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Review Article

Cephalosporins: A Comprehensive Review and Anticipated Directions for the Future

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Abstract

Bacterial infections are very commonly acquired infections. Cephalosporins are broad-spectrum antibiotics used to manage a wide-variety of infections caused by gram-positive and gram-negative bacteria. The knowledge of the basic chemistry helps in understanding the pharmacokinetic, antimicrobial and toxicological profiles of cephalosporins. Cephalosporins are antibiotics with bactericidal activity which act by inhibiting the synthesis of cell wall in bacteria. The drugs of this class are classified into five generations in which the antimicrobial spectrum shifts from gram-positive bacteria to gram-negative bacteria with increasing generations of Cephalosporins. Antibiotic-producing bacteria contain a wide range of complex defense mechanisms to protect themselves from their own antibiotics and it results in the development of antibiotic resistance. The various mechanisms by which bacteria develop resistance are: production of β-lactamases, alteration of the porin channels, alteration of molecular structure of transpeptidase, and upregulation of cephalosporin efflux pumps. The new cephalosporins are the foundation for the real warning signs to open up new and interesting possibilities for serious infections in the future thereby ensuring rational selection of antibiotics for various infections.

Key words: cephalosporins; future prospects; spectrum of activity; antimicrobial spectrum; five generations; bacterial resistance; current scenario

Introduction

Infection due to various types of micro-organisms is always a part of our life (human life). Bacterial infections are very normally acquired infections. Different types of bacteria are beneficial to human beings and also to other living things which live in soil, in water and on plants as well as some of bacteria are responsible for generating an infection in human body or living things like typhoid, cholera, plague, pneumonia, and tuberculosis.[1] In developing nations like India, where Gram-positive and Gram-negative bacteria are prevalent and linked to high rates of morbidity and mortality in both communities and hospitals, the frequency of bacterial infection is quite high.[2] However, the development of various antibacterial agents which act through different mechanisms have drastically changed the modern medicine. The "golden age" of antibiotic discovery, roughly from the 1940s to the 1970s, produced nearly all of the compounds that are still used today. Since the 1980s, new antibiotics have primarily been created by changing the side chains of already-known compounds.[1] Cephalosporins are broad-spectrum antibiotics used to manage a wide-variety of infections of gram-positive and gram-negative bacteria.[3] The five generations of Cephalosporins are frequently prescribed and administered many times as first-line therapy for infections ranging from mild to severe ones, from an uncomplicated cellulitis or urinary tract infection, to pyelonephritis, bacteraemia or septic shock. Cephalosporin has become an important part of hospital formularies.[4] This antibacterial agent was isolated from the fungus Cephalosporium acremonium by Brotzu in 1948. Cephalosporins are the β- lactam antibiotics similar in action to penicillins, which are known to affect the transpeptidation reaction during peptidoglycan synthesis and thereby inhibit the cell wall synthesis.[5] With isolation of the active nucleus of cephalosporin C, 7-aminocephalosporanic acid, and with the addition of side chains, it became possible to produce semisynthetic compounds with antibacterial activity very much greater than that of the parent substance resulting in the development of five-generations of Cephalosporins.

Chemistry: Regardless of the nature of their side chains or their affinity for the enzyme, compounds containing 7-aminocephalosporanic acid are relatively stable in diluted acid and relatively resistant to penicillinase. Changes in antibacterial activity are linked to changes at position 7 of the β-lactam ring. The drugs' metabolism and pharmacokinetic properties are altered by substitutions at position 3 of the dihydrothiazine ring.[6] Mechanism of action: Cephalosporins are antibiotics with bactericidal activity. The bacterial cell wall consists of glycopeptide polymers, an N-Acetyl muramic acid and N-Acetyl Glucosamine (NAM-NAG) amino-hexose backbone linked via bridges between amino acid side chains. In gram-positive microorganisms, the cell wall is 50–100 layers thick whereas, in gram-negative bacteria, it is only 1 or 2 layers thick. The cross-linking is catalysed by a transpeptidase, the enzyme that cephalosporins inhibit, thereby causing cell lysis (cell bust) and death. In gram-negative bacteria, cephalosporins enter the cell through the porins in order to exhibit the above mechanism.[7]

Different classes of cephalosporins:

A different type of generations of the Cephalosporins were based on the time of discovery and this trend was followed until the third-generation cephalosporins. However, the drugs in the fourth and fifth generations were classified according to their identified activity against selected organisms. The antimicrobial spectrum shifts from grampositive bacteria to gram-negative bacteria with increasing generations of Cephalosporins. The antimicrobial spectrum of Cephalosporins has been described in Table 01. However, none of the cephalosporins are known to be active against atypical respiratory pathogens. The common side effects (ADR) associated with Cephalosporins are hypersensitivity reactions and diarrhea. Some cephalosporins are found to be potentially nephrotoxic in nature which require dose modifications. The overviews of various drugs, doses along with their common drugs have been described in Table 02.

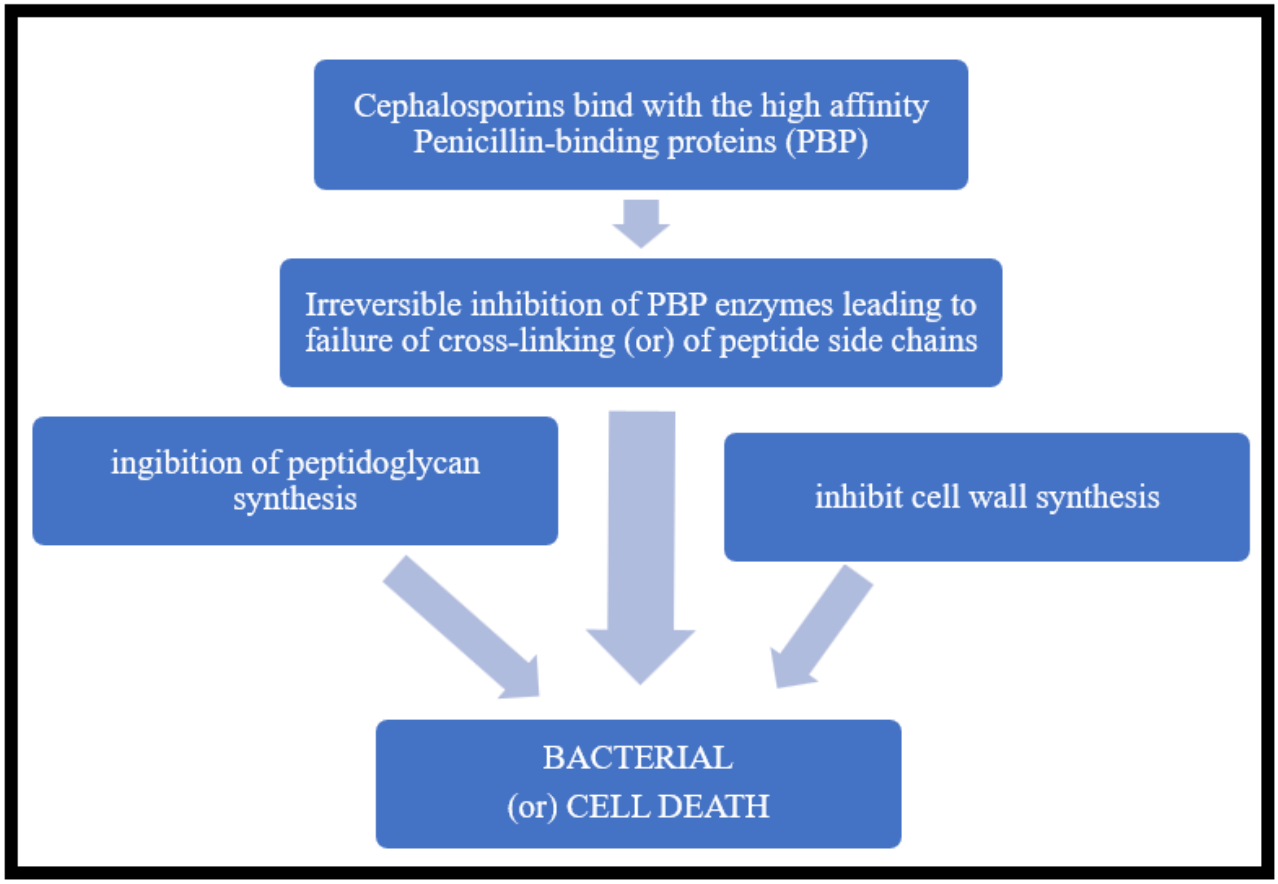

Figure 1: Flowchart illustrating the mechanism of action of Cephalosporins

First-generation Cephalosporins

The first-generation cephalosporins, also called as 'Narrow-spectrum cephalosporins' (Oral-Cephradine, Cephalexin, Cefadroxil and parenterals like Cefazolin, Cephalothin, Cephapirin), are known to have good activity against gram-positive cocci like *Staphylococcus Aureus, Staphylococcus Epidermidis, Streptococcus pneumoniae, Streptococcus pyogenes*, Anaerobic streptococcus and modest activity against gram-negative rods like *Escherichia coli, Klebsiella pneumoniae* and *Proteus mirabilis*. The most commonly used agents are Cephalexin and Cefazolin. Cephalexin is the prototype drug of the first generation, oral cephalosporins. Cefazolin has the longest duration of action in comparison to the other first-generation parenterals with well penetration into the bones. However, these drugs have poor Cerebrospinal fluid (CSF) penetration.

Second-generation Cephalosporins

The second-generation cephalosporins, also called as 'Intermediate-spectrum cephalosporins' (Oral- Cefaclor, Cefprozil, Cefuroxime axetil and Parenterals like Cefuroxime sodium, Cefoxitin, Cefotetan), have enhanced activity against gram- negative micro-organisms which include gram-negative cocci like *Neisseria gonorrhoea*, gram-negative rods like *Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Hemophilus influenzae* and modest activity against gram-positive cocci like *Staphylococcus Aureus, Streptococcus pneumoniae, Streptococcus pyogenes, Anaerobic streptococcus*.

Cefuroxime and Cefoxitin are the drugs commonly used in this class. Cefuroxime sodium is the prototype drug of the second-generation parenterals having long half-life and the drug crosses the blood-brain barrier. Cefuroxime is the only second-generation drug available as oral preparation as Cefuroxime axetil and parenteral preparation are Cefuroxime sodium.

Sr. No.	GENERATIONS	DRUGS	ANTIMICROBIAL SPECTRUM
1.	First- Generation Cephalosporins (Narrow-spectrum)	Cephradine Cephalexin Cefadroxil Cefazolin Cephalothin Cephapirin	**Gram-positive cocci** *Staphylococcus Aureus* *Staphylococcus Epidermidis* *Streptococcus pneumoniae* *Streptococcus pyogenes* *Anaerobic streptococcus* **Gram-negative rods** *Escherichia-coli (E-coli)* *Klebsiella pneumoniae* *Proteus mirabilis*
2.	Second-Generation cephalosporins (Intermediatespectrum)	Cefaclor Cefprozil Cefuroxime axetil Cefuroxime sodium Cefoxitin Cefotetan	**Gram-positive cocci** *Staph. Aureus* *Streptococcus pneumoniae* *Streptococcus pyogenes* *Anaerobic streptococcus* **Gram-negative cocci** *Neisseria gonorrhoea* **Gram-negative rods** *Enterobacter aerogenes* *Escherichia coli* *Klebsiella pneumoniae* *Proteus mirabilis* *Hemophilus influenza*
3.	Third-generation cephalosporins (Broad-spectrum)	Cefixime Cefpodoxime axetil Ceftibutan Ceftriaxone Cefotaxime Ceftizoxime Ceftazidime Cefoperazone	**Gram-positive cocci** *Streptococcus pneumoniae* *Streptococcus pyogenes* *Anaerobic streptococci* **Gram-negative cocci** *Neisseria gonorrhoeae* **Gram-negative rods** *Enterobacter aerogenes* *Escherichia coli* *Haemophilus influenzae* *Klebsiella pneumoniae* *Proteus mirabilis* *Pseudomonas aeruginosa* *Serratia marcescens*
4.	Fourth-generation cephalosporins (Broad-spectrum)	Cefepime Cefpirome Ceftolozane	Antibacterial coverage comparable to that of the third-generation class; however, demonstrate greater stability against Pseudomonas
5.	Fifth-generation cephalosporins (Anti-MRSA drugs)	Ceftaroline Ceftobiprole	**Methicillin-resistant** *Staphylococcus Aureus* *Methicillin-susceptible* *Staphylococcus Aureus* **Methicillin-resistant** *Staphylococcus Epidermidis* *Streptococcus pneumonia* Some Gram-negative bacteria No Pseudomonas coverage

Table 1: The antimicrobial spectrum of various Cephalosporins

Third-generation Cephalosporins

The third-generation cephalosporins being the most widely used agents, also called as 'Broad-spectrum cephalosporins' (Oral-Cefixime, Cefpodoxime axetil, Ceftibuten and Parenterals-Ceftriaxone, Cefotaxime, Ceftizoxime, Ceftazidime, Cefoperazone), are less active against gram-positive cocci, although Ceftriaxone is known to have excellent activity. These drugs are known to be highly active against gram-negative cocci like Neisseria gonorrhoea, gram-negative rods like Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,

Hemophilus influenzae, Serratia marcescens. Ceftazidime is the only third-generation drug active against Pseudomonas aeruginosa, hence can be classified as 4th generation cephalosporins when classified according to the antimicrobial spectrum. Ceftriaxone has the longest half-life among all the cephalosporins, hence permitting once-a-day dosing. The drug is excreted through bile, and thus can be used in renal sufficiency. The third-generation drugs have good CSF penetration and hence can be used for the treatment of meningitis. Cefoperazone can prolong the prothrombin time, an effect that may be associated with clinically significant bleeding amongst patients receiving anticoagulation or with vitamin K deficiency; hence the drug should be used with caution.

Fourth-generation Cephalosporins

Commonly called as 'Antipseudomonal Cephalosporins', these agents (Parenterals- Cefepime, Cefpirome, Ceftolozane) expand their gram-negative activity to Pseudomonas aeruginosa and have weaker activity against gram-positive bacteria. However, Cefepime is known to have a similar spectrum as that of ceftriaxone.

Fifth-generation Cephalosporins:

Anti-MRSA Cephalosporins are the agents with structural modifications which allows binding to and inactivation of the altered PBPs expressed by Methicillin-resistant Staphylococcus Aureus (MRSA), Methicillin-resistant Staphylococcus Epidermidis (MRSE), and Penicillin-resistant Streptococcus pneumoniae. The gram-negative spectrum of this class is similar to that of the third-generation agents. However, Ceftobiprole is found to be active against Pseudomonas also.

Combining Cephalosporins with β- lactamase inhibitors

β- lactamases are a family of enzymes produced by many gram-positive and gram-negative bacteria that inactivates β- lactam antibiotic by opening the β- lactam ring, which in turn causes bacterial resistance. Hence β-lactamase inhibitors are combined with Cephalosporins for enhanced activity of Cephalosporin. The Cephalosporins commonly used in combination with β- lactamase inhibitors are:

Ceftazidime+Avibactam,

Cefoperazone+Sulbactam,

Ceftolozane+Tazobactam.

Mechanisms Of Bacterial Resisatnce to Cephalosporins

The global public health threat posed by the emergence of harmful microorganisms resistant to antibiotics is significant. Antibiotic resistance genes, however, are not just found in medical settings; they are also broadly distributed in a variety of bacterial communities in the environment. High morbidity and mortality rates were seen in the pre-antibiotic era as a result of simple infections. Antimicrobials were later developed, owing to the brilliant minds of Sir Alexander Fleming and Paul Ehrlich, and they let humanity survive the death blow from microbial illnesses.[8, 9] Antibiotic-producing bacteria contain a wide range of complex defense mechanisms to protect themselves from their own antibiotics. It is only natural that organisms which produce antibiotic would also have defenses against those very same drugs. Furthermore, it is also thought that the coexistence of producer and non-producer environmental bacteria led to the co evolution of resistance mechanisms in that bacterium.[8] A summary of different mechanisms of resistance has been represented in Fig-02.

β-lactamases

β-lactamases breaks the β-lactam ring rendering the cephalosporin inactive. β-lactamases act at the base of the β-lactam ring, severing the bond between carbon 'C' and nitrogen 'N' (opening the ring). The fundamental structure of cephalosporins turns inactive. Cephalosporins are rendered inactive because of this structural alteration preventing cephalosporin interaction with transpeptidase. Cephalosporins are more stable to many β-lactamases that would degrade the penicillins. However, there may be strains of *Klebsiella* and *E. coli* that will still be able to bind as well as hydrolyze cephalosporins.

Alteration of the porin channels

Porins are proteins found in the outer membrane that influence cellular permeability and antibiotic resistance. In other words, it serves as a point of entry for cephalosporins to the cell wall. An outer membrane encloses the peptidoglycan cell wall in gram-negative bacteria. Cephalosporins must cross these porins in the outer membrane of a gram-negative bacterium in order to enter the cell. By altering the porin channels, some bacteria are able to develop a resistance to cephalosporins, preventing them from inhibiting cell wall synthesis.

Alteration of molecular structure of transpeptidase

By alteration of cephalosporin binding to transpeptidase, some bacteria can produce resistance to cephalosporins. Usually, a point mutation in the cephalosporin binding pocket causes this. A point mutation is a type of genetic modification in which only one nucleotide base from the DNA or RNA sequence of an organism is altered, added, or removed. Hence, a cephalosporin cannot inhibit the cell wall synthesis if it cannot bind to transpeptidase.

Up regulation of cephalosporin efflux pumps

Efflux of antibiotics is another commonly used mechanism for self-resistance, although it usually occurs in conjunction with other mechanisms, such as modification of the antibiotic or the target.[8] Some bacteria can boost the efflux pumps that actively move a cephalosporin out of the cell once it has entered by increasing efflux. Cephalosporin efflux, on the other hand, lowers the intracellular concentration of cephalosporins and lessens their ability to block cell wall formation, which promotes bacterial survival.

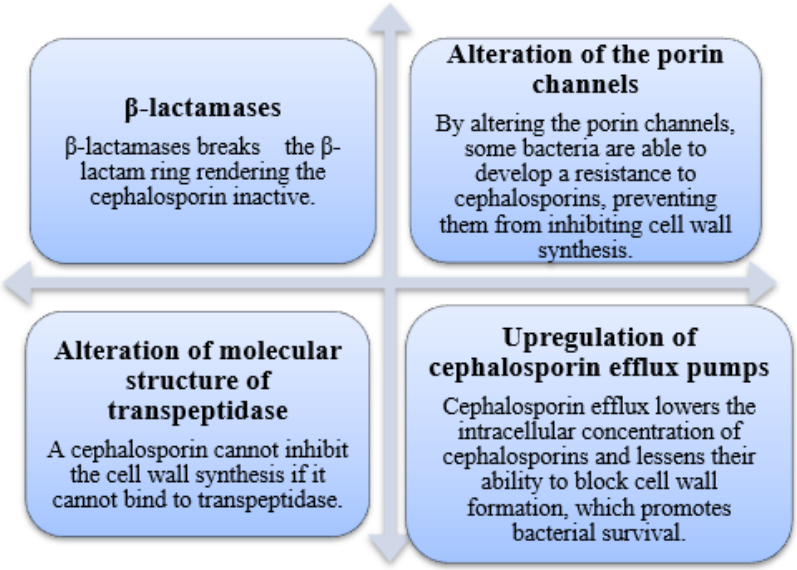

Figure 2: Summary of different mechanisms of resistance by Cephalosporins

Antibiotic-producing bacteria contain a wide range of complex defense mechanisms to protect themselves from their own antibiotics and it results in the development of antibiotic resistance. The various mechanisms by which bacteria develop resistance are: production of β-lactamases, alteration of the porin channels, alteration of molecular structure of transpeptidase, and upregulation of cephalosporin efflux pumps

Recent Advancements on Cephalosporins

Cefiderocol

Cefiderocol, formerly known as S-649266, is a catechol type siderophore injectable siderophore cephalosporin that is a first in its class. The spectrum of activity includes both lactose-fermenting and non-fermenting Gramnegative pathogens, including carbapenem-resistant Enterobacterales. This structure and its distinct mechanism of action confer enhanced stability against hydrolysis by many β-lactamases, including extended spectrum β-lactamases and carbapenemases. The US Food and Drug Administration recently approved Cefiderocol for the treatment of complicated urinary tract infections, including pyelonephritis, and it is currently being tested in phase III trials for nosocomial pneumonia and infections brought on by Gram-negative pathogens that are carbapenemresistant. For the treatment of carbapenem-resistant Gram-negative bacterial infections, patients with sepsis, urinary tract infections, and pneumonia, the mortality rate with Cefiderocol was higher than the best available therapy (Colistin).[10]

IV: Intravenous; IM: Intramuscular; Q4-6H- Every 4hrs to 6hrs; Q6-12H-Every 6hrs to 8hrs; Q6H-Every 6hrs; Q8H- Every 8hrs; Q12H-Every 12hrs;

Ceftobiprole

In Europe, Ceftobiprole medocaril is now accepted as an extended-spectrum cephalosporin for treating adult skin and soft tissue infections (SSTIs), such as diabetic foot infections, as well as community-acquired and nosocomial, non-ventilator-associated pneumonia, community-acquired pneumonia and hospital-acquired pneumonia (CAP and HAP). For the treatment of Methicillin-susceptible *Staphylococcus Aureus* (MSSA) and Methicillin-resistant *Staphylococcus* Aureus (MRSA), ceftobiprole was compared to various comparators (such as Vancomycin, Linezolid, and Ceftazidime) with the following data: - Methicillin-resistant *S. aureus* (MRSA; 55.6 vs. 22.2%) and methicillin-sensitive *Staphylococcus aureus* (MSSA; 44.4 vs. 46.7%). In the ceftobiprole group, the 30-day all-cause death rate was 8.9% (4/45) compared to 16.0% (8/50) in the comparison group. In penicillin-allergic patients with severe gram-positive infections, ceftobiprole is also crucial. A daptomycin-based strategy combined with a ceftobiprole adjunct also appears promising in terms of clinical applicability for the treatment of endocarditis.[11]

DRUGS		DOSAGE	INDICATION	DOSE ADJUSTMENT	
				RENAL IMPAIRMENT	HEPATIC IMPAIRMENT
First- Generation Cephalosporins (Narrow-Spectrum Cephalosporin)					
ORAL	Cephradine	250-500mg Q6-12H	• Skin and soft tissue infections • Serious infections due to MSSA	Yes	No
	Cephalexin	250-500mg Q6H		Yes	No
	Cefadroxil	500mg Q12H		Yes	No
PARENTERAL	Cefazolin	1-2gm Q6H		Yes	No

(IV/IM)	Cephalothin	1-2gm Q4-6H	• Perioperative surgical prophylaxis	Yes	No
	Cephapirin	500mg-1gm Q4-6H		Yes	No
Second-Generation Cephalosporins (Intermediate-spectrum Cephalosporins)					
ORAL	Cefaclor	250-500mg Q8H	• Upper respiratory tract infections- Sinusitis, Otitis media • Cefoxitin/cefotetan gynaecologic infections, perioperative surgical prophylaxis	Yes	No
	Cefprozil	250-500mg Q12-24H		Yes	No
	Cefuroxime	250-500mg Q8-12H		Yes	No
PARENTERAL (IV/IM)	Cefuroxime Sodium	750mg-1.5gm Q8-12H		Yes	No
	Cefoxitin	1-2gm Q4-6H		Yes	No
	Cefotetan	1-2gm Q12H		Yes	No
Third-Generation Cephalosporins (Broad-spectrum Cephalosporin's)					
ORAL	Cefixime	200-400mg Q12-24H	• Community-acquired pneumonia, meningitis, urinary tract infections • Streptococcal endocarditis • Gonorrhoea • Severe Lyme disease	Yes	No
	Cefpodoximeaxetil	200mg Q12H		Yes	No
	Ceftibuten	400mg Q12H		Yes	No
PARENTERAL (IV/IM)	Ceftriaxime	1-2gm Q12H		No	No
	Ceftotaxime	1-2gm Q8H		Yes	No
	Ceftizoxime	1-2gm Q8-12H		Yes	No
	Ceftazidime	1-2gm Q8H		Yes	No
	Cefoperazone	1-2gm Q12H		Yes	Close monitoring
Fourth-Generation Cephalosporins (Broad-spectrum Cephalosporin's)					
PARENTERAL (IV/IM)	Cefepime	500mg-2gm Q12H	• Nosocomial infections: pneumonia, meningitis, urinary tract infections, intra-abdominal infections (with metronidazole)	Yes	NO
	Cefpirome	1-2gm Q12H		Yes	NO
	Ceftolozane	1-2gm Q8H		Yes	NO
Fifth-Generation Cephalosporins (Broad-spectrum Cephalosporin's)					
PARENTERAL (IV/IM)	Ceftaroline	600mg Q12H	• Community acquired pneumonia • Skin and soft tissue infections	Yes	No
	Ceftobiprole	500mg Q12H		Yes	No

Table 2: List of Cephalosporins based on their generations

Ceftobiprole

In Europe, Ceftobiprole medocaril is now accepted as an extended-spectrum cephalosporin for treating adult skin and soft tissue infections (SSTIs), such as diabetic foot infections, as well as community-acquired and nosocomial, non-ventilator-associated pneumonia, community-acquired pneumonia and hospital-acquired pneumonia (CAP and HAP). For the treatment of *Methicillin susceptible Staphylococcus Aureus* (MSSA) and *Methicillin-resistant Staphylococcus Aureus* (MRSA), ceftobiprole was compared to various comparators (such as Vancomycin, Linezolid, and Ceftazidime) with the following data: - *Methicillin-resistant S. aureus* (MRSA; 55.6 vs. 22.2%) and *methicillin-sensitive Staphylococcus aureus* (MSSA; 44.4 vs. 46.7%). In the ceftobiprole group, the 30-day all-cause death rate was 8.9% (4/45) compared to 16.0% (8/50) in the comparison group. In penicillin allergic patients with severe gram-positive infections, ceftobiprole is also crucial. A daptomycin-based strategy combined with a ceftobiprole adjunct also appears promising in terms of clinical applicability for the treatment of endocarditis.[11]

Ceftaroline

The drug Ceftaroline has a broad range of activity against Gram-positive bacteria that commonly cause CAP and SSTIs, such as MSSA and MRSA, as well as against some resistant *Staphylococcus aureus* strains (Vancomycin intermediate, heterogeneous vancomycin intermediate, vancomycin-resistant, or daptomycin non-susceptible) and Multidrug-resistant (MDR) *Streptococcus pneumoniae*.[12] Ceftaroline had a 64.9% combined clinical cure rate compared to a 69.7% monotherapy cure rate. Ceftaroline treatments were incredibly successful as first-line treatments in patients with right-sided endocarditis (80.8%) and MRSA (77.3%), as well as in general (75.0%).[13]

Although there is little information on the medication concentrations in CSF, ceftaroline may also be used to treat severe infections, such as primary (such as post-traumatic) and secondary (such as post-surgical) bacterial meningitis.[14] Vancomycin and ceftaroline both have comparable antibacterial efficacy in treating MRSA in an experimental meningitis model. In their most recent comprehensive study, Pani et al. verified the use of ceftaroline as the fifth off-label indication for meningitis.[15, 16]

Ceftazidime/Avibactam

A third-generation cephalosporin and the non-lactam/lactamase inhibitor avibactam are combined intravenously, which has activity against *P. aeruginosa*, Extended spectrum Beta-lactamases (ESBL)-producing bacteria, and bacteria that produce carbapenemases. Ceftazidime/ Avibactam (C/A) has been licensed for use in the treatment of Complicated intra-abdominal infections(cIAI), Complicated urinary tract infections(cUTI), and *Non-Pseudomonal* (NP)-resistant infections caused by microorganisms.[17,18] There was no discernible difference in the death rates between C/A alone and combination therapy. C/A was mostly administered as monotherapy (81%) for a mean length of 13 days. The 14-day mortality rate was 14%[19] Tumbarello et al. conducted a retrospective longitudinal investigation of 138 patients with *Klebsiella pneumoniae* carbapenemases-producing *Klebsiella Pneumoniae* (KPC-Kp) bacteremia, in which C/A use was significantly associated with reduced mortality (36.5 vs. 55.8%, P = 0.05) and the only predictor that was significantly correlated with survival.20 Based on study conducted by shield et el. found that C/A had greater rates of clinical success (P = 0.006), survival (P = 0.01), and renal safety (P = 0.002) compared to regimens comprising amino glycosides and colistin.[21]

Conclusion

Cephalosporins are diverse, extremely useful group of beta-lactam antibiotics with bactericidal activity. They play a major role in treatment of various infections, ranging from mild to severe ones. The antibiotic spectra of cephalosporins, which are divided into first through fifth generations, can be grouped roughly by generation, with increasing gram-negative activity in each higher generation and decreasing gram-positive activity with increasing generation. The knowledge of the basic chemistry helps in understanding the pharmacokinetic, antimicrobial and toxicological profiles of the cephalosporins, thereby ensuring rational selection of antibiotics for various infections. The emergence of cephalosporin resistant strains of various infectious species should be considered while making treatment decisions. The new cephalosporins are the foundation for the real warning signs to open up new and interesting possibilities for serious infections in the future. In future, patients will be addressed with the desirable approach to various infections in terms of their clinical situation, inherent features of the host, the sensitivity profile, and local epidemiology, for which evidence of the use of new cephalosporin in the treatment of severe infections will fill the remaining gaps.

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