

## Types of Antibiotics: $\beta$ -lactam Antibiotics and More

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**Antibiotics are drugs used to treat and prevent bacterial infections. The discovery of penicillin by Alexander Fleming revolutionized the medical field by allowing for the treatment of tuberculosis, among other horrible diseases. Since then, many other types of antibiotics have been developed.**



### $\beta$ -lactam Antibiotics

**$\beta$ -lactam antibiotics** are characterized by **four  $\beta$ -lactam rings**. Examples include penicillins, cephalosporins, clavams (also called oxazepam), cephamycins and carbapenems, monobactams, and nocardicin; almost all are derived **initially from microbes** through a fermentation process.

**Penicillin G** was the first  $\beta$ -lactam antibiotic discovered. It has a bicyclic structure, consisting of a four-member  $\beta$ -lactam ring and a five-membered hydrothiazole ring. Their activity is related to the  $\beta$ -lactam ring opening. A large ring strain leads to both its high antibacterial potency and its instability under acidic and basic conditions.

There were limits to penicillin G's clinical application, however, due to the presence of bacteria resistant to penicillin G, the **parenteral administration requirement**, and **allergic susceptibility**.

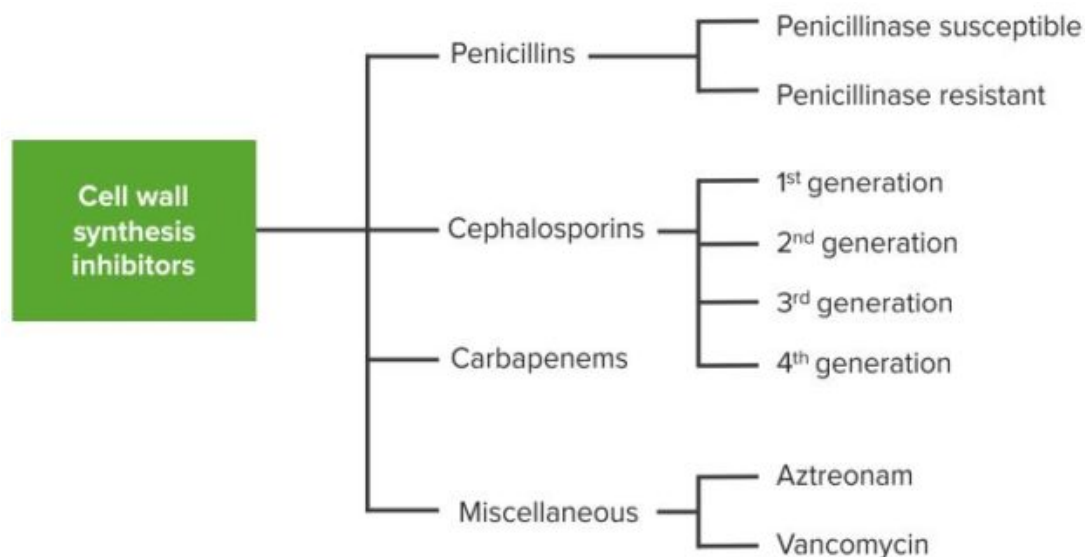
In 1957, the fundamental structural unit of penicillin G, **6-aminopenicillanic acid** (6-APA), was discovered, which led to the production of new, **semisynthetic penicillins**. Chemical modifications were achieved on the **6 $\beta$ -amino**, the **6 $\alpha$** , and the **C3-carboxylic acid groups**. These modifications significantly improved stability and potency. The introduction of a moderately and sterically **hindered substitution group** at the 6 $\alpha$  position enhanced penicillin's **resistance to  $\beta$ -lactamase**, a bacteria-produced enzyme that could kill penicillin.

Currently, only penicillin G and penicillin V are naturally **occurring approved drugs**, while the others are all **semisynthetic products**.

## Cephalosporins

**Cephalosporins** come from **Cephalosporium acremonium**. Today, there are four classes of **cephalosporin antibiotics** based on their activity spectrum, resistance to  $\beta$ -lactamase, and potency differences against **gram-positive/negative organisms**. The significant difference between penicillin and cephalosporin structures is that the latter enlarges to a **six-membered ring** attached to the common  **$\beta$ -lactam core**.

**Cephalosporin's** backbone is **cephem**, which consists of a **bicycle system** with a four-membered  $\beta$ -lactam ring and a **hydrocyclothiazide ring**. Compared to the five-member hydrothiazole ring, the cephalosporins exhibit less ring strain than penicillin. Hence, they are less potent than penicillin; however, they are more stable under acidic conditions and cause **fewer allergic reactions**. Cephalosporins have a prominent place in modern antibiotic therapy.



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## Monobactams

The term **monobactam** describes the novel group of monocyclic bacterially produced  **$\beta$ -lactam antibiotics** with a simple core structure, characterized by the **2-oxoazetidine-1-sulfonic acid functional group**. These compounds were discovered from **soil bacteria** and detected using **supersensitive antimicrobial screens** with ***Pseudomonas aeruginosa*** and ***Escherichia coli***.

The first **monobactams** reported were given the names sulfazecin and isosulfazecin (N-acyl derivatives of (S)-3-amino-2-oxo-1-azetidone sulfonic acid (3-aminomonobactamic acid)), produced from fermented **bacterial strains** rather than more conventional sources, such as fungi or actinomycetes. Subsequently, over five years, 14 naturally occurring monobactams were isolated and characterized from gram-negative bacteria.

These  $\beta$ -lactams produced no side effects: however, they only possessed a narrow **spectrum of activity against gram-negative organisms**, in contrast to broad-spectrum penicillins and cephalosporins.

These naturally-occurring compounds led to the synthesis of many completely **synthetic monobactams**. For example, **aztreonam** is a totally synthetic analog of naturally occurring monobactams.

## Nocardicins

Related to the monobactams, **nocardicins** also contain a core  $\beta$ -lactam but exhibit a ring-opened attachment with no sulfur in the molecule. These  $\beta$ -lactams are **N-acyl derivatives of 3-amino-nocardicinic acids**. Seven nocardicins were isolated from the metabolites of **Nocardia uniformis**, named nocardicins A-G. **Nocardicin A** is the major component and has the highest activity.

Both nocardicins and monobactams have similar mechanisms of action to other  $\beta$ -lactam antibiotics. They imitate **penicillin-binding proteins** in bacteria cell wall formation. Although there is no valuable antibiotic based on modifying nocardicin A, its simple structure, without a bicyclic ring core structure, indicated that the bicyclic core structure, found in the more traditional  $\beta$ -lactam antibiotics, may not be necessary. The monocyclic nucleus has only one four-membered ring, which has a lower ring strain than penicillin.

A less **rigid structure** leads to the **lower activity of the  $\beta$ -lactam ring**. As a result, **nocardicin A possesses only moderate activity in vitro** against some gram-negative bacteria. It is a narrow-spectrum antibiotic.

## Other Antibiotics

### Carbapenem

**Carbapenem** antibiotics occur naturally. Their derivatives are based on this structure, with **substituted groups on C2 and C6**. The first **carbapenem antibiotic**, thienamycin, was also first discovered in 1976, isolated from the fermentation broth of **Streptomyces cattleya**. Thienamycin has high potency, broad-spectrum, antibacterial activity, and relatively **high resistance to  $\beta$ -lactamases**. The discovery of thienamycin represented a new family of  $\beta$ -lactam antibiotics, and more than **40 natural carbapenem antibiotics** have been isolated.

Most of the naturally occurring **carbapenem antibiotics** have a **1-hydroxyethyl group on C6**. The configuration differences at the **chiral center, C8**, result in epimers. Due to the low isolation efficiency and multiple products formed under fermentation conditions, all carbapenem antibiotics for clinical use are produced by total synthesis. However, this process is more expensive than producing penicillin and its derivatives directly from fermentation.

Although **thienamycin** is highly potent and **resistant to  $\beta$ -lactamases**, its instability is

a limiting factor in clinical use. Thus, more chemically modified carbapenem antibiotics were synthesized, and several carbapenem antibiotics, such as imipenem, have also been prescribed.

## Erythromycin

**Erythromycin** is a macrolide antibiotic with an antimicrobial spectrum similar to or slightly wider than that of penicillin and is often prescribed for people who are allergic to penicillins. For respiratory tract infections, it has better coverage of atypical organisms, including ***Mycoplasma* and *legionellosis***.

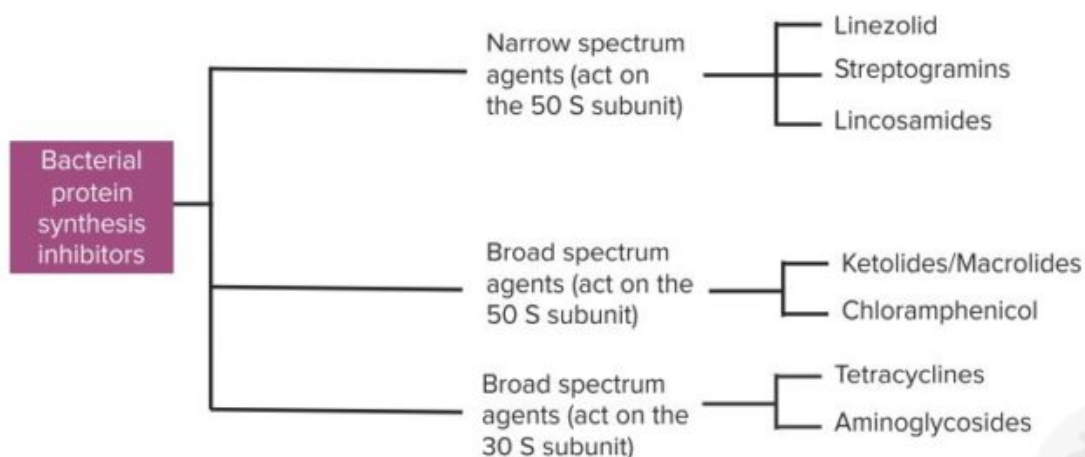
This macrocyclic compound contains a **14-membered lactone ring** with ten asymmetric centers and two sugars (L-cladinose and D-desosamine), making it difficult to produce synthetically. Erythromycin is produced by fermentation from a strain of the actinomycete ***Saccharopolyspora erythraea***.

The avermectins form a series of 16-membered macrocyclic lactone derivatives with potent **anthelmintic and insecticidal properties**. These naturally occurring compounds are generated as fermentation products by ***Streptomyces avermitilis***, a soil actinomycete. Eight different avermectins were isolated as four pairs of homologous compounds, with a major (a-component) and minor (b-component) component, usually in **ratios of 80:20 to 90:10**.

## Tetracycline

**Tetracycline** compounds form another group of **broad-spectrum antibiotics** whose general usefulness has been reduced because of bacterial resistance. They are defined as a **subclass of polyketides** with an **octahydro tetracene-2-carboxamide skeleton**. Tetracyclines are generally used to treat urinary tract and intestinal infections. They are also used to treat infections caused by **chlamydia**, especially in patients allergic to  $\beta$ -lactams and macrolides.

However, the use of tetracyclines for these indications has decreased due to the widespread development of drug resistance. Currently, they are used primarily for treating moderately severe acne and rosacea, though they may be used to treat **Legionnaires' disease**. They also are used in veterinary medicine, particularly on swine.



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