielke, J.P. Knockout of Glutamate transporters reveals a major role for Astroglial transport in excitotoxicity and clearance of Glutamate.

[40]. Dale, G. E., Then, R. L., Stuber. D. Characterization of the gene for chromosomal trimethoprim-sensitive dihydrofolate reductase of Staphylococcus aureus ATCC 25923. Antimicrobial Agents and Chemotherapy.

[41]. Huovinen, P., Sundström, L., Swedberg, G., & Sköld, O. Trimethoprim and sulfonamide resistance. Antimicrobial Agents and Chemotherapy.

[42]. Sundstrom, L., Rådstrom, P., Swedberg, G., Skold. O. Site-specific recombination promotes linkage between trimethoprim- and sulfonamide resistance genes. Sequence characterization of dhfrV and sulI and a recombination active locus of Tn21. Molecular Genetics and Genomics.