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Development and Research of Cephalosporin Antibiotics

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ABSTRACT

Cephalosporins are a class of broad-spectrum antibiotics. Due to their broad spectrum, high efficacy, strong antibacterial activity, and minimal side effects, they have gained significant clinical attention. With the increase in bacterial infections and the widespread use of cephalosporins, there has been an increase in bacterial resistance to cephalosporin drugs and an increase in adverse reactions. The development of new cephalosporin drugs has become a major direction. This study reviews the changes in cephalosporin synthesis routes and the historical development of cephalosporin drugs, and discusses the challenges and progress in antibiotic drug research. It aims to provide insights for developing new cephalosporin drugs that are more effective against resistant bacteria and have stronger activity.

KEYWORDS

Antimicrobial drugs; Antibiotics; Cephalosporins

1. INTRODUCTION

Cephalosporins are a broad category of semi-synthetic β-lactam antibiotics. In the retrospective review published in 2010 at the "50th American Society for Multidisciplinary Antimicrobial Agents and Chemotherapy Conference (ICAAC)," which covered the years ICAAC 50 (1961-2010), cephalosporins including cephalosporin, oxacillin, carbapenem, and 7α-methoxycarbapenem. The core structure of these drugs is 7-aminocephalosporin (7-ACA), with side-chain substituents that influence their antibacterial spectrum, activity and stability against β-lactamases. Cephalosporins work by inhibiting D-alanyl-D-aspartyl transpeptidase, disrupting bacterial cell wall synthesis, which exhibit strong antibacterial effects, high resistance to penicillinase, high clinical efficacy, low toxicity and fewer allergic reactions compared to penicillins. Since the introduction of cefotaxime in the 1960s, nearly 70 cephalosporin drugs have been widely used clinically over half a century, ranking first among all types of antibiotics and holding a significant position in anti-infective therapy. This article provides an overview of the development and current research status of cephalosporin drugs for reference by medical professionals.

1.1. History of Antimicrobial Drug Development

The glorious history of antibiotic development saw its peak from the 1830s to the 1880s. Historical data shows that antibiotics were commercially very successful. In 2000, broad-spectrum and enhanced antibiotics ranked third in sales among therapeutic products, following antidepressants and anti-ulcer drugs. Among the top 50 best-selling drugs in the United States in 2000, five were antibiotics, including Augmentin, Ciprofloxacin, Azithromycin, Levofloxacin, and Clarithromycin. Augmentin generated $1.8 billion in sales in 2001, making it the second-largest selling drug for GlaxoSmithKline that year.

1.2. Research and Development Status of Antimicrobial Drugs

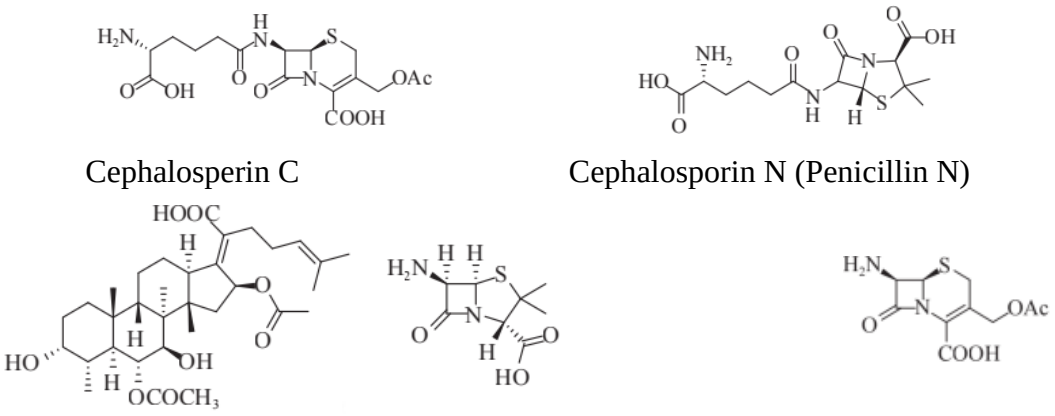
Since the 1990s, the number of new antimicrobial drugs approved has declined, and the increase in drug resistance has raised concerns. The CDC reports that over 2 million people are infected with resistant bacteria each year, leading to 230,000 deaths. Globally, about 700,000 deaths occur annually due to drug-resistant infections. Despite increased global spending on drug research and development, progress in antimicrobial drug development has stalled. The main issue is that pharmaceutical companies are unwilling to develop new drugs, resulting in a lack of new drug varieties. Antimicrobial drugs are expensive to develop, clinical trials take a long time, and resistance quickly emerges after new drugs are launched. In 2021, the World Health Organization noted that there has been almost no progress in developing new antibiotics. The focus of pharmaceutical R&D has shifted from infectious diseases to oncology, with many large pharmaceutical companies exiting the antimicrobial drug market. The regulatory environment for antimicrobial drugs is stringent, compared to the more lenient regulatory environment for cancer drugs. Cancer treatments have significant side effects, but effective drugs can be approved and marketed. Low reimbursement rates for health insurance lead to insufficient revenue for antimicrobial drugs. Antimicrobial drugs are typically used as first-line treatments, only when older therapies fail. In summary, cancer drugs have shifted the focus of the pharmaceutical industry due to favorable regulatory environments and high financial returns. In 2015, none of the top 100 best-selling drugs globally were antimicrobial drugs, while there were 19 cancer drugs. In 2021, only 27 new antimicrobial drugs were in clinical development targeting priority pathogens, down from 31 in 2017.

1.3. Revitalization of Antimicrobial Drug Research and Development

Faced the threat posed by drug-resistant bacteria, governments around the world have taken measures to promote the development of antimicrobial drugs. The United States established BARDA in 2010 and implemented a fast-track policy for QIDP drugs, including FDA expedited review, priority NDA review, and a five-year market exclusivity. In June 2020, the UK launched an antibiotic "order" program, investing £10 million annually in Pfizer and Shionogi. Sweden also initiated a similar "order" model. In 2021, the United States passed the PASTEUR Act. These initiatives aim to revitalize the antimicrobial drug market and build a "arsenal" against superbugs.

2. THE DEVELOPMENT OF CEPHALOSPORIN DRUGS

In 1948, the Italian Brotzu isolated a strain of Botrytis cinerea (Cephalosporium acremonium) from the outlet of a seepage in the Sardinian coast; in the same year, Abraham and Newton from Oxford University obtained strains from Brotzu and began their research. They isolated many compounds from the cephalosporin strain, including five closely related compounds named cephalosporins P1 to P5, as well as individual compounds cephalosporins C, N, and P (see Figure 1). Later studies revealed that cephalosporins N and P were not actually cephalosporins; cephalosporin P is a steroid, while cephalosporin N is actually penicillin N. The team determined the structure of cephalosporin C in 1961 based on infrared spectroscopy, elemental analysis, and creative degradation studies.



Cephalosperin C | Cephalosporin N (Penicillin N)

Cephalosporin P (steroid) | 6-aminocephalosporanic acid (6-APA) | 7-aminocephalosporanic acid (7-ACA)

Figure 1. Cephalosporin Compounds

Cephalosporin C, though not highly potent in antibacterial activity, has a much lower toxicity than penicillin and is stable against acids and penicillinase. The structure of cephalosporin C was determined in 1961, with its core nucleus being 7-ACA (7-aminocephalosporanic acid). Studies confirmed that it is similar to the core structure of penicillin, 6-APA (6-aminocephalinic acid), and it was known that 6-APA could be prepared through enzymatic hydrolysis by penicillinase fermentation, serving as a scaffold for new penicillin analogs. However, 7-ACA cannot be produced by fermentation and requires chemical synthesis. Teams led by Abraham and Newton were the first to synthesize 7-ACA chemically and found that its antibacterial activity against Staphylococcus far exceeds that of cephalosporins. Subsequently, process chemists developed a two-step method for synthesizing 7-ACA, improving yields.

With the first breakthrough achieved, improvements followed swiftly. By altering the solvent, scientists increased the yield of 7-ACA to over 40%, and simplified the process. By 1969, the optimized synthesis route had an overall yield exceeding 90%. In the 1980s, a two-step enzymatic synthesis route using crude cephalosporin C was developed.

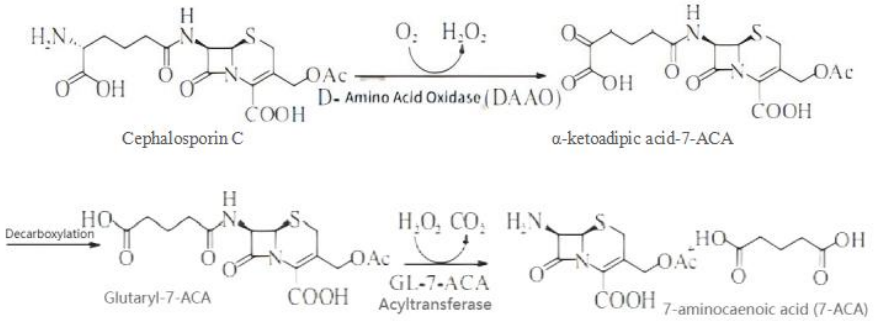


Figure 2. Biocatalytic Conversion of Cephalosporin C to 7-ACA

In the 1880s, a two-step enzymatic route allowing the use of crude C-cephalosporin as raw material (see Figure 2) was developed. In the first step of the enzymatic process, crude C-cephalosporin is oxidized and deaminated by D-amino acid oxidase (D-amino acid oxidase, DAAO) to form α-ketohexanedioic acid-7-ACA. This reaction releases peroxides, which induce oxidative decarboxylation to produce glutaraldehyde-7-ACA. In the second enzymatic step, acylase is used to hydrolyze glutaraldehyde-7-ACA to produce 7-ACA and glutaric acid. On this basis, Boehringer Mannheim developed an efficient process using DAAO immobilized on a polymer, achieving 94% conversion in step 1 and 96% conversion in step 2, with each reaction taking only about 30 min, significantly increasing production capacity. With the optimization of the manufacturing process, industrial-scale production of 7-ACA became possible, and 7-ACA, as the starting material for

synthesizing cephalosporin drugs, ultimately led to the clinical development and successful market launch of cefotaxime (Cephalothin). Following the publication of the structure of 7-ACA, cephalosporin drugs experienced rapid development. Cefotaxime was approved for sale as a first-generation cephalosporin in 1964. Today, most 7-ACA is produced through biocatalytic routes. Its mass production is seen as a sign of the advent of cephalosporin drugs. Cephalosporin drugs are usually divided into five generations according to their development age, stability against β-lactamase and antibacterial action against G-bacteria.

2.1. First Generation Cephalosporins

The first generation of cephalosporin drugs were developed and marketed in the 1960s and 1970s, including cefotaxime, ceftazidime, cefazolin, and cephalexin. Cefotaxime and ceftazidime were the earliest cephalosporin drugs to be used clinically, respectively launched in 1962 and 1965. However, ceftazidime was withdrawn from the market in the 1980s due to its nephrotoxicity. Cephalexin and cefazolin followed shortly after. These drugs are stable against penicillinase produced by Staphylococcus aureus but unstable against most β-lactamases. The first generation of cephalosporin drugs were initially injectable formulations. In 1967, Eli Lilly developed the first orally available cephalosporin, cephalexin. Subsequently, other orally available cephalosporins such as cefradine and cefhemazine were also introduced. The main characteristics of the first generation of cephalosporin drugs include:

(1) The antibacterial activity of G + bacteria is stronger than that of the second and third generation cephalosporin drugs;

(2) Poor activity against most G-bacteria;

(3) The stability of various β-lactamases is much worse than that of the second, third and fourth generation cephalosporins, which are easily destroyed by the β-lactamase produced by G-bacteria and AmpC cephalosporinase;

(4) It has certain toxicity to the kidney, and some varieties of renal toxicity is significantly higher than that of second, third and fourth generation cephalosporins. At present, first-generation cephalosporins are mainly used in clinical treatment for penicillin-resistant Staphylococcus aureus and other G + bacteria and some sensitive G-bacteria infections.

2.2. Second-Generation Cephalosporins

The second generation of cephalosporin drugs, primarily developed in the 1970s, includes cefmetazole, cefuroxime, cefonicid, and cefoxitin. Cefteram was developed in Japan and launched in 1981. These drugs have broad-spectrum antibacterial activity, enhanced activity against G bacteria, and high stability against β-lactamases. Among oral formulations, cefaclor and ceftazidime have high bioavailability and are widely used clinically. Although cefoxitin is a strong inducer of AmpC cephalosporinase, its effects are reversible after discontinuation.

The characteristics of the second generation cephalosporins include:

(1) The activity of G + bacteria is similar to that of the first generation;

(2) The activity of most G-bacteria is enhanced, and tetracycline has high activity against anaerobic bacteria, but it is ineffective against Pseudomonas aeruginosa;

(3) Stable to β-lactamase and penicillinase;

(4) Renal toxicity is small. Clinically, it is mainly used to treat infections caused by sensitive bacteria such as E. coli, Klebsiella, enterobacter and indole-positive Proteus.

2.3. Third Generation Cephalosporins

Third-generation cephalosporins were developed from the late 1970s to the early 1980s, including cefsulodin, cefoperazone, cefotaxime, ceftazidime and ceftriaxone. Cefsulodin and cefoperazone exhibit significant antibacterial activity against Pseudomonas aeruginosa. Some third-generation cephalosporins, such as ceftriaxone, ceftazidime and cefotaxime, can cross the blood-brain barrier to treat meningitis. However, TEM-1 and TEM-2 β-lactamases can hydrolyze some third-generation cephalosporins, affecting their clinical use.

Oral third-generation cephalosporins, which were launched in the early to mid-1980s, have improved stability against TEM β-lactamases. Commonly used drugs include cefotuolumpate, cefpodoxime ester, cefbutene and cefdinir, etc. Cefotaxime, ceftazidime, ceftazidime, and ceftriaxone are resistant to TEM-1, TEM-2, and SHV-1 β-lactamases. However, with clinical use, ESBLs and AmpC cephalosporinases have emerged.

The main characteristics of third-generation cephalosporins include:

(1) It has certain activity against G + bacteria, but not as strong as the first and second generation cephalosporin drugs, and it is good for penicillin-resistant or intermediate resistant pneumococcus;

(2) Strong activity against G-bacteria, the antibacterial spectrum is wider than that of second-generation cephalosporin drugs, which can cover enterobacteriaceae and Pseudomonas aeruginosa. Some varieties also have certain activity against fragile bacilli.

(3) The t1/2 of plasma is long, and a certain amount of it enters cerebrospinal fluid in many varieties, which can be used for the treatment of central nervous system bacterial infection;

(4) High stability against β-lactamases, including penicillinase and cephalosporinase;

(5) It has no basic toxicity to the kidney. The third generation cephalosporin drugs are mainly used in clinical treatment of severe infections with unknown pathogens, such as severe urinary tract infection, drug-resistant G-bacteria infection, sepsis, meningitis and pneumonia, etc.

2.4. Fourth Generation Cephalosporins

Fourth-generation cephalosporins, such as cefpirome and cefepime, inherit the advantages of the first three generations and exhibit enhanced activity against G + bacteria, similar to second-generation cephalosporins. They are effective against a variety of G + and G-bacteria, particularly resistant strains and those with high β-lactamase stability. Fourth-generation cephalosporins have a high affinity for penicillin-binding proteins, allowing them to rapidly diffuse into the bacterial cytoplasm and maintain high concentrations. They show good antibacterial activity against G + bacteria, G-bacteria, and some anaerobic bacteria, especially showing strong activity against streptococci.

Characteristics of the fourth generation cephalosporins:

(1) Highly stable against a variety of β-lactamases, and more active than third generation against most drug-resistant strains;

(2) Broad spectrum of activity, better than third generation against both G and G + bacteria. It is mainly used to treat severe G-bacterial infections, including those resistant to third generation drugs. However, it has limited stability against certain ESBLs and is usually not used for routine treatment of ESBL-producing strains.

2.5. Fifth Generation Cephalosporins

The fifth generation cephalosporins such as cefacloza and cefepime have significantly improved the activity of resistant gram-positive bacteria such as methicillin-resistant Staphylococcus aureus (MRSA).

The characteristics of the fifth generation cephalosporins include:

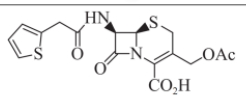
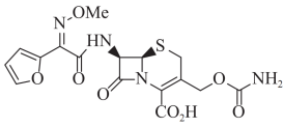
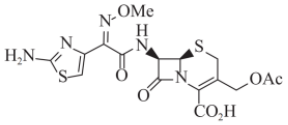
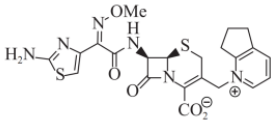
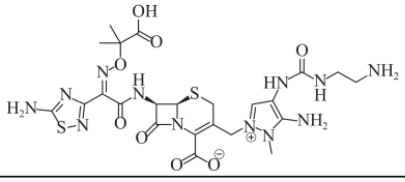
(1) Expanded spectrum of antibacterial activity: coverage of multidrug-resistant Gram-positive bacteria.

Effective against MRSA and drug-resistant staphylococcus: fifth-generation cephalosporins such as cefalolin and cefepime have enhanced antibacterial activity against MRSA and penicillin-resistant pneumococci (PRSP), making up for the shortcomings of traditional cephalosporins.

(2) Activity against Gram-negative bacteria: moderate activity against Escherichia coli, Klebsiella pneumoniae, etc., but slightly lower than that of third or fourth generation cephalosporins.

(3) Breakthrough of drug resistance mechanism: improve the stability of β-lactamase by chemical structure modification, and partially overcome MRSA drug resistance.

Table 1. Five generations of typical cephalosporin drugs

Classification of Cephalosporins	Typical Drugs	Tme to Market	Chemical Structure
First Generation	Cefalotin	1964	
Second Generation	Cefuroxime	1978	
Third Generation	Cefotaxime	1980	
Fourth Generation	Cefpirome	1992	
Fifth Generation	Ceftolozane	2015	

3. RECENT RESEARCH ON NEW CEPHALOSPORINS

Cephalosporin + enzyme inhibitor compound preparations:

Compound formulations can enhance and synergize the efficacy of cephalosporin antibiotics. Cephalosporins, when formulated with β-lactamase inhibitors such as sulbactam, restore their antibacterial activity and spectrum, thereby improving clinical outcomes. The first compound formulation developed by Pfizer, Sulperazone, which combines cefoperazone (third-generation cephalosporin) with sulbactam (β-lactamase inhibitor), has been clinically applied. Sulperazone expands the antibacterial spectrum of third-generation cephalosporins like cefoperazone and shows good antibacterial activity against various resistant bacteria, including Haemophilus influenzae, Staphylococcus species, Enterobacter aerogenes, Klebsiella pneumoniae, and Escherichia coli. Sulbactam irreversibly inhibits the production of β-lactamase in resistant strains, preventing these strains from degrading cephalosporin antibiotics and exhibiting synergistic antibacterial effects with cephalosporins. In addition to cefoperazone-sulbactam, other compound formulations such as cefoperazone/tazobactam, cefotaxime/sulbactam, ceftriaxone/tazobactam have also been developed. These compound formulations enhance the bactericidal activity of cephalosporins, addressing resistance issues in some bacteria, and have become important drugs in anti-infective therapy.

Currently, research and development of cephalosporin drugs mostly focus on modifying the 7-position amino group and the 3-position side chain of the core compound 7-ACA, aiming to discover new compounds with broader antibacterial spectra and stronger activity. For example, replacing the 7-position amino group of 7-ACA with an aminothiazolium or aminothiadiazolium group, and introducing different groups at the 3-position side chain. Due to the weak affinity of β-lactam drugs for PBP 2a, it has long been believed that all β-lactam drugs are ineffective against clinically isolated MRSA. However, several cephalosporin drugs introduced at the ICAAC conference have shown activity against MRSA due to their high affinity for PBP 2a, even when MICS is ≤ 4 μg/mL. The earliest cephalosporin drugs with anti-MRSA activity include TOC-39, BMS-247243, and a series of compounds synthesized by Microcide in the United States, such as MC-02306 and RWJ-442831.

4. DEVELOPMENT DIRECTION

Since the birth of cephalosporin drugs, they have played an important role in controlling various kinds of bacterial infections, but unreasonable application is also common. The unreasonable use of cephalosporin drugs will mainly produce two problems:

(1) The number of drug-resistant bacteria producing ESBLs increased.

The problem of drug resistance is mainly manifested by the aggravation of bacterial drug resistance, especially the increase of strains producing ESBLs and aminoglycoside enzyme inactivating enzymes.

(2) Change of pathogenic bacteria;

The changes of pathogenic bacteria are mainly manifested as:

a. An increase in the proportion of G-infections, especially those caused by Enterobacteriaceae and non-glucose fermenting bacteria (Pseudomonas aeruginosa, Acinetobacter and Alcaligenes);

b. Increased prevalence of drug-resistant staphylococci (such as MRSA, methicillin-resistant epidermal staphylococci and methicillin-resistant coagulase-negative staphylococci);

c. Increased proportion of fungal infections.

Due to the current low point or bottleneck in the development of cephalosporin drugs, it is crucial to use existing cephalosporins cautiously and reasonably to maintain their efficacy. Therefore, clinical practice must strictly adhere to indications and apply cephalosporin drugs appropriately. In response to the increasingly common issue of bacterial resistance, researchers are actively seeking cephalosporin drugs with new antibacterial properties. In recent years, the main directions for the development of cephalosporin drugs have focused on the following four aspects:

a. To study and find a new generation of cephalosporin drugs that can improve the activity of anti-G +, Pseudomonas aeruginosa and anaerobic bacteria, especially effective against MRSA;

b. To modify the compounds with high activity to make prodrugs and improve their pharmacokinetic properties;

c. Research and development of cephalosporin drugs with dual action against G + bacteria and G- bacteria;

d. Development of new combination preparations of cephalosporin drugs and β-lactamase inhibitors.

With the development of related disciplines such as medicinal chemistry and pharmacology, and the in-depth study of the chemical structure, antibacterial mechanism, drug resistance and drug toxicity of drugs, it is believed that more excellent new cephalosporin drugs will be continuously marketed.

5. SUMMARY

Cephalosporins, as an important branch of β-lactam antibiotics, have become one of the core drugs in anti-infective therapy since the launch of cephalexin in the 1960s. The discovery of cephalosporin C in 1948 and the determination of the 7-ACA core structure in 1961 laid the chemical foundation for cephalosporins. Through side chain modification and process optimization (such as enzymatic synthesis of 7-ACA), industrial production has been gradually achieved. Currently, cephalosporins face a crisis of drug resistance and research and development bottlenecks. The prevalence of drug-resistant strains such as ESBLs and AmpC-producing Enterobacteriaceae and methicillin-resistant Staphylococcus aureus (MRSA) has severely weakened the efficacy of traditional cephalosporins. The high cost of new drug development and rapid loss of efficacy, along with regulatory policies and medical insurance reimbursement mechanisms, limit market returns. By modifying the 7-amino group and 3-side chain of the 7-ACA core (such as introducing amino thiazole oxime groups), the activity against MRSA and other drug-resistant bacteria is enhanced. The development of fifth-generation cephalosporins significantly improves the affinity for PBP 2a, breaking through the MRSA resistance barrier. Combination preparations and combination therapies refer to the use of cephalosporins with β-lactamase inhibitors (such as cefoperazone/sulbactam), restoring antibacterial activity and expanding the antibacterial spectrum. At the same time, scientists are also exploring synergistic solutions with immunomodulators or other antibacterial drugs to address multi-drug resistant infections. Process innovation has also played a decisive role in the development of cephalosporin antibiotics; for example, enzymatic synthesis of 7-ACA (such as catalyzed by D-amino acid oxidase) has greatly increased yield and environmental friendliness, supporting large-scale production. Looking to the future, intelligent research and development, including computer-aided drug design (CADD) and artificial intelligence (AI), will accelerate the structural prediction and optimization of new cephalosporins. The development of interdisciplinary fields will promote the integration of genomics and metabolomics technologies to analyze resistance mechanisms and guide precise medication. Cephalosporins remain irreplaceable in anti-infective therapy, but their future development needs to balance innovation and research and development, rational application, and resistance control. Through interdisciplinary collaboration, policy support and global strategies, cephalosporins are expected to continue their mission as the "antibacterial cornerstone" in the era of resistance and provide more lasting protection for human health.

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