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.

### β-lactam Antibiotics

β-lactam antibiotics are characterized by their four-membered β-lactam rings. Examples include penicillins, cephalosporins, clavams (also called oxapenams), cephamycins and carbapenems, monobactams, and nocardicins; almost all derived initially from microbes through a fermentation process.

Penicillin G was the first β-lactam antibiotic discovered. It has a bicyclic structure consisting of a four-member β-lactam ring and a five-membered hydrothiazole ring. The activity of these antibiotics is related to the opening of the β-lactam ring. 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 route of needing parenteral administration, and
allergic susceptibility.

In 1957, the fundamental structure unit of penicillin G, 6-aminopenicillanic acid (6-APA) was announced. This discovery led to the production of new semisynthetic penicillins. Chemical modifications were achieved on the 6β-amino, the 6α, and the C3-carboxylic acid groups and these modifications significantly improved the stability and potency. By introducing a moderately and sterically hindered substitution group at the 6α position, this chemistry enhanced the resistance to β-lactamase, an enzyme produced by bacteria to destroy 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, cephalosporin antibiotics are classified into four classes based on their spectrum of activity, resistance to β-lactamase, and their potency differences against gram-positive/negative organisms. The significant difference between penicillin and cephalosporin structures can be seen in the enlargement from a five-membered to a six-membered ring attached to the common β-lactam core.

The backbone of the cephalosporin is cephem, which consists of a bicycle system with a four-membered β-lactam ring and a hydrocyclothiazide ring. Compared to the five-member hydrothiazole ring, the cephalosporins exhibit less ring strain than penicillin. Hence, the potency is relatively lower than penicillin. However, they are more stable under acidic conditions and exhibit fewer allergic reactions; these cephalosporins have a prominent place in modern antibiotic therapy.

Monobactams

The term monobactam describes the novel group of monocyclic bacterially produced β-lactam antibiotics having 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-azetidine sulfonic acid (3-aminomonobactamic acid)) produced in fermentation from bacterial strains and not from the more common sources: fungi or actinomycetes. Subsequently, over a 5-year period, 14 naturally occurring monobactams were isolated and characterized from gram-negative bacteria.

These β-lactams produced no side effects; however, they only possessed a narrow spectrum of activity toward gram-negative organisms, in contrast to the 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 the naturally occurring monobactams.

Nocardicins

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

Both nocardicins and monobactams possess similar mechanisms of action as other β-lactam antibiotics and act as imitators of penicillin-binding proteins, PBPs, in bacteria cell wall formation. Although no valuable antibiotic based on modifying nocardicin A was found, its simple structure without a bicyclic ring core structure indicated that a bicyclic core structure found in the more traditional β-lactam antibiotics may not be necessary. The monocyclic nucleus only has one four-membered ring, which has less ring strain in comparison to penicillin.

A less rigid structure leads to the lower activity of the β-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 are naturally occurring. Derivatives of carbapenem antibiotics 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 β-lactamases.

The discovery of thienamycin represented a new family of β-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 clinic use are produced by total synthesis, although this
leads to a high cost compared to producing penicillin and its derivatives directly from fermentation.

Although thienamycin is high in potency and resistant to β-lactamases, its instability is a limiting factor in clinic use. Thus, more chemically modified carbapenem antibiotics were synthesized and several carbapenem antibiotics, for example, imipenem have also been prescribed.

Erythromycin

**Erythromycin** is a macrolide antibiotic that has an antimicrobial spectrum similar to or slightly wider than that of penicillin and is often prescribed for people who have an allergy 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 a compound that is difficult to produce via synthetic methods. 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 with the onset of bacterial resistance. They are defined as a subclass of polyketides having an **octahydrotetracene-2-carboxamide skeleton**. Tetracyclines are generally used in the treatment of infections of the urinary tract and the intestines, and are used in the treatment of infections caused by *chlamydia*, especially in patients allergic to β-lactams and macrolides.

However, their use for these indications has decreased due to widespread development of drug resistance to these compounds. Their most common current use is in the treatment of moderately severe acne and rosacea. In addition, they may be used to treat **Legionnaires’ disease**. They also are used in veterinary medicine, particularly on swine.
Review Questions

1. Penicillin and cephalosporin are two bactericidal antibiotics. What is their more of action?
   
   A. They activate autolytic enzymes  
   B. The inhibit beta-lactamases  
   C. The inhibit cell wall transpeptidases  
   D. The inhibit protein synthesis  
   E. Both A & C are correct answers

2. Which of the following is likely the reason why penicillin G has limited use for the development of new antibiotics?
   
   A. It has a low therapeutic index  
   B. Beta-lactamase sensitivity  
   C. It has a low bacteriostatic efficacy  
   D. It has a long half-life  
   E. Both A and C are correct

3. Penicillin G is most effective against:
   
   A. Beta-lactamase producing bacteria  
   B. Gram-negative bacteria  
   C. Gram-positive bacteria  
   D. Helicobacter pylori infections

References


**Answers to Practice Questions**

E 2. B 3. C

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