

University of Technology
Applied Science Department
Biotechnology Division



Antibiotics

4th Class

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2013-2014

Part2

Metabolism

The metabolism of the drug occurs in the liver and based on many factors like sex, age and bacteria which live in the intestinal tract. Metabolism consists of two phases are:

Phase I: Include oxidation, hydrolysis and reduction of a lipid-soluble or nonpolar drug that makes drug water soluble. Frequently, this reaction is mediated by a cytochrome p450 enzyme that introduces an atom of oxygen to the drug.

Phase II: (conjugation) which consists of adding a compound that will allow the intermediate to be excreted in the bile or urine.

I. Antibacterial Drugs

Classification of Antibacterial Drugs

1. According to the Effectiveness

- A. Bactericidal (penicillin, cephalosporin and aminoglycoside).
- B. Bacteriostatic (tetracycline, sulfanamid and erythromycin).

2. According to the Spectrum

- A. Broad spectrum (tetracycline, sulfanamid and chloramphenicol).
- B. Extend spectrum (enrofloxacin, trimethoprim and tricarcillin).
- C. Narrow spectrum (penicillin, cephalosporin and aminoglycosid).

3. According to the Nature

- A. Natural
- B. Synthetic
- C. Semisynthetic

4. According to the Mechanism of Action

A. Antibacterial which inhibit cell wall synthesis (penicillin, cephalosporin, bacteracin and cycloserin).

B. Antibacterial which inhibit protein synthesis (aminoglycoside, streptomycin, tetracycline, chloramphenicol and erythromycin).

C. Antibacterial which inhibit permeability of cell wall (polymyxin).

D. Antibacterial which inhibit folic acid of cell wall (sulfonamide, trimethoprim and cephalosporin).

E. Antibacterial which inhibit nucleic acid synthesis:

1. RNA (rifampin).

2. DNA (enrofloxacin and flumequin).

β-Lactam Antibiotics

β-Lactam antibiotics (beta-lactam antibiotics) are a broad class of antibiotics, consisting of all antibiotic agents that contains a β-lactam nucleus in their molecular structures. This includes penicillin derivatives (penams), cephalosporins (cephems), monobactams, and carbapenems.^[1] Most β-lactam antibiotics work by inhibiting cell wall biosynthesis in the bacterial organism and are the most widely used group of antibiotics. Up until 2003, when measured by sales, more than half of all commercially available antibiotics in use were β-lactam compounds.

Bacteria often develop resistance to β-lactam antibiotics by synthesizing a β-lactamase, an enzyme that attacks the β-lactam ring. To overcome this resistance, β-lactam antibiotics are often given with β-lactamase inhibitors such as clavulanic acid.

Mechanism of Action

β-Lactam antibiotics are bacteriocidal, and act by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls. The peptidoglycan layer is important for cell wall structural integrity, especially in Gram-positive

organisms, being the outermost and primary component of the wall. The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by transpeptidases known as penicillin-binding proteins (PBPs). PBPs vary in their affinity for binding penicillin or other β -lactam antibiotics. The amount of PBPs varies among bacterial species.

β -Lactam antibiotics are analogues of D-alanyl-D-alanine—the terminal amino acid residues on the precursor NAM/NAG-peptide subunits of the nascent peptidoglycan layer.

The structural similarity between β -lactam antibiotics and D-alanyl-D-alanine facilitates their binding to the active site of PBPs. The β -lactam nucleus of the molecule irreversibly binds to (acylates) the residue of the PBP active site. This irreversible inhibition of the PBPs prevents the final crosslinking (transpeptidation) of the nascent peptidoglycan layer, disrupting cell wall synthesis.

β -Lactam antibiotics block not only the division of bacteria, including cyanobacteria, but also the division of cyanelles, the photosynthetic organelles of the glaucophytes, and the division of chloroplasts of bryophytes. In contrast, they have no effect on the plastids of the highly developed vascular plants. This is supporting the endosymbiotic theory and indicates an evolution of plastid division in land plants.

Under normal circumstances, peptidoglycan precursors signal a reorganisation of the bacterial cell wall and, as a consequence, trigger the activation of autolytic cell wall hydrolases. Inhibition of cross-linkage by β -lactams causes a build-up of peptidoglycan precursors, which triggers the digestion of existing peptidoglycan by autolytic hydrolases without

the production of new peptidoglycan. As a result, the bactericidal action of β -lactam antibiotics is further enhanced.

Medical Use

β -Lactam antibiotics are indicated for the prophylaxis and treatment of bacterial infections caused by susceptible organisms. At first, β -lactam antibiotics were mainly active only against Gram-positive bacteria, yet the recent development of broad-spectrum β -lactam antibiotics active against various Gram-negative organisms has increased their usefulness.

Adverse Effects

Common adverse drug reactions (ADRs) for the β -lactam antibiotics include diarrhea, nausea, rash, urticaria, superinfection (including candidiasis). Infrequent ADRs include fever, vomiting, erythema, dermatitis, angioedema, pseudomembranous colitis. Pain and inflammation at the injection site is also common for parenterally administered β -lactam antibiotics.

Allergy/Hypersensitivity

Immunologically mediated adverse reactions to any β -lactam antibiotic may occur in up to 10% of patients receiving that agent (a small fraction of which are truly IgE-mediated allergic reactions, see amoxicillin rash). Anaphylaxis will occur in approximately 0.01% of patients.^{[3][4]} There is perhaps a 5%-10% cross-sensitivity between penicillin-derivatives, cephalosporins, and carbapenems; but this figure has been challenged by various investigators.

Nevertheless, the risk of cross-reactivity is sufficient to warrant the contraindication of all β -lactam antibiotics in patients with a history of severe allergic reactions (urticaria, anaphylaxis, interstitial nephritis) to any β -lactam antibiotic.

A Jarisch-Herxheimer reaction may occur after initial treatment of a spirochetal infection such as syphilis with a β -lactam antibiotic.

Modes of Resistance

By definition, all β -lactam antibiotics have a β -lactam ring in their structure. The effectiveness of these antibiotics relies on their ability to reach the PBP intact and their ability to bind to the PBP. Hence, there are two main modes of bacterial resistance to β -lactams: Enzymatic hydrolysis of the β -lactam ring.

If the bacterium produces the enzyme β -lactamase or the enzyme penicillinase, the enzyme will hydrolyse the β -lactam ring of the antibiotic, rendering the antibiotic ineffective.^[10] (An example such enzyme is NDM-1, discovered in 2009.) The genes encoding these enzymes may be inherently present on the bacterial chromosome or may be acquired via plasmid transfer (plasmid mediated resistance), and β -lactamase gene expression may be induced by exposure to β -lactams.

The production of a β -lactamase by a bacterium does not necessarily rule out all treatment options with β -lactam antibiotics. In some instances, β -lactam antibiotics may be co-administered with a β -lactamase inhibitor. For example, Augmentin (FGP) is made of amoxicillin, a β -lactam antibiotic, and clavulanic acid, a β -lactamase inhibitor. The clavulanic acid is designed to overwhelm all β -lactamase enzymes, bind irreversibly to them, and effectively serve as an antagonist so that the amoxicillin is not affected by the β -lactamase enzymes.

However, in all cases where infection with β -lactamase-producing bacteria is suspected, the choice of a suitable β -lactam antibiotic should be carefully considered prior to treatment. In particular, choosing appropriate β -lactam antibiotic therapy is of utmost importance against organisms with inducible β -lactamase expression. If β -lactamase production is inducible, then failure to use the most appropriate β -lactam antibiotic therapy at the onset of treatment will result in induction of β -lactamase production, thereby making further efforts with other β -lactam antibiotics more difficult.

Biosyntheses

To date, two distinct methods of biosynthesizing the β -lactam core of this family of antibiotics have been discovered. The first pathway discovered was that of the penams and cepheems. This path begins with a nonribosomal peptide synthetase (NRPS), ACV synthetase (ACVS), which generates the linear tripeptide δ -(L- α -aminoadipyl)-L-cysteine-D-valine (ACV). ACV is oxidatively cyclized (two cyclizations by a single enzyme) to bicyclic intermediate isopenicillin N by isopenicillin N synthase (IPNS) to form the penam core structure.^[12] Various transamidations lead to the different natural penicillins.



This figure outlines the different methods of β -lactam closure among the various classes of β -lactam compounds. Penams and cepems are cyclized oxidatively (first row); clavams and carbapenems are closed by ATP-utilizing amidation (second and third row); and some monobactams may be closed by a third method (fourth row).

The biosynthesis of cepems branch off at isopenicillin N by an oxidative ring expansion to the cepem core. As with the penams, the variety of cephalosporins and cephamycins come from different transamidations, as is the case for the penicillins.

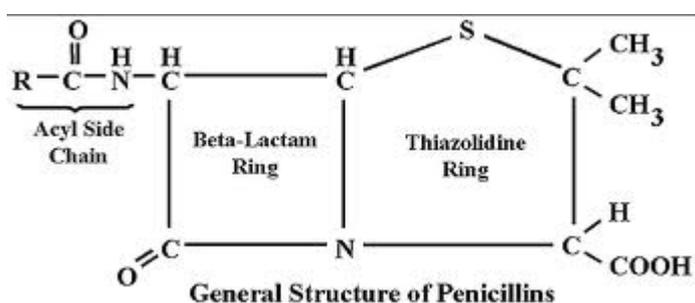
While the ring closure in penams and cepems is between positions 1 and 4 of the β -lactam and is oxidative, the clavams and carbapenems have their rings closed by two-electron processes between positions 1 and 2 of the ring. β -Lactam synthetases are responsible for these cyclizations, and the carboxylate of the open-ring substrates is activated by ATP. In

clavams, the β -lactam is formed prior to the second ring; in carbapenems, the β -lactam ring is closed second in sequence.

The biosynthesis of the β -lactam ring of tabtoxin mirrors that of the clavams and carbapenems. The closure of the lactam ring in the other monobactams, such as sulfazecin and the nocardicins, may involve a third mechanism involving inversion of configuration at the β -carbon.

Antibacterial which inhibit cell wall synthesis

Penicillin



Penicillin is a group of antibiotics derived from *Penicillium* fungi. They include penicillin G, procaine penicillin, benzathine penicillin, and penicillin V. Penicillin antibiotics are historically significant because they

are the first drugs that were effective against many previously serious diseases, such as syphilis, and infections caused by staphylococci and streptococci. Penicillins are still widely used today, though many types of bacteria are now resistant. All penicillins are β -lactam antibiotics and are used in the treatment of bacterial infections caused by susceptible, usually Gram-positive, organisms.

History

The discovery of penicillin is attributed to Scottish scientist and Nobel laureate Alexander Fleming in 1928. He showed that, if *Penicillium rubens* were grown in the appropriate substrate, it would exude a substance with antibiotic properties, which he dubbed penicillin. This serendipitous observation began the modern era of antibiotic discovery. The development of penicillin for use as a medicine is attributed to the Australian Nobel laureate Howard Walter Florey, together with the German Nobel laureate Ernst Chain and the English biochemist Norman Heatley. However, several others reported the bacteriostatic effects of *Penicillium* earlier than Fleming. The use of bread with a blue mould (presumed to be *Penicillium*) as a means of treating suppurating wounds was a staple of folk medicine in Europe since the middle ages.

The first published reference appears in the publication of the Royal Society in 1875, by John Tyndall. Joaquim Monteiro Caminhoá, Professor of Botany and Zoology of the Faculty of Medicine of Rio de Janeiro, Brazil, also recognised the antibiotic activity of *Penicillium* and other fungi in 1877. In his book, "Elements of General and Medical Botany" (under a section titled 'Useful fungi, harmful and curious'), he stated:

In 1895, Vincenzo Tiberio, physician of the University of Naples published a research about a mold (*Penicillium*) in a water well that had an antibacterial action.

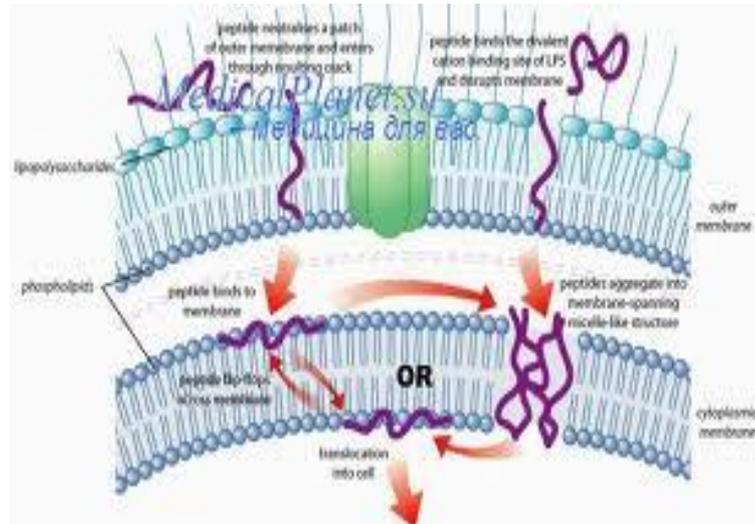
Ernest Duchesne documented it in an 1897 paper, which was not accepted by the Institut Pasteur because of his youth. In March 2000, doctors at the San Juan de Dios Hospital in San José, Costa Rica, published the manuscripts of the Costa Rican scientist and medical doctor Clodomiro (Clorito) Picado Twilight (1887–1944). They reported Picado's observations on the inhibitory actions of fungi of the genus *Penicillium* between 1915 and 1927. Picado reported his discovery to the Paris Academy of Sciences, yet did not patent it, even though his investigations started years before Fleming's. Joseph Lister was experimenting with *Penicillium* in 1871 for his aseptic surgery. He found that it weakened the microbes, but then he dismissed the fungi. These early investigations did not lead to the use of antibiotics to treat infection because they took place in obscure circumstances, and the idea that infections were caused by transmissible agents was not widely accepted at the time.

Sterilization measures had been shown to limit the outbreak and spread of disease; however, the mechanism of transmission of disease by parasites, bacteria, viruses and other agents was unknown. In the late 19th century, knowledge was increasing of the mechanisms by which living organisms become infected, how they manage infection once it has begun and, most importantly in the case of penicillin, the effect that natural and man-made agents could have on the progress of infection. Fleming recounted that the date of his discovery of penicillin was on the morning of Friday, September 28, 1928. It was a fortuitous accident: in his laboratory in the basement of St. Mary's Hospital in London (now part of Imperial College), Fleming noticed a Petri dish containing *Staphylococcus* plate culture he mistakenly left open, was contaminated by blue-green mould,

which formed a visible growth. There was a halo of inhibited bacterial growth around the mould. Fleming concluded the mould released a substance that repressed the growth and lysing the bacteria. He grew a pure culture and discovered it was a *Penicillium* mould, now known to be *Penicillium notatum*. Charles Thom, an American specialist working at the U.S. Department of Agriculture, was the acknowledged expert, and Fleming referred the matter to him. Fleming coined the term "penicillin" to describe the filtrate of a broth culture of the *Penicillium* mould. Even in these early stages, penicillin was found to be most effective against Gram-positive bacteria, and ineffective against Gram-negative organisms and fungi. He expressed initial optimism that penicillin would be a useful disinfectant, being highly potent with minimal toxicity compared to antiseptics of the day, and noted its laboratory value in the isolation of *Bacillus influenzae* (now *Haemophilus influenzae*). After further experiments, Fleming was convinced penicillin could not last long enough in the human body to kill pathogenic bacteria, and stopped studying it after 1931. He restarted clinical trials in 1934, and continued to try to get someone to purify it until 1940.

Mechanism of Action

Penicillin and other β -lactam antibiotics act by inhibiting penicillin-binding proteins, which normally catalyze cross-linking of bacterial cell walls.



Bacteria that attempt to divide in the presence of penicillin fail to do so and end up shedding their cell walls in the process. Bacteria constantly remodel their peptidoglycan cell walls, simultaneously building and breaking down portions of the cell wall as they grow and divide. β -Lactam antibiotics inhibit the formation of peptidoglycan cross-links in the bacterial cell wall, but have no direct effect on cell wall degradation. The β -lactam moiety (functional group) of penicillin binds to the enzyme (DD-transpeptidase) that links the peptidoglycan molecules in bacteria. The enzymes that hydrolyze the peptidoglycan cross-links continue to function, which weakens the cell wall of the bacterium (in other words, the antibiotic cause's cytolysis or death due to osmotic pressure). In addition, the build-up of peptidoglycan precursors triggers the activation of bacterial cell wall hydrolases and autolysins, which further digest the bacteria's existing peptidoglycan. This imbalance between cell wall production and degradation is responsible for the rapid cell-killing action of this class of drugs, even in the absence of cell division. In addition, the relatively small size of the penicillin molecule allows it to penetrate deeply into the cell wall, affecting its entire depth. This is in contrast to the other major class of antibiotics that inhibit cell wall synthesis, the glycopeptide antibiotics (which includes vancomycin and teicoplanin).

Gram-positive bacteria are called protoplasts when they lose their cell walls. Gram-negative bacteria do not lose their cell walls completely and are called spheroplasts after treatment with penicillin.

Penicillin shows a synergistic effect with aminoglycosides, since the inhibition of peptidoglycan synthesis allows aminoglycosides to penetrate the bacterial cell wall more easily, allowing their disruption of bacterial protein synthesis within the cell. This results in a lowered MBC for susceptible organisms.

Penicillins, like other β -lactam antibiotics, block not only the division of bacteria, including cyanobacteria, but also the division of cyanelles, the photosynthetic organelles of the glaucophytes, and the division of chloroplasts of bryophytes. In contrast, they have no effect on the plastids of the highly developed vascular plants. This supports the endosymbiotic theory of the evolution of plastid division in land plants

Biosynthesis

Overall, there are three main and important steps to the biosynthesis of penicillin G (benzylpenicillin).

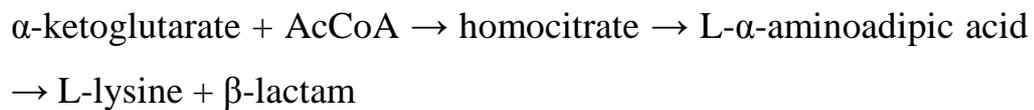
- The first step is the condensation of three amino acids — L- α -aminoadipic acid, L-cysteine, L-valine into a tripeptide. Before condensing into the tripeptide, the amino acid L-valine must undergo epimerization to become D-valine. The condensed tripeptide is named δ -(L- α -aminoadipyl)-L-cysteine-D-valine (ACV). The condensation reaction and epimerization are both catalyzed by the enzyme δ -(L- α -aminoadipyl)-L-cysteine-D-valine synthetase (ACVS), a nonribosomal peptide synthetase or NRPS.
- The second step in the biosynthesis of penicillin G is the oxidative conversion of linear ACV into the bicyclic intermediate

isopenicillin N by isopenicillin N synthase (IPNS), which is encoded by the gene *pcbC*. Isopenicillin N is a very weak intermediate, because it does not show strong antibiotic activity.^[13]

- The final step is an transamidation by isopenicillin N N-acyltransferase, in which the α -aminoadipyl side-chain of isopenicillin N is removed and exchanged for a phenylacetyl side-chain. This reaction is encoded by the gene *penDE*, which is unique in the process of obtaining penicillins.

Production

Penicillin is a secondary metabolite of certain species of *Penicillium* and is produced when growth of the fungus is inhibited by stress. It is not produced during active growth. Production is also limited by feedback in the synthesis pathway of penicillin.



The by-product, L-lysine, inhibits the production of homocitrate, so the presence of exogenous lysine should be avoided in penicillin production.

The *Penicillium* cells are grown using a technique called fed-batch culture, in which the cells are constantly subject to stress, which is required for induction of penicillin production. The available carbon sources are also important: Glucose inhibits penicillin production, whereas lactose does not. The pH and the levels of nitrogen, lysine, phosphate, and oxygen of the batches must also be carefully controlled. The biotechnological method of directed evolution has been applied to produce by mutation a large number of *Penicillium* strains. These techniques include error-prone PCR, DNA shuffling, ITCHY, and strand-

overlap PCR. Semisynthetic penicillins are prepared starting from the penicillin nucleus 6-APA.

Medical uses

The term "penicillin" is often used generically to refer to benzylpenicillin (penicillin G), procaine benzylpenicillin (procaine penicillin), benzathine benzylpenicillin (benzathine penicillin), and phenoxymethylpenicillin (penicillin V).

Procaine penicillin and benzathine penicillin have the same antibacterial activity as benzylpenicillin but act for a longer time span. Phenoxymethylpenicillin is less active against Gram-negative bacteria than benzylpenicillin. Benzylpenicillin, procaine penicillin and benzathine penicillin are given by injection (parenterally), but phenoxymethylpenicillin is given orally.

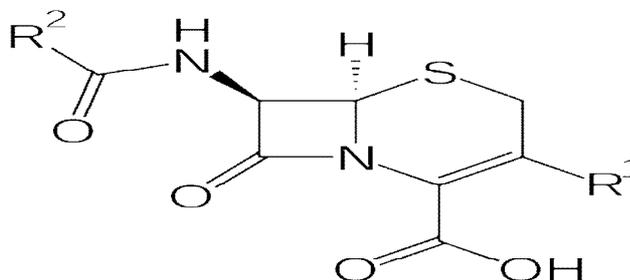
Adverse Effects

Common adverse drug reactions ($\geq 1\%$ of patients) associated with use of the penicillins include diarrhoea, hypersensitivity, nausea, rash, neurotoxicity, urticaria, and superinfection (including candidiasis). Infrequent adverse effects (0.1–1% of patients) include fever, vomiting, erythema, dermatitis, angioedema, seizures (especially in epileptics), and pseudomembranous colitis.

Cephalosporin

The cephalosporins are a class of β -lactam antibiotics originally derived from the fungus *Acremonium*, which was previously known as

"Cephalosporium". Together with cephamycins they constitute a subgroup of β -lactam antibiotics called cephems.



History

Cephalosporin compounds were first isolated from cultures of *Cephalosporium acremonium* from a sewer in Sardinia in 1948 by Italian scientist Giuseppe Brotzu. He noticed that these cultures produced substances that were effective against *Salmonella typhi*, the cause of typhoid fever, which had beta-lactamase. Guy Newton and Edward Abraham at the Sir William Dunn School of Pathology at the University of Oxford isolated cephalosporin C. The cephalosporin nucleus, 7-aminocephalosporanic acid (7-ACA), was derived from cephalosporin C and proved to be analogous to the penicillin nucleus 6-aminopenicillanic acid (6-APA), but it was not sufficiently potent for clinical use. Modification of the 7-ACA side-chains resulted in the development of useful antibiotic agents, and the first agent cefalotin (cephalothin) was launched by Eli Lilly and Company in 1964.

Classification of Cephalosporin

Cephalosporins are grouped into generation based on their spectrum of antimicrobial activity. The first cephalosporins were designated first generation while later more extended spectrum cephalosporins were

classified as second generation cephalosporins. Each newer generation has significantly greater gram-negative antimicrobial properties than the preceding generation. In most cases with decreased activity against gram-positive organism. Fourth generation cephalosporins, however, have true broad spectrum activity.

First Generation

First generation cephalosporins are moderate spectrum agents. They are effective alternatives for treating staphylococcal and streptococcal infections and therefore are alternative for skin and soft tissue infections. As well as for streptococcal pharyngitis. Like cephadroxil and cephalixin.

Second Generation

The second generation cephalosporins have a greater gram-negative spectrum while retaining some activity against gram-positive bacteria. They are useful agents for treating upper and lower respiratory tract infections and otitis media. These agents are also active against E.coli, klebsiella and proteus, which makes them potential alternatives for treating urinary tract infections caused by these organisms. This generation includes cefaclor and cefoxitin.

Third Generation

Third generation cephalosporins have a broad spectrum of activity and further increased activity against gram-negative organisms. Some members of this group have decreased activity against gram-positive organisms. the parenteral third generation cephalosporins have excellent activity against most strains of streptococcus pneumonia including the vast majority of those with intermediate and high level resistance to pencillin. This group includes ceftriaxone and cefixime.

Fourth Generation

Fourth generation cephalosporins are extend spectrum agents with similar activity against gram-positive organisms as first generation cephalosporins. They also have a greater resistance to beta-lactamases than the third generation cephalosporins. Many can cross blood brain barrier and are effective in meningitis. This group includes cefepime.

Mechanism of Action

Cephalosporins are bactericidal and have the same mode of action as other beta-lactam antibiotics (such as penicillins) but are less susceptible to penicillinases. Cephalosporins disrupt the synthesis of the peptidoglycan layer of bacterial cell walls. The peptidoglycan layer is important for cell wall structural integrity. The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by transpeptidases known as penicillin-binding proteins (PBPs). PBPs bind to the D-Ala-D-Ala at the end of mucopeptides (peptidoglycan precursors) to crosslink the peptidoglycan. Beta-lactam antibiotics mimic the D-Ala-D-Ala site, thereby competitively inhibiting PBP crosslinking of peptidoglycan.

Resistance

Resistance to cephalosporin antibiotics can involve either reduced affinity of existing penicillin-binding-protein components or the acquisition of a supplementary beta-lactam-insensitive penicillin-binding-protein. Currently some *Citrobacter freundii*, *Enterobacter cloacae* and *Escherichia coli* strains are resistant to cephalosporin. Some *Morganella morganii*, *Proteus vulgaris*, *Providencia rettgeri*, *Pseudomonas aeruginosa* and *Serratia marcescens* strains have also developed resistance to cephalosporin to varying degrees.

Medical use

Cephalosporins are indicated for the prophylaxis and treatment of infections caused by bacteria susceptible to this particular form of antibiotic. First-generation cephalosporins are active predominantly against Gram-positive bacteria, and successive generations have increased activity against Gram-negative bacteria (albeit often with reduced activity against Gram-positive organisms).

Adverse Effects

Common adverse drug reactions (ADRs) ($\geq 1\%$ of patients) associated with the cephalosporin therapy include: diarrhea, nausea, rash, electrolyte disturbances, and/or pain and inflammation at injection site. Infrequent ADRs (0.1–1% of patients) include vomiting, headache, dizziness, oral and vaginal candidiasis, pseudomembranous colitis, superinfection, eosinophilia, and/or fever.

The commonly quoted figure of 10% of patients with allergic hypersensitivity to penicillins and/or carbapenems also having cross-reactivity with cephalosporins originated from a 1975 study looking at the original cephalosporins,^[2] and subsequent "safety first" policy meant this was widely quoted and assumed to apply to all members of the group.^[3] Hence it was commonly stated that they are contraindicated in patients with a history of severe, immediate allergic reactions (urticaria, anaphylaxis, interstitial nephritis, etc.) to penicillins, carbapenems, or cephalosporins.^[4] This, however, should be viewed in the light of recent epidemiological work suggesting that, for many second-generation (or later) cephalosporins, the cross-reactivity rate with penicillin is much lower, having no significantly increased risk of reactivity in the studies

examined. The British National Formulary previously issued blanket warnings of 10% cross reactivity, but, since the September 2008 edition, suggests that, in the absence of suitable alternatives, oral cefixime or cefuroxime and injectable cefotaxime, ceftazidime, and ceftriaxone can be used with caution; but that the use of cefaclor, cefadroxil, cefalexin, and cefradine should be avoided.

Several cephalosporins are associated with hypoprothrombinemia and a disulfiram-like reaction with ethanol. These include latamoxef, cefmenoxime, moxalactam, cefoperazone, cefamandole, cefmetazole, and cefotetan. This is thought to be due to the N-methylthiotetrazole (NMTT) side-chain of these cephalosporins, which blocks the enzyme vitamin K epoxide reductase (likely causing hypothrombinemia) and aldehyde dehydrogenase (causing alcohol intolerance).