Antibacterial Antibiotics 1st lecture

HISTORICAL BACKGROUND

Since Alexander Fleming accidentally discovered penicillin in 1929, the numbers of antibiotics that have been added to our therapeutic armamentarium has grown tremendously.

Vuillemin define *antibiosis* (literally "against life") as the biological concept of survival of the fittest, in which one organism destroys another to preserve itself. The word *antibiotic* was derived from this root. The use of the term by the lay public, as well as the medical and scientific communities, has become so widespread that its original meaning has become obscured. In 1942, Waksman3 proposed the widely cited definition that "an antibiotic or antibiotic substance is a substance produced by microorganisms, which has the capacity of inhibiting the growth and even of destroying other microorganisms. "Later proposals have sought both to expand and to restrict the definition to include any substance produced by a living organism that is capable of inhibiting the growth or survival of one or more species of microorganisms in low concentrations.

Therefore, a substance is classified as an antibiotic if the following conditions are met:

1. It is a product of metabolism (although it may be duplicated or even have been anticipated by chemical synthesis).
2. It is a synthetic product produced as a structural analog of a naturally occurring antibiotic.
3. It antagonizes the growth or survival of one or more species of microorganisms.
4. It is effective in low concentrations.

The isolation of the antibacterial antibiotic tyrocidine from the soil bacterium *Bacillus brevis* by Dubois suggested the probable existence of many antibiotic substances in nature and provided the impetus for the search for them. An organized search of the order Actinomycetales led Waksman and associates to isolate streptomycin from *Streptomyces griseus*. The discovery that this antibiotic possessed in vivo activity against *Mycobacterium tuberculosis* in addition to numerous species of Gram-negative bacilli was electrifying.

CURRENT STATUS

Commercial and scientific interest in the antibiotic field has led to the isolation and identification of antibiotic substances that may be numbered in the thousands. Numerous semisynthetic and synthetic derivatives have been added to the total. Very few such compounds have found application in general medical practice, however, because in addition to the ability to combat infections or neoplastic disease, an antibiotic must possess other attributes.

First, it must exhibit sufficient selective toxicity to be decisively effective against pathogenic microorganisms or neoplastic tissue, on the one hand, without causing significant toxic effects, on the other.

Second, an antibiotic should be chemically stable enough to be isolated, processed, and stored for a reasonable length of time without deterioration of potency. The amenability of an antibiotic for oral or parenteral administration to be converted into suitable dosage forms to provide active drug in vivo is also important.

Third, the rates of biotransformation and elimination of the antibiotic should be slow enough to allow a convenient dosing schedule, yet rapid and complete enough to facilitate removal of the drug and its metabolites from the body soon after administration has been discontinued. Some groups of antibiotics, because of certain unique properties, have been designated for specialized uses, such as the treatment of tuberculosis (TB) or fungal infections. Others are used for cancer chemotherapy.

COMMERCIAL PRODUCTION

The commercial production of antibiotics for medicinal use follows a general pattern, differing in detail for each antibiotic. The general scheme may be divided into six steps:

(a) preparation of a pure culture of the desired organism for use in inoculation of the fermentation medium;
(b) fermentation, during which the antibiotic is formed;
(c) isolation of the antibiotic from the culture medium;
(d) purification;
(e) assays for potency, sterility, absence of pyrogens, and other necessary data; and
(f) formulation into acceptable and stable dosage forms.

MECHANISMS OF ACTION

Antibiotics that interfere with the metabolic systems found in microorganisms and not in mammalian cells are the most successful anti-infective agents. For example, antibiotics that interfere with the synthesis of bacterial cell walls have a high potential for selective toxicity. The mechanisms of action of some of the more common antibiotics are summarized in the table below:
In many instances, the mechanism of action is not fully known; for a few (e.g., penicillins), the site of action is known, but precise details of the mechanism are still under investigation.
The distinction may be important for the treatment of serious, life-threatening infections, particularly if the natural defense mechanisms of the host are either deficient or overwhelmed by the infection. In such situations, a bactericidal agent is obviously indicated. Much work remains to be done in this area, and as mechanisms of action are revealed, the development of improved structural analogs of effective antibiotics probably will continue to increase.

TABLE of Mechanisms of Antibiotic Action

Site of Action	Antibiotic	Process Interrupted	Type of Activity
Cell wall	Bacitracin	Mucopeptide synthesis	Bactericidal
	Cephalosporin	Cell wall cross-linking	Bactericidal
	Cycloserine	Synthesis of cell wall peptides	Bactericidal
	Penicillins	Cell wall cross-linking	Bactericidal
	Vancomycin	Mucopeptide synthesis	Bactericidal
Cell membrane	Amphotericin B	Membrane Function	Fungicidal
	Nystatin	Membrane function	Fungicidal
	Polymyxins	Membrane integrity	Bactericidal
Ribosomes	Chloramphenicol	Protein Synthesis	Bacteriostatic
50S subunit	Erythromycin	Protein synthesis	Bacteriostatic
	Lincomycins	Protein synthesis	Bacteriostatic
30S subunit	Aminoglycosides	Protein synthesis and fidelity	Bactericidal
	Tetracyclines	Protein synthesis	Bacteriostatic
Nucleic acids	Actinomycin	DNA and mRNA synthesis	Pancidal
	Griseofulvin	Cell division, microtubule assembly	Fungistatic
DNA and/or RNA	Mitomycin C	DNA synthesis	Pancidal
	Rifampin	mRNA synthesis	Bactericidal

CHEMICAL CLASSIFICATION

The chemistry of antibiotics is so varied that a chemical classification is of limited value. Some similarities can be found, however, indicating that some antibiotics may be the products of similar mechanisms in different organisms and that these structurally similar products may exert their activities in a similar manner. For example, several important antibiotics have in common a macrolide structure (i.e., a large lactone ring). This group includes erythromycin and oleandomycin. The tetracycline family comprises a group of compounds very closely related chemically. Several compounds contain closely related amino sugar moieties, such as those found in streptomycins, kanamycins, neomycins, paromomycins, and gentamicins. The antifungal antibiotics nystatin and the amphotericins are examples of a group of conjugated polyene compounds. The bacitracins, tyrothricin, and polymyxin are among a large group of polypeptides that exhibit antibiotic action.

The penicillins and cephalosporins are β-lactam ring–containing antibiotics derived from amino acids.

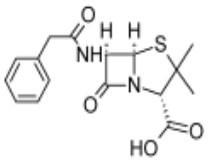
MICROBIAL RESISTANCE

The normal biological processes of microbial pathogens are varied and complex. Thus, it seems reasonable to assume that there are many ways in which they may be inhibited and that different microorganisms that elaborate antibiotics antagonistic to a common "foe" produce compounds that are chemically dissimilar and that act on different processes. In fact, nature has produced many chemically different antibiotics that can attack the same microorganism by different path ways. The diversity of antibiotic structure has proved to be of real clinical value. As the pathogenic cell develops drug resistance, another antibiotic, attacking another metabolic process of the resisting cell, remains effective. The development
of new and different antibiotics has been very important in providing the means for treating resistant strains of organisms
that previously had been susceptible to an older antibiotic. More recently, the elucidation of biochemical mechanisms of microbial resistance to antibiotics, such as the inactivation of penicillins and cephalosporins by β-lactamase–producing bacteria, has stimulated research in the development of semisynthetic analogs that resist microbial biotransformation. The evolution of *nosocomial* (hospital acquired) strains of staphylococci resistant to penicillin and of Gram-negative bacilli (e.g., *Pseudomonas* and *Klebsiella* spp., *Escherichia coli*, and others) often resistant to several antibiotics has become a serious medical problem. No doubt, the promiscuous and improper use of antibiotics has contributed to the emergence of resistant bacterial strains. The successful control of diseases caused by resistant strains of bacteria will require not only the development of new and improved antibiotics but also the rational use of available agents.

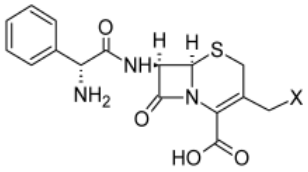
β-LACTAM ANTIBIOTICS

Antibiotics that possess the β-lactam (a four-membered cyclic amide) ring structure are the dominant class of agents currently used for the chemotherapy of bacterial infections.

The first antibiotic to be used in therapy, penicillin.



The second major group of β-lactam antibiotics, the cephalosporins.



Cephalosporin

Mechanism of Action

The properties of these antibacterial are:

- broad spectrum of antibacterial action,

- potent and rapid bactericidal action against bacteria in the growth phase
- and a very low frequency of toxic and other adverse reactions in the host.

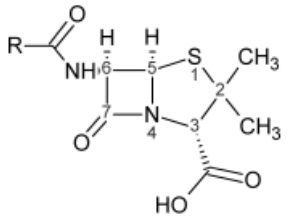
The basic mechanism involved is inhibition of the biosynthesis of the dipeptidoglycan that provides strength and rigidity to the cell wall.
Penicillins and cephalosporins acylate a specific bacterial D-transpeptidase, thereby rendering it inactive for its role in forming peptide cross-links of two linear peptidoglycan strands by transpeptidation and loss of D-alanine. Bacterial D-alanine carboxypeptidases are also inhibited by β-lactam antibiotics.

These penicillin-binding proteins (PBPs) have the following functional properties:
• PBPs 1a and 1b are transpeptidases involved in peptidoglycan synthesis associated with cell elongation. Inhibition
results in spheroplast formation and rapid cell lysis, caused by *autolysins* (bacterial enzymes that create nicks
in the cell wall for attachment of new peptidoglycan units or for separation of daughter cells during cell division).
• PBP 2 is a transpeptidase involved in maintaining the rod shape of bacilli. Inhibition results in ovoid or round forms that undergo delayed lysis.
• PBP 3 is a transpeptidase required for septum formation during cell division. Inhibition results in the formation of
filamentous forms containing rod-shaped units that cannot separate. It is not yet clear whether inhibition of PBP 3 is
lethal to the bacterium.
• PBPs 4 through 6 are carboxypeptidases responsible for the hydrolysis of D-alanine–D-alanine terminal peptide bonds of the cross-linking peptides. Inhibition of these enzymes is apparently not lethal to the bacterium, even though cleavage of the terminal D-alanine bond is required before peptide cross-linkage.

Penicillins

Nomenclature

The *Chemical Abstracts* system initiates the numbering with the sulfur atom and assigns the ring nitrogen the 4-position. Thus, penicillins are named as 4-thia-l-azabicyclo [3.2.0] heptanes, according to this system.



Stereochemistry

The penicillin molecule contains three chiral carbon atoms (C-3, C-5, and C-6). All naturally occurring and microbiologically active synthetic and semisynthetic penicillins have the same absolute configuration about these three centers. The
-carbon atom bearing the acylamino group (C-6) has the L configuration,
- the carbon to which the carboxyl group is attached has the D configuration. Thus, the acylamino and carboxyl groups are *trans* to each other.
- The atoms composing the 6-aminopenicillanic acid (6-APA) portion of the structure are derived biosynthetically

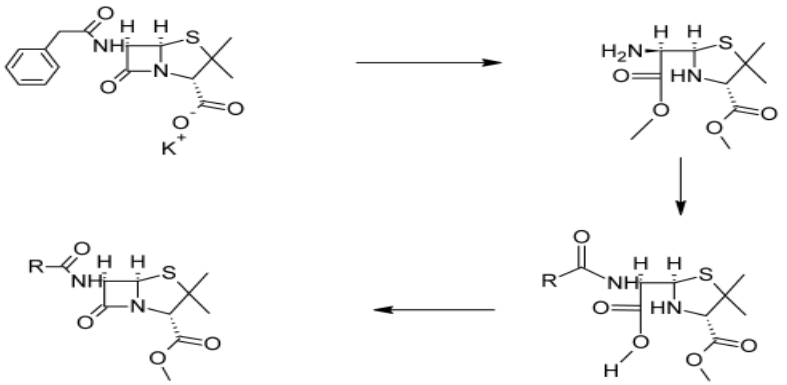
from two amino acids, L-cysteine (S-1, C-5, C-6, C-7, and 6-amino) and L-valine (2,2-dimethyl, C-2, C-3, N-4, and 3-carboxyl). The absolute stereochemistry of the penicillins is designated 3S:5R:6R, as shown below.

Synthesis

Two major methods used in synthesis of penicillins

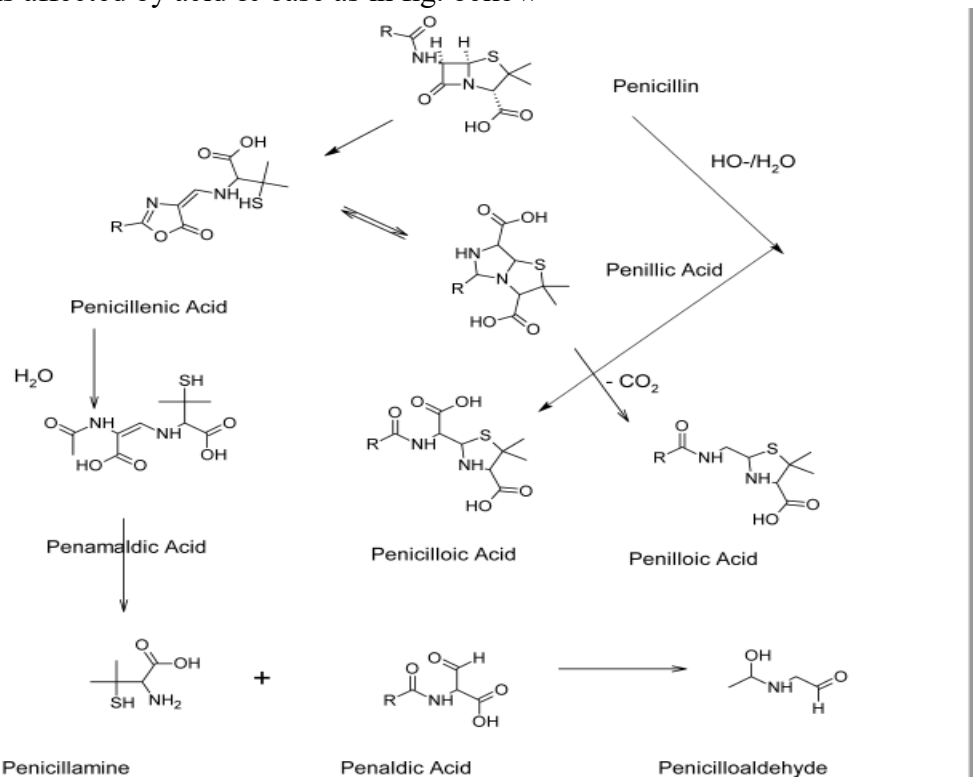
-First the isolation of 6-APA from a culture of *P. chrysogenum*. This compound can be converted to penicillins by acylation of the 6-amino group.

-Second synthetic penicillins by converting a natural penicillin, such as penicillin G potassium, to an intermediate as in (Fig.bellow), from which the acyl side chain has been cleaved and which then can be treated to form biologically active penicillins with various new side chains.



Chemical Degradation

- Penicillins affected by acid & base as in fig. bellow



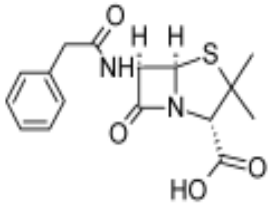
- Oxidizing agents also inactivate penicillins, but reducing agents have little effect on them.

-Temperature affects the rate of deterioration; although the dry salts are stable at room temperature and do not require refrigeration,

-prolonged heating inactivates the penicillins.

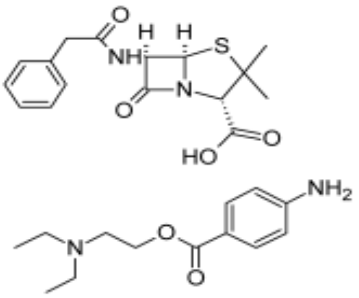
Penicillin's products 2nd lecture

Penicillin G



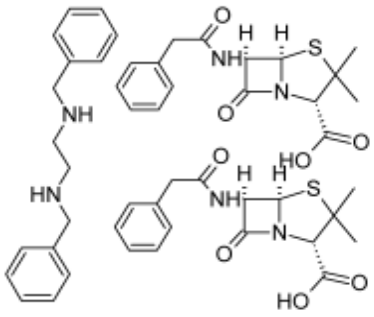
penicillin G remains the agent of choice for the treatment of more different kinds of bacterial infection than any other antibiotic. It was first made available as the water-soluble salts of potassium, sodium, and calcium. These salts of penicillin are inactivated by the gastric juice and are not effective when administered orally unless antacids, such as calcium carbonate, aluminum hydroxide, and magnesium trisilicate; or a strong buffer, such as sodium citrate, is added. Also, because penicillin is absorbed poorly from the intestinal tract, oral doses must be very large, about five times the amount necessary with parenteral administration.
The rapid elimination of penicillin from the bloodstream through the kidneys by active tubular secretion and the need to maintain an effective concentration in blood have led to the development of "repository" forms of this drug. most repository forms are suspensions of high–molecular weight amine salts of penicillin in a similar base.

Penicillin G Procaine



The first widely used amine salt of penicillin G was made with procaine. This salt is considerably less soluble in water than the alkali metal salts. Free penicillin is released only as the compound dissolves and dissociates.

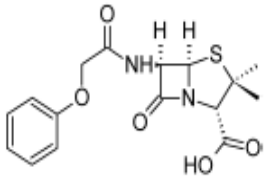
Penicillin G Benzathine



Since penicillin G benzathine, is the salt of a diamine, 2 moles of penicillin are available from each molecule. It is very insoluble in water. This property gives the compound great stability and

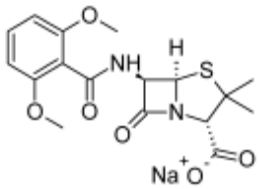
prolonged duration of effect. At the pH of gastric juice, it is quite stable, and food intake does not interfere with its absorption. It is available in tablet form and in several parenteral preparations.

Penicillin V



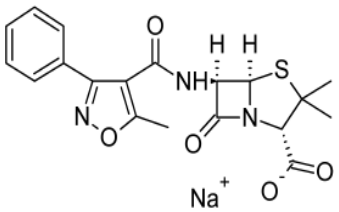
It is a biosynthetic product, it has wide use because of its resistance to hydrolysis by gastric juice and its ability to produce uniform concentrations in blood (when administered orally), the potassium salt is usually used for oral and parenteral solutions.

Methicillin Sodium



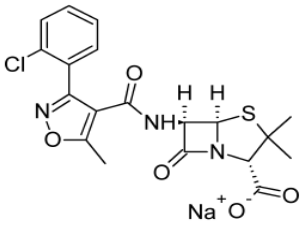
It is a synthetic analog. Methicillin sodium is particularly resistant to inactivation by the penicillinase found in staphylococci and somewhat more resistant than penicillin G to penicillinase from *Bacillus cereus*. Methicillin and many other penicillinases resistant penicillins induce penicillinase formation, an observation that has implications concerning use of these agents in the treatment of penicillin G sensitive infections. Clearly, the use of a penicillinase-resistant penicillin should not be followed by penicillin G. Methicillin sodium has been introduced for use in the
treatment of staphylococcal infections caused by strains resistant to other penicillins. The incidence of interstitial nephritis, a probable hypersensitivity reaction, is reportedly higher with methicillin than with other penicillins.

Oxacillin Sodium



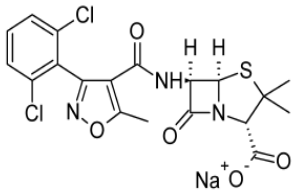
Oxacillin sodium, is the salt of a semisynthetic penicillin that is highly resistant to inactivation by penicillinase. Apparently, the steric effects of the 3-phenyl and 5-methyl groups of the isoxazolyl ring prevent the binding of this penicillin to the β-lactamase active site and, Oxacillin sodium, which is available in capsule form, is reasonably well absorbed from the gastrointestinal (GI) tract, particularly in fasting patients. it is excreted rapidly through the kidneys. Oxacillin experiences some first-pass metabolism in the liver to the 5-hydroxymethyl derivative. This metabolite has antibacterial activity comparable to that of oxacillin but is less avidly protein bound and more rapidly excreted.

Cloxacillin Sodium



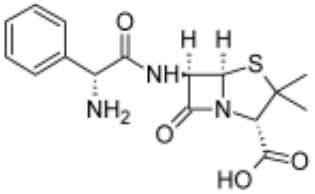
The chlorine atom *ortho* to the position of attachment of the phenyl ring to the isoxazole ring enhances the activity of cloxacillin sodium, over that of oxacillin, not by increasing its intrinsic antibacterial activity but by enhancing its oral absorption, leading to higher plasma levels. In almost all other respects, it resembles oxacillin.

Dicloxacillin Sodium



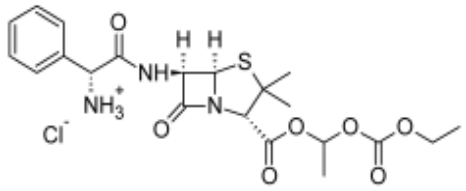
Its medicinal properties and use are similar to those of cloxacillin sodium. Progressive halogen substitution, however, also increases the fraction bound to protein in the plasma, potentially reducing the concentration of free antibiotic in
plasma and tissues. Its medicinal properties and use are the same as those of cloxacillin sodium.

Ampicillin



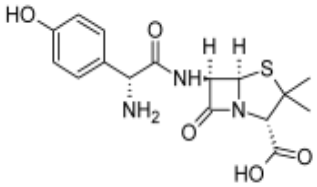
Ampicillin, meets another goal of the research on semisynthetic penicillins an antibacterial spectrum broader than that of penicillin G. This product is active against the same Gram-positive organisms that are susceptible to other penicillins, and it is more active against some Gram-negative bacteria and enterococci than are other penicillins.
Obviously, the α-amino group plays an important role in the broader activity, but the mechanism for its action is unknown. It has been suggested that the amino group confers an ability to cross cell wall barriers that are impenetrable to other penicillins. Ampicillin is not resistant to penicillinase, and it produces the allergic reactions and other untoward effects found in penicillin-sensitive patients. Because such reactions are relatively rare, however, it may be used to treat infections caused by Gram negative bacilli for which a broad-spectrum antibiotic, such as a tetracycline or chloramphenicol, may be indicated but not preferred because of undesirable reactions or lack of bactericidal effect.
Ampicillin is not so widely active; it is particularly useful for the treatment of acute urinary tract infections caused by *E. coli* or *Proteus mirabilis* and is the agent of choice against *Haemophilus influenzae* infections. Ampicillin, together with probenecid, to inhibit its active tubular excretion, has become a treatment of choice for gonorrhea in recent years. Incomplete absorption and excretion of effective concentrations in the bile may contribute to the effectiveness of ampicillin in the treatment of salmonellosis and shigellosis.
Ampicillin is water soluble and stable in acid. The protonated amino group of ampicillin has protonated extensively in acidic media, which explains ampicillin's stability to acid hydrolysis and instability to alkaline hydrolysis. It is administered orally and oral doses must be repeated about every 6 hours

Bacampicillin Hydrochloride



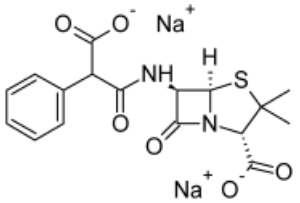
Bacampicillin hydrochloride is the hydrochloride salt of the 1- ethoxy-carbonyl-oxyethyl ester of ampicillin.
It is a prodrug of ampicillin with no antibacterial activity. After oral absorption, bacampicillin is hydrolyzed rapidly by esterases in the plasma to form ampicillin. Oral absorption of bacampicillin is more rapid and complete than that of ampicillin and less affected by food. Plasma levels of ampicillin from oral bacampicillin exceed those of oral ampicillin or amoxicillin but thereafter are the same as for ampicillin and amoxicillin. Effective plasma levels are sustained for 12 hours, allowing twice-a-day dosing.

Amoxicillin



Amoxicillin a semisynthetic penicillin, is simply the *p*-hydroxy analog of ampicillin, prepared by acylation of 6-APA with *p*-hydroxy-phenylglycine. Its antibacterial spectrum is nearly identical with that of ampicillin, and like ampicillin, it is resistant to acid, susceptible to alkaline and β-lactamase hydrolysis, and weakly protein bound. Early clinical reports indicated that orally administered amoxicillin possesses significant advantages over ampicillin, including more complete GI absorption to give higher plasma and urine levels, less diarrhea, and little or no effect of food on absorption. Thus, amoxicillin has largely replaced ampicillin for the treatment of certain systemic and urinary tract infections for which oral administration is desirable. Amoxicillin is reportedly less effective than ampicillin in the treatment of bacillary dysentery, presumably because of its greater GI absorption.

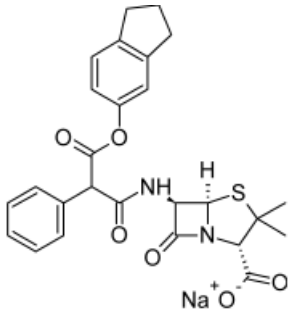
Carbenicillin Disodium, Sterile



Carbenicillin disodium, is a semisynthetic penicillin. Examination of its structure shows that it differs from ampicillin in having an ionizable carboxyl group rather than an amino group substituted on the α-carbon atom of the benzyl side chain. Carbenicillin has a broad range of antimicrobial activity, broader than any other known penicillin, a property attributed to the unique carboxyl group. It has been proposed that the carboxyl group improves penetration of the molecule through cell wall barriers of Gram-negative bacilli, compared with other penicillins. Carbenicillin is not stable in acids and is inactivated by penicillinase. It is a malonic acid derivative and, as such, decarboxylates readily to penicillin G, which is acid labile. It must be administered by injection and is usually given intravenously.
Carbenicillin has been effective in the treatment of systemic and urinary tract infections caused by *P. aeruginosa*, indole-producing *Proteus* spp., and *Providencia* spp., all of which are resistant to ampicillin. The low toxicity of carbenicillin, with the exception of allergic sensitivity, permits the use of large dosages in serious infections. Most clinicians prefer to use a combination of

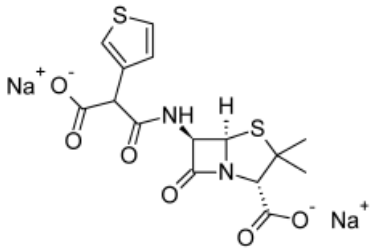
carbenicillin and gentamicin for serious pseudomonal and mixed coliform infections. The two antibiotics are chemically incompatible, however, and should never be combined in an intravenous solution.

Carbenicillin Indanyl Sodium



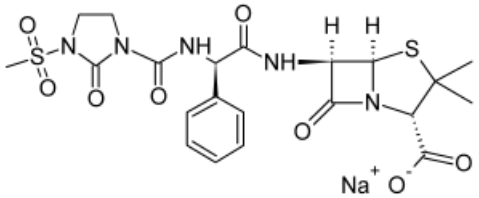
Efforts to obtain orally active forms of carbenicillin led to the eventual release of the 5-indanyl ester carbenicillin indanyl, usual oral dose of indanyl carbenicillin is absorbed. After absorption, the ester is hydrolyzed rapidly by plasma and tissue esterases to yield carbenicillin. Thus, although the highly lipophilic and highly protein-bound ester has in vitro activity comparable with that of carbenicillin, its activity in vivo is due to carbenicillin. Indanyl carbenicillin thus provides an orally active alternative for the treatment of carbenicillin sensitive systemic and urinary tract infections caused by *Pseudomonas* spp., indole-positive *Proteus* spp., and selected species of Gram-negative bacilli.

Ticarcillin Disodium, Sterile



Ticarcillin disodium, is an isostere of carbenicillin in which the phenyl group is replaced by a thienyl group. This semisynthetic penicillin derivative, like carbenicillin, is unstable in acid and, therefore, must be administered parenterally. It is similar to carbenicillin in antibacterial spectrum and pharmacokinetic properties. Two advantages for ticarcillin are claimed:
(a) slightly better pharmacokinetic properties, including higher serum levels and a longer duration of action; and
(b) greater in vitro potency against several species of Gram-negative bacilli, most notably *P. aeruginosa* and *Bacteroides fragilis*. These advantages can be crucial in the treatment of serious infections requiring high-dose therapy.

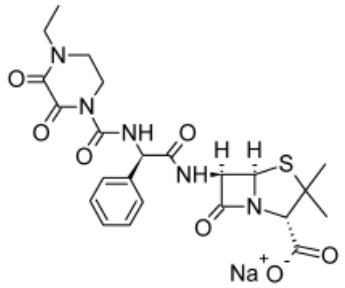
Mezlocillin Sodium, Sterile



Mezlocillin is an acylureidopenicillin with an antibacterial spectrum similar to that of carbenicillin and ticarcillin; however, there are some major differences. It is much more active against most *Klebsiella* spp., *P. aeruginosa*, anaerobic bacteria (e.g., *Streptococcus faecalis* and *B. fragilis*), and *H. influenzae*. It is recommended for the treatment of serious infections caused by these organisms.

Mezlocillin is not generally effective against β-lactamase–producing bacteria, nor is it active orally.

Piperacillin Sodium, Sterile



Piperacillin is the most generally useful of the extended spectrum acylureidopenicillins. It is more active than
mezlocillin against susceptible strains of Gram-negative aerobic bacilli, such as *Serratia marcescens*, *Proteus*, *Enterobacter*, *Citrobacter* spp., and *P. aeruginosa*. Piperacillin is also active against anaerobic bacteria, especially *B. fragilis* and *S. faecalis* (enterococcus). β-Lactamase–producing strains of these organisms are, however, resistant to piperacillin, which is hydrolyzed by *S. aureus* β-lactamase. The β-lactamase susceptibility of piperacillin is not absolute because β-lactamase–producing, ampicillin-resistant strains of *N. gonorrhoeae* and *H. influenzae* are susceptible to piperacillin.
Piperacillin is destroyed rapidly by stomach acid; therefore, it is active only by intramuscular or intravenous administration.