

Cephalosporin Antibiotics History and Update

*Nidhi Rao, Dharmendra Singh Rajput

Department of Pharmacy Practice, Indubhai Patel College of Pharmacy and Research Centre, Dharmaj, Anand, Gujrat-388430, India

ARTICLE INFO

Received: 01.01.2021

Accepted: 15.01.2021

Final Version: 27.01.2021

*Corresponding Author:
Email:
nrao2312@gmail.com

ABSTRACT

Cephalosporins are a large group of antibiotics derived from the mold and acrimonious. Cephalosporin's are grouped into 5 generations: first generation cephalosporin's, second generation cephalosporin's, third generation cephalosporin's, fourth generation cephalosporin's, fifth generation cephalosporin's. First-generation cephalosporins are indicated for surgical prophylaxis and for treatment of infections in patients who are allergic to penicillin's. Activity against gram-negative bacilli increases from first- to third-generation drugs, but sensitive isolates should be treated with first-generation agents to prevent resistance. No cephalosporin is active against the enterococci. Some experimental cephalosporins have improved activity against *P. aeruginosa*. A few of these agents have a very long half-life. Cephalosporin's are bactericidal and work in a similar way to penicillin's. Cephalosporin is a β -lactam antibiotic that inhibits bacterial cell wall synthesis. Cephalosporin's are used to treat bacterial infections like skin or soft tissue infections, urinary tract infections (UTIs), strep throat, meningitis, gonorrhoea, etc. Cephalosporins have low toxicity and are generally safe. The most common adverse reactions from cephalosporins are nausea, vomiting, lack of appetite, and abdominal pain.

Keywords: Cephalosporin's; Structure of cephalosporins; MOA of cephalosporins; ADR of cephalosporins

Introduction

Since cephalothin and cephaloridine were introduced in 1964, cephalosporin's have become a widely used and rapidly expanding class of antibacterial agents. A large number of derivatives have been synthesized by modifying the 7-amino-cephalosporinic-acid (7 ACA) [1].

Cephalosporins are antibiotics grouped into five generations based on their spectrum of coverage against gram-positive and gram-negative bacteria as well as their temporal discovery. First-generation cephalosporins include cefazolin, cefalexin, cefazedone, cefadroxil, and cephalixin. First-generation cephalosporins have active coverage against most gram-positive cocci such as staphylococci spp. and streptococci spp. while having minimal coverage against gram-negative bacteria. Gram-negative bacteria that are more susceptible to first-generation cephalosporins are *Proteus mirabilis*, *E. coli*, and *Klebsiella pneumonia* [2]. Second-generation

cephalosporins have coverage against *Haemophilus influenza* (*H. influenza*), *Moraxella catarrhalis*, and *Bacteroides* spp. Third-generation cephalosporins have less coverage against most gram-positive organisms but have increase coverage against enterobacteriaceae, *Neisseria* spp., and *H. influenza*. Fourth-generation cephalosporins have similar coverage as third-generation cephalosporins but with additional coverage against gram-negative bacteria with antimicrobial resistance, e.g., beta-lactamase. Fifth-generation cephalosporins have coverage against methicillin-resistant staphylococci and penicillin-resistant pneumococci [3].

In recent years a number of highly active cephem derivatives have been reported, and some of them developed and introduced into clinical practice [1].

Cephalosporin, any of a group of β -lactam antibiotics that inhibit the synthesis of a structural component of the bacterial cell wall. The cephalosporins were first isolated from cultures of the fungus *Cephalosporium acremonium*.

Modifications of the β -lactam ring have resulted in more than 20 derivatives with a range of antibacterial properties. The cephalosporins are often used as an alternative in patients who are sensitive to penicillin [4].

Literature Review

History

The first chemical compounds of the cephalosporin group were isolated from *Cephalosporium acremonium*, a cephalosporin-producing fungus first discovered by Giuseppe Brotzu in 1948 from a sewage outfall off the Sardinian coast. From crude filtrates of the *Cephalosporium acremonium* culture scientists got new antibacterial activity. It was noted that the crude filtrate could inhibit the growth of *Staphylococcus aureus* [5].



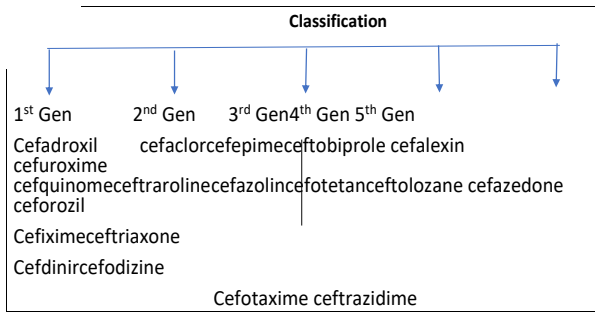
Giuseppe Brotzu [A]

- 1945 – Cephalosporin were first detected in *cephalosporium acremonium*.
- 1948 – Cephalosporins are semisynthetic antibiotic derivatives of cephalosporin C. Brotzu published his result in 1948.
- 1964 - Alarmed by the need to ahead of rapidly mutating bacterial strains, researchers since then have developed 4 generation cephalosporins.
- 1971 – In January 1971 Eli Lilly introduced Keflex, generic name cephalexin
- 1996– In January 1996 a progressive reintroduction of cephalosporins was including the novel 4th generation cephalosporin cefepime.
- 2003 – February 11, 2003 Ranbaxy laboratories has rolled out its high-end cephalosporin or cefprozil under the brand name Refzil. Cephalosporins have an estimated Rs 1000 crore in India.
- 2005 – In fact the risk that a patient with a history of penicillin allergy will experience a reaction to a 1st generation cephalosporin not more than 0.5%, 2nd generation cephalosporin not more than 0.2% and a 3rd generation cephalosporin practically nil in at least 25 studies.
- 2010 - February 28, 2010 most patients who have a history of penicillin allergy can safely take antibiotic called cephalosporins US researchers say.

CLASSIFICATION

- Cephalosporins are bactericidal beta-lactam antibiotic derived from the fungus *acremonium*-they disrupt peptidoglycan formation in the cell wall [10].
- They have no activity against LAME: *Listeria*, Atypicals (*mycoplasma/chlamydia*), MRSA and

enterococci (only MRSA exception being 5th generation drug: ceftobiprole etc.) [7].



1st generation cephalosporins

- cefadroxil, cefalexin, cefazolin, cefazedone
- common characters:
 - Activity on gram-positive bacteria: First > Second > Third
 - Activity on gram-negative bacteria: First < Second < Third
 - Stability to β-lactamase produce by gram-negative rods: First < Second < Third
 - Renal toxicity: First > Second > Third
- Clinical uses:
 - Penicillin-resistant staphylococcal infection
 - Minor by sensitive bacteria

2nd generation cephalosporins

- Cefaclor, cefuroxime, cefotetan, cefprozil
- Common characters:
 - More stable to β-Lactamase
 - More active on gram negative bacteria
 - Less active on gram positive bacteria
 - Less renal toxicity
 - Effective on anaerobes
 - No effect on pseudomonas aeruginosa
- Clinical uses:
 - Gram negative bacterial infection
 - Anaerobic infections

3rd generation cephalosporins

- Cefixime, ceftriaxone, cefdinir, cefodizine, ceftazidime
- Common characters:
 - Much more active on gram negative bacteria
 - Stable to extended β-Lactamase produced by gram negative bacteria
 - Effective on anaerobes and pseudomonas aeruginosa
 - No renal toxicity
 - Penetrating body fluid and tissues well
- Clinical uses:
 - A wide variety of serious infections caused by organisms that are resistant to most other drugs

4th generation cephalosporins

- Cefepime, cefquinome
- Common characters:
 - Enhanced antimicrobial activity
 - Stable to ESBLs
 - More activity on gram positive cocci
- Clinical uses:

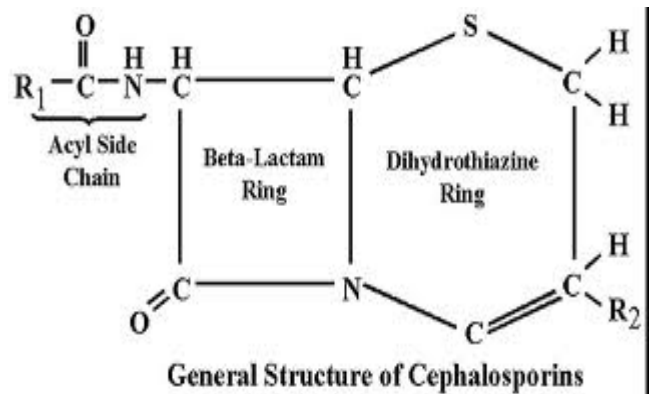
Infections caused by organisms that are resistant to third generation cephalosporins

5th generation cephalosporins

- Ceftobiprole, ceftrazoline, ceftolozane
- Common characters:
 - Exhibits broad-spectrum activity against gram positive bacteria
- Clinical uses:
 - In bacterial infections which resistant penicillin antibiotic

Structure of cephalosporin

Cephalosporin is a β-lactam antibiotic that inhibits bacterial cell wall synthesis. In 1948 Dr. Abraham first isolated cephalosporin C from a fungus Cephalosporium acremonium. Cephalosporins have broader gram -ve coverage than penicillin yet no one of the cephalosporins is active against MRSA and enterococci. Basic structure of cephalosporin is 7-aminocephalosporanic acid [7].



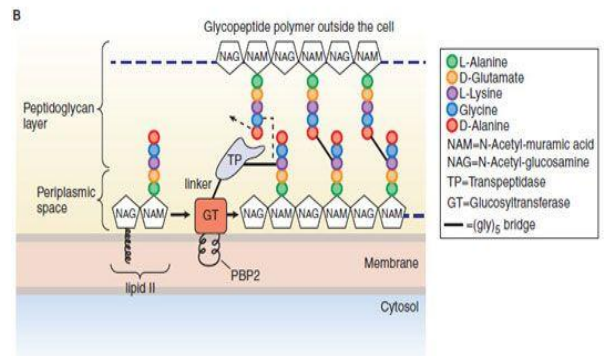
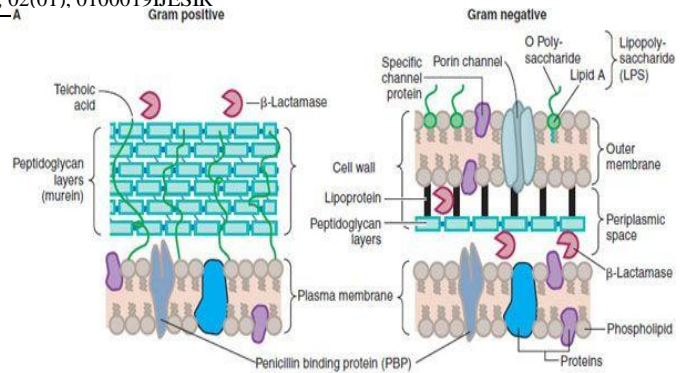
Structure of cephalosporin

Mechanism of action

- **Cephalosporins** are bactericidal and have the same mode of action as other β-Lactam antibiotics (such as penicillin) but are less susceptible to penicillinases [11].
- **Cephalosporin** disrupts the synthesis of the peptidoglycan layer of bacterial cell walls [11].
- **Bacteria** synthesize a cell wall that is strengthened by cross-linking peptidoglycan units via penicillin-binding proteins (PBP, peptidoglycan transpeptidase). Initially

derived from the fungus *Cephalosporium* sp., cephalosporins are a large group of bactericidal antimicrobials that work via their beta-lactam rings. The beta-lactam rings bind to the penicillin-binding protein and inhibit its normal activity. Unable to synthesize a cell wall, the bacteria die.

➤ **Staphylococcus aureus** that is initially susceptible to cephalosporins can develop resistance by changing the structure of the penicillin-binding proteins. *S. aureus* does this by having a gene that encodes a modified penicillin-binding protein; this prevents the cephalosporin's beta-lactam rings to inactivate the protein. The bacterium that develops this mechanism of resistance is called methicillin-resistant *Staphylococcus aureus* (MRSA). As indicated above, out of the five generations of cephalosporin, only the fifth generation ceftaroline has coverage against methicillin-resistant *Staphylococcus aureus*. Another very important mechanism of resistance is by producing the enzyme beta-lactamase, which cleaves the beta-lactam ring preventing it from attaching to the penicillin-binding proteins, e.g., peptidoglycan transpeptidase. Beta-lactamase inhibitors can be co-formulated with cephalosporins to increase their spectrum of activity, e.g., ceftazidime/avibactam, and ceftolozane/tazobactam [14].



Results and Discussion

Clinical uses

- Cephalosporins induce their antimicrobial effect by inhibiting the integration of bacterial peptidoglycan [2].
- Cephalosporins are active in vitro against many gram-positive aerobic bacteria and some gram-negative aerobic bacteria [2].
- Later-generation cephalosporins also are used in the later stages of livestock raising for adding weight [2].
- Cephalosporins is use to treat a variety of bacterial infections, especially for people who are allergic to penicillin, another common antibiotic [8].

Some examples of infections that cephalosporins can treat include:

- skin or soft tissue infections
- urinary tract infections (UTIs)
- strep throat
- ear infections
- pneumonia
- sinus infections
- meningitis
- gonorrhoea

Adverse Effects

Cephalosporins have low toxicity and are generally safe. The most common adverse reactions from cephalosporins are nausea, vomiting, lack of appetite, and abdominal pain [2].

The less common adverse reaction includes:

Hypersensitivity reaction

A hypersensitivity reaction to cephalosporin is infrequent and is more common in first and second-generation cephalosporins. Common allergic reaction to cephalosporin includes rash, hives, and swelling. Rarely will the hypersensitivity reaction result in anaphylaxis. Patients who are allergic to penicillin might show a hypersensitive reaction to cephalosporins as well. This cross-reactivity is once again more common in first and second-generation cephalosporins because they have R-groups more similar to penicillin G. Third generation and beyond show minimal cross-reactivity [2].

Drug-induced immune haemolytic anemia (DIIHA)

Drug-induced immune haemolytic anemia is a blood disorder that occurs when a medicine triggers the body's defence (immune) system to attack its own red blood cells. This causes red blood cells to break down earlier than normal, a process called haemolysis.

Anemia is a condition in which the body does not have enough healthy red blood cells. Red blood cells provide oxygen to body tissues.

Normally, red blood cells last for about 120 days in the body. In haemolytic anemia, red blood cells in the blood are destroyed earlier than normal.

In some cases, a drug can cause the immune system to mistake your own red blood cells for foreign substances. The body responds by making antibodies to attack the

body's own red blood cells. The antibodies attach to red blood cells and cause them to break down too early [9].

Disulfiram-like reaction

Cephalosporins containing a methyltetrazolethiol side chain can inhibit the aldehyde dehydrogenase enzyme resulting in the accumulation of acetaldehyde. Cefamandole, cefoperazone, and moxalactam are the most common cephalosporin to present with this reaction [2].

Vitamin K deficiency

Vitamin K deficiency could also result from the use of cephalosporins which inhibit Vitamin K epoxide reductase, the enzyme needed to reduce the vitamin K after it has been oxidized in the carboxylation of glutamic acid residues of the coagulation factors [10].

Pseudomembranous colitis

Pseudomembranous colitis results from changes to the bacterial flora after you use cephalosporin and other antibiotics. In some cases, taking cephalosporin and antibiotics can cause C. diff to grow out of control and release toxins (poisons) into intestinal tissues. These toxins attack the lining of the intestine and cause pseudomembranous colitis symptoms [11].

Increase nephrotoxicity of aminoglycosides

Aminoglycosides accumulate in the renal lysosomes and may interfere with Na⁺-, K⁺-dependent adenosine triphosphatase activity. Experiments with cephaloridine and cephaloglycin, two nephrotoxic cephalosporins, indicate that they cause mitochondrial injury that leads to impaired cellular respiration [12].

Drug Interactions: Don't take a cephalosporin if you're taking Theracrys (BCG live intravesical).

Ask your doctor about taking a cephalosporin if you're taking:

- Drugs for acid reflux like Pepcid (famotidine), Tagamet (cimetidine), or Zantac (ranitidine)

- Other heartburn medications like Aciphex (rabeprazole), Dexilant (dexlansoprazole), Nexium (esomeprazole)
- Vivotif (live typhoid vaccine) [13]

References

1. André Bryskier: "New concepts in the field of cephalosporins: C-3' quaternary ammonium cepems (Group IV)", April 1997, Volume 3, Supplement 1, S1-S101.
2. Shayne C. Gad, in Encyclopedia of Toxicology (Second Edition): "cephalosporin",2005.
3. Toai Bui1; Charles V. Preuss2: "Cephalosporins", March 24 2020.
4. The Editors of Encyclopaedia Britannica:"Cephalosporin", Feb 05 2020
5. The free encyclopaedias "Discovery and development of cephalosporins"
6. Prof. P. Ravisankar: "cephalosporins-history"
7. Gaurabkarki:"cephalosporin: structure, classification, clinical use and mode of action" April 8, 2018.
8. Jill Seladi-schulman: "cephalosporins" January 28, 2019 .
9. U.S. National library of medicine: "drug- induced immune hemolytic anemia"
10. .Martin J Shearer: "Mechanism of Cephalosporin-induced Hypoprothrombinemia: Relation to Cephalosporin Side Chain, Vitamin K Metabolism, and Vitamin K Status" January 1988 The Journal of Clinical Pharmacology 28(1):88-95
11. Cleveland clinic medical professional: "Pseudomembranous Colitis" June 6, 2018
12. Silverblatt F: "Pathogenesis of nephrotoxicity of cephalosporins and aminoglycosides: a review of current concepts" Sep-Oct 1982;4 Suppl:S360-5.
13. Frieda Wiley: "What Are Cephalosporins?" October 19, 2015