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Cephalosporins : An imperative antibiotic over the generations

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Abstract

Cephalosporins are the most commonly prescribed class of antibiotics, and its structure and pharmacology are similar to that of penicillin. It's a bactericidal, and its structure contains beta-lactam ring, as like of penicillin, which intervenes in bacterial cell wall synthesis. Cephalosporins are derived from the mold *Acremonium* (previously called as *Cephalosporium*). It was first discovered in 1945; scientists have been improving the structure of cephalosporins to make it more effective against a wider range of bacteria. Whenever the structure of cephalosporins modified, a new "generation" of cephalosporins are made. So far, there are five generations of cephalosporins available. They are prescribed against various organisms and infections. The cephalosporin antibiotics interfere with cell-wall synthesis of bacteria, leading to the breakdown of the infectious organism. To achieve this effect, the antibiotic must cross the bacterial cell wall and bind to the penicillin-binding proteins. Various generations of cephalosporins, mechanisms of resistance, pharmacokinetics, adverse reactions, and their clinical use were reviewed in this article. Most of the cephalosporins are available as parenteral, but the oral formulations are also available for certain drugs. Rather than learn all cephalosporins, it is reasonable for the clinician to be familiar with selected cephalosporins among the parenteral and oral formulations.

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INTRODUCTION

The word antibiotic was originated from the word 'antibiosis' which means 'against life.' Earlier, antibiotics were considered as an organic agent formed by a single organism, which is poisonous to other microorganisms. The outcome of this conception, an antibiotic, was widely described as a substance obtained by biological sources (Schlegel, 1993). Cephalosporins are the most commonly prescribed class of antibiotics, and its structure and pharmacology are similar to that of penicillin. It's a bactericidal, and its structure contains beta-lactam ring, as of penicillin, which intervenes in bacterial cell wall synthesis. Cephalosporin compounds were first formed from "*Cephalosporium acremonium*" from a sewage outfall in Sardinia in 1948 by an Italian scientist "Giuseppe Brotzu" (Morse *et al.*, 2004). This article reviewed about the various generations of cephalosporins, and their mode of action, mechanism of resistance, pharmacokinetics, adverse reactions and their clinical use.

MATERIALS AND METHODS

Classification of cephalosporins

Cephalosporins are classified into various genera-

tions according to their microbial spectrum. The list of various Cephalosporin drugs and their generations is given in Table 1.

First-Generation

The first-generation cephalosporin's are active against gram-positive microorganisms like; *streptococcus* and *staphylococcus.* They also have a little gram-negative spectrum (Beers *et al.*, 2003).

Second-Generation

The second-generation cephalosporin's are more active against gram-negative microorganisms (*Haemophilus influenzae, Enterobacter aerogenes*) when compared with the first generation, but their spectrum against Gram-positive organisms is less when compared with the first generation (Brunton *et al.*, 2007).

Third Generation

The third-generation cephalosporin's are called broad-spectrum antibiotics, and they are effective against both gram-positive and gram-negative organisms, but their optimum activity is mostly against gram-negative organisms (Tumah, 2005).

Fourth Generation

The fourth-generation cephalosporin's are called as extended-spectrum antibiotics, but they are resistant to beta-lactamases (Tumah, 2005).

Fifth-Generation

The fifth-generation cephalosporin's have enhanced activity against methicillin-resistant *Staphylococcus aureus* (MRSA) (Deck and Winston, 2015).

Mode of action

The cephalosporin's are intervening with a synthesis of bacterial cell-wall, and it leads to the death of micro-organisms, causing infections. To gain this outcome, the antibiotic drug should interfere with the cell wall of bacteria, and then it binds to the transpeptidase enzyme (penicillin-binding proteins) (Martens, 1989).

Moreover, variance in penicillin-binding protein can explain the differences in the activity of cephalosporin's opposes *Enterobacteriaceae and P. aeruginosa*. The post-antibiotic effect is the reduction of the growth of bacteria after a short susceptibility to antimicrobials. Antibiotics, like cephalosporin's, makes the more post-antibiotic effect in Gram-positive organisms; even so chloramphenicol tetracycline, aminoglycosides, rifampicin, and fluoroquinolones accurately produce less effect in gram-negative micro-organisms. Cephalosporin's produce negligible or nil post-antibiotic effect in gram-negative bacteria.

The experimental data in animal studies (especially those rendered neutropenic), shows, the treatment for gram-negative organism/infection was succeeded only when the serum drug concentrations was maintained constantly, otherwise, above the minimal inhibitory concentration (MIC) by reducing the dosing intervals, but the concentration-dependent killing was not observed. Getting or maintaining a high serum drug concentration: MIC ratio will help to prevent the upcoming of resistance (Aronoff and Shales, 1987).

RESULTS AND DISCUSSION

Mechanism of resistance

Cephalosporin's resistance occurs by various mechanisms like alteration of penicillin-binding proteins, B-lactamase production, and change in the cell wall permeability of gram-negative organisms. Inducible enzymes can also be seen in *Serratia*, *indole-positive Proteus, P. aeruginosa*, *Citrobacter,* and *enterobacter* species (Livermore, 1987). B-lactamase production is induced powerfully by clavulanic acid, ampicillin, imipenem, cefoxitin. Earlier (first-generation) cephalosporins are resistant to *Staphylococcal penicillinases* (Kernodle, 1990). Cefazolin is not much liable to hydrolysis by some varieties of penicillinases than other cephalosporins. The second and third-generation cephalosporin's are well built to hydrolysis by commonly facing lactamases of gram-negative organisms. Third-generation cephalosporins are comparatively stable to RS Type-I enzymes in various systems. The limiting spread of these drugs can make them vulnerable to hydrolysis, and it may lead to the inactivation of cephalosporins.

In a group consisting of *Enterobacter cloacae*, it relatively produces enzymes in large amounts. This minute amount of bacterias are hard to observe due to the standard MIC detection test contains about 10^5 micro-organisms, and the resistant ones are not found. These variants are impervious to 3^{rd} generation cephalosporins; when the vulnerable organisms of the inoculum are killed by the inclusion of a cephalosporin, the impervious members grow more and more, resulting in therapeutic failure.

These organisms may begin to be steady in the surroundings and lead to widespread resistance in the hospital. Checking an inoculum of organisms (>107), as advised by (Jimenez-Lucho *et al.*, 1986), can help detect these resistant groups before the starting of the treatment. Cell-wall impenetrability is stated as a way of incompliance when others have been rejected, though there is proof that the cell-wall of gram-negative (but not gram-positive) bacterias

may avoid some cephalosporins or permit slow diffusion through the outer membrane of the organism.

Pharmacokinetics

Oral Cephalosporins

Generally, oral cephalosporins are absorbed fastly. Cefaclor, Cephradine, Cefadroxil Cephalexin, are fully absorbed, but Cefixime and cefuroxime Axetil are absorbed to a minimal amount. The above compounds gain their therapeutic level, mostly in tissues like bones, pleural fluids, and synovial fluids. All other oral drugs are excreted in the urine except cefixime, which is eliminated mainly by non-renal routes (Bergan, 1987).

Parenteral cephalosporins

The parenteral cephalosporins are given both intramuscularly or intravenously and abundantly spread to the tissues and fluids, including mainly the bones, synovial fluids, pleural, and cerebrospinal fluids. First or second-generation cephalosporins diffuse through the cerebrospinal fluid, even during the presence of infected meninges; Ceftriaxone, ceftizoxime, ceftazidime, cefotaxime, cefuroxime can gain their therapeutic levels in the cerebrospinal fluid, even the meninges are infected. The cephalosporins cross the placenta, and small amounts are excreted in breast milk (Bergan, 1987).

Cefuroxime, cefonicid, cefazolin, ceftazidime, ceftizoxime are slowly metabolized. Cefamandolenafate is fastly hydrolyzed to cefamandole, which is its parent compound. Cephapirin, cefotaxime, and cefalothin are metabolized to a desacetyl metabolite. Many reports have proven that the desacetyl metabolite of cefotaxime combines synergistically with its parent compound called cefotaxime, against various types of bacterial strains, which also includes anaerobes. For therapy of sepsis and prophylaxis in a biliary origin, however, tissue and serum levels are most necessary for better treatment (Munro and Sorrell, 1986).

Adverse reactions

Generally, the cephalosporins makes lesser adverse reactions. Cross-hypersensitivity with penicillins is mostly seen in less than 2% of people. Skin rash, accompanied by arthritis and fever (serum sickness-like syndrome), are found during cefaclor therapy, but these reactions are uncommon (Norby, 1987). Renal impairment was observed after intake of cephalosporin, along with increases in serum creatinine and blood urea nitrogen levels. Cephaloridine was first found as an agent of nephrotoxicity in 1965. Cefamandole and cefazolin produce proximal tubular necrosis in subjects and have reported as less nephrotoxic in rabbits.

Cephalosporins can increase the nephrotoxicity caused by aminoglycosides. This reaction was seen during the treatment of cephalothin and the tests conducted show that penicillins provide safety from aminoglycoside toxicity, rather than assisting the concept that cephalosporins increase nephrotoxicity. Gastrointestinal complications like vomiting, diarrhea, and nausea are seen in oral therapy. Tally and associates (Tally *et al.*, 1981) have concluded that cefixime induces diarrhea in 13.4% of individuals under therapy and change in bowel habits 12.8%. Cholecystitis, resulting due to the development of biliary deposits, are noticed frequently during ceftriaxone treatment, but it can be due to the occurrence of precipitate formed by calcium salt of ceftriaxone in the gallbladder.

Clinical use

Oral Cephalosporins

Cefadroxil, cephradine, cefaclor, and cephalexin are used for the therapy of both acute and chronic upper and lower respiratory tract infections associated with *H. influenzae*, *Streptococcus pyogenes*, *Klebsiella*, *Streptococcus pneumoniae*, *S. aureus*. Utilization of both erythromycin/sulfamethoxazole and amoxicillin/clavulanic acid is effective and less costly when compared with the use of oral cephalosporins employed against ampicillin-resistant strains of *B. catarrhalis* and *H. influenza* (Mcleod and Smith, 1990). Cefuroxime axetil can also be used for simple urinary tract infections, but complicated urinary tract infections necessitate other treatment regimens. Cefuroxime axetil has shown its effectiveness against the majority of organisms associated with otitis media.

The drug use is limited in a pediatric group due to a lack of an oral liquid formulation, which frequently encounters this type of disease. Cefuroxime axetil is not above penicillin, amoxicillin/clavulanic acid in the therapy for infections in the upper respiratory tract. A combination of cefuroxime Axetil and probenecid is useful in a once-daily dose for simple endocervical, rectal, and urethral gonorrhea. Single-dose intake was found to be useful in the treatment of infections like acute otitis media, pharyngitis, urinary tract infections, bronchitis produced by organisms. Otitis infections, the efficacy of cefixime, is identical to that of cefaclor and amoxicillin. Cefixime treatment shows many gastrointestinal complications. While comparing with cefixime and amoxicillin is rather more potent against middle-ear, *H. influenza*, *B. catarrhalis* infections, but is less effective against *S. Pneumoniae*.

According to current information, cefixime does not render any clear dominance over other early antimi-

Table 1: List of various generation Cephalosporins

Classification	Drug	Dosage	Route of administration	Dosing Interval (h)	Renal
1st Generation (Narrow Spectrum)	Cefazolin	1-2gm	IV/IM	8	Yes
	Cephalothin	1-2gm	IV/IM	4-6	Yes
	Cephapirin	0.5-1gm	IV/IM	4-6	Yes
	Cephalexin	250-500mg	PO	6	Yes
	Cefadroxil	500mg	PO	12	Yes
	Cephradine	250mg <500mg>	PO PO	6 12	Yes
2nd Generation (Intermediate Spectrum)	Cefamandole	1-2gm	IV/IM	4-6	Yes
	Cefuroxime	0.75-1.5gm 250-500mg	IV/IM PO	8 12	Yes
	Cefoxitin	1-2gm	IV/IM	4-6	Yes
	Cefotetan	1-2gm	IV/IM	12	Yes
	Cefmetazole	2gm	IV	6-12	Yes
	Cefaclor	250-500mg	PO	8	Yes
	Cefprozil	250-500mg	PO	12-24	Yes
	Cefpodoxime	200-400mg	PO	12	Yes
	Loracarbef	200-400mg	PO	12	Yes
3rd Generation (Broad Spectrum)	Cefotaxime	1-2gm	IV/IM	6-8	Yes
	Ceftriaxone	1-2gm	IV/IM	12-24	
	Ceftizoxime	1-2gm	IV/IM	8-12	Yes
	Ceftazidime	1-2gm	IV/IM	8	Yes
	Cefoperazone	1-2gm	IV/IM	12	
	Cefixime	400mg 200mg	PO PO	24 12	Yes
4th Generation (Broad Spectrum)	Cefepime	2gm	IV	12	Yes
5th Generation (Extended Spectrum)	Ceftaroline	600 mg	IV	12	Yes
	Ceftobiprole	500mg	IV	12	Yes

crobial compounds used for the treatment of otitis media. The high incidence of diarrhea associated with treatment restricts the use of cefixime in the pediatric group. The restricted extent of *S.pneumoniae*, cefixime may be less potent for the treatment of bacterial bronchitis than amoxicillin (Kiani *et al.*, 1988). Cefixime is as potent as amoxicillin for the treatment of urinary tract infections in adults.

First-Generation Parenteral Cephalosporins

The first-generation cephalosporins are given in pre and post-operative conditions for maintaining hygiene in contaminated procedures like a cesarean section, vaginal hysterectomy, cholecystectomy. These are also widely employed in patients subjected to clean surgeries like arthroplasty, cardiovascular procedures. The infection can produce significantly elevated mortality and morbidity. Cefazolin is more disposed to B-lactamase when compared with cephalothin (Drusano *et al.*, 1982).

Second-Generation Parenteral Cephalosporins

Cefoxitin is more potent against the *B. fragilis* species and many gram-negative and gram-positive organisms. Cefoxitin is worth in the treatment of pelvic and intraabdominal infections, as these are polymicrobial that includes anaerobic bacteria and gram-negative enteric bacilli. Cefoxitin is frequently employed as a preventive agent in patients subjected to pelvic or colorectal surgery. The agent alone seems to be as useful as the combination of clindamycin and an aminoglycoside. Cefoxitin has been also preferred in treating simple and dissipated gonococcal infections produced by penicillinase-inducing *N. gonorrhoeae* (PPNG) strains. The third-generation cephalosporin, like ceftriaxone, is more potent and is considered widely.

Cefotetan has been manifested useful in the treat-

ment of obstetric, gynecologic, lower respiratory tract, skin and soft-tissue, serious urinary tract, and intra-abdominal infections caused by organisms. Minimal clinical evidence were obtained with cefoxitin than with cefotetan, and the two agents have demonstrated to be efficacious for the treatment of community-acquired intra-abdominal infections in relatively ill patients, also for obstetric and gynecologic infections (Sweet *et al.*, 1988), Superficial soft tissue and skin infections, and prevention in colorectal surgery.

Cefoxitin is more active than cefotetan. Cefmetazole is as useful as cefoxitin for the therapy of gynaecologic and intra-abdominal infections (Griffith *et al.*, 1989). Cefmetazole is similarly used for surgical prophylaxis. Cefamandole is employed as a relative to chloramphenicol and ampicillin for infections caused by *H. influenzae*, but therapeutic failures have been described (Sanders, 1985).

Cefamandole is not useful in the therapy of meningitis. Ceforoxime is more potent against *Pneumococci, H. influenzae*, *Staphylococcus aureus, and Streptococcus pyogenes*, its wide usage, and its extent of diffusion into the cerebrospinal fluid, it is used for the treatment of meningitis in the pediatric group. Information of extended sterilization of the cerebrospinal fluid, failure in therapy, and recurrence in patients with *H. influenzae* type-B infection have raised confusion regarding the use of cefuroxime in meningeal infections.

Cefonicid have the longest elimination half-life among the first and second-generation cephalosporins, and thus resulting in single-dose administration. It is given usually for mild to moderate infections, which includes urinary tract infections, skin and soft-tissue infections, and community-acquired pneumonia (Donowitz and Mandell, 1988). There are worries over the effectiveness of cefonicid in complicated *S. aureus* species infections like endocarditis since the drug's use has triggered failures (Chambers *et al.*, 1984).

Third-Generation Parenteral Cephalosporins

Cefotaxime is a commonly prescribed drug for the treatment of meningitis caused by gram-negative bacilli. The agent is used against meningitis caused by B-lactamase-inducing *H. influenzae* type B and is as effective as a combination of ampicillin with chloramphenicol (Jacobs *et al.*, 1985). It is more potent against *Neisseria meningitidis*, *S. pneumoniae, H.influenzae*. It is often employed for actual therapy of meningitis in infants and young childrens. Ceftizoxime and cefotaxime are useful against complicated gram-negative bacillary infections like gynecologic infections, serious urinary tract, bone, intraabdominal, skin, lower respiratory tract, and gynecologic infections. These agents are also effective against infections caused by bacterias impervious to penicillins or earlier cephalosporins; as substitutes to aminoglycosides in some instances; and in infections resulting from *K.pneumoniae*.

Third-generation cephalosporins are exposed to faster development of resistance during treatment for infections associated with *Citrobacter, Serratia,* or *Enterobacter* organisms (Neu, 1984). Ceftriaxone activity is supreme against *N.gonorrhoeae* including, tetracycline-resistant *N. gonorrhea*, chromosomally-mediated resistant *N.gonorrhoeae,* and PPNG. A single 250-mg intramuscular dose can be greatly efficacious against simple gonorrhea in adults. Ceftriaxone is beneficial in the therapy of chancroid (Taylor *et al.*, 1985).

As ceftriaxone is powerful against organisms that cause meningeal infections in paedeatric populations, it is employed as an alternative of ampicillin plus chloramphenicol for accurate therapy. Ceftriaxone is frequently used for experimental monotherapy against joint, lower respiratory tract, skin, serious urinary tract and bone infections, and also for bacteremias secondary to pathogens impervious to earlier cephalosporins. Single-dose ceftriaxone therapy has manifested as effective in complicated bacterial infections as cefotaxime, administered every 4 to 8 h. Third-generation cephalosporin's are used appropriately to treat salmonellosis induced by ampicillin- and chloramphenicol resistant strains. Ceftriaxone is effective for eliminating pharyngeal transmission of *N. meningitis*. Ceftriaxone allows single dosing, and it is employed in the outpatient surroundings.

Due to its predominant antipseudomonal effect, ceftazidime is regularly employed for emipical treatment in neutropaenic subjects with fever. In patients with fever and intense neutropenia ($<100/mm^3$) or encountered with *P. aeruginosa*, it should always be combined with an aminoglycoside. Ceftazidime is effective against hospital-acquired gram-negative infections, but its value for the single-therapy of gynecologic and intra-abdominal infections is restricted due to its minimum effect against the Bacterial species. In some experiments, the development of infections with gram-positive bacteria have been persistent when ceftazidime was only used. Ceftazidime has exceptional diffusion into the cerebrospinal fluid and are effective against *P. aeruginosa* meningitis.

Ceftazidime is also employed in the treatment of meningitis caused by gram-negative enteric bacilli such as *Klebsiella, Proteus,* and *E. coli* species. Cef-

operazone act against *P. aeruginosa* when compared with other third-generation cephalosporins. Cefoperazone is not suggested as the unique therapy of complicated *P. aeruginosa* complications. The medicine has been advantageous in the treatment of serious bones, urinary tract, skin, joint, and lower respiratory tract infections. The use of Moxalactam is controversial because the drug has been linked with a high prevalence of complicated bleeding events in several patients.

Fourth-Generation Parenteral Cephalosporins

Some experiments have revealed the efficiency of cefepime and Cefpirome in the therapy of gynecological infections, complicated and uncomplicated urinary tract infections (Garau *et al.*, 1997), skin and soft tissue infection, upper and lower respiratory tract infections. In intubated patients, the susceptibility to early-onset pneumonia is due to normal residents of the oropharyngeal cavity, such as methicillin-susceptible *H. influenza, S. aureus, S. pneumoniae*. Late-onset hospital-acquired pneumonia is frequently to be induced due to organisms like *P. aeruginosa* or hospital *Enterobacteriaceae*.

Non-fermentative Gram-negative bacilli are found in some geographic locations (Garau *et al.*, 1997). Patients with early-onset ventilator-associated pneumonia, along with no basic risk factors such as earlier antibiotic therapy, current hospitalization, aspiration, or a serious underlying condition, may be treated with agents such as B-lactams plus B-lactamase inhibitors, or second or third-generation cephalosporins (Garau *et al.*, 1997).

The therapeutic efficiency of cefpirome 2 g bid was contrasted with ceftazidime 2 g three times daily (TID), in the treatment of ICU patients with severe pneumonia (Garau *et al.*, 1997). Out of 471 susceptible organisms were isolated from diseased subjects (mainly *H. influenzae*, *S. aureus*, *S. pneurnoniae*, *P. aeruginosa*,), 81.5% were treated with ceftazidime and cefpirome. Cefepime 2 g bid appreciably effective in the therapy of complicated community-acquired or hospital-acquired pneumonia.

A satisfactory response was reported in a contrasting study in 75% of the cefepime patients and 74% of a person taking cefotaxime, ceftazidime 2 g tid (Leophonte *et al.*, 1993). A detailed examination consisting of complicated community-acquired pneumonia, curative rates were found to be 87% in the cefepime category and 86% in the ceftazidime category (Bush and Bradford, 2016).

Fifth-Generation Parenteral Cephalosporins

ceftazidime/avibactam and ceftolozane/tazobactamare agents that kill the bacteria and it attach to PBPs, the important enzymes which are participating in the concluding step of synthesis of the cell wall in both gram-positive (Singh *et al.*, 2019) and gram-negative bacterias.

Each agent is connected to a beta-lactamase inhibitor that does not have a therapeutically significant in vitro effect against the pathogen, but it assists to secure the cephalosporin from deterioration. Combination of Tazobactam and new cephalosporin, ceftolozane is a permanent prohibitor of class C cephalosporinases and class A penicillinases establishes covalent bonds to some plasma-mediated and Chromosomal beta-lactamases.

Avibactam, is a new beta-lactamase prohibitor that is merged with ceftazidime. The intact third-generation cephalosporins inhibits extended-spectrum beta-lactamases (ESβLs), class D oxacillinases, serine carbapenemases, prohibiting class A penicillinases, class C cephalosporinases.

CONCLUSIONS

Cephalosporins are a diverse, extremely useful group of beta-lactam antibiotics employing a mechanism of action that requires bacterial replication for efficacy. The primary mechanisms by which bacteria develop resistance to cephalosporins include mutations of the antibiotic target (PBPs) or inactivation of the drug by beta-lactamases. 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. In contrast, gram-positive activity decreases with increasing generation except for the first- and fourth-generation drugs, which have similar gram-positive activity. Rather than learn all cephalosporins, it is reasonable for the clinician to be familiar with selected cephalosporins among the parenteral and oral formulations. Useful specifics facts are: ceftriaxone has pharmacokinetics that allows the least frequent dosing, cefepime and ceftazidime have anti-Pseudomonas activity, and cefoxitin has the most anaerobic activity. *Enterococci* and MRSA are resistant to all currently approved cephalosporins. No oral cephalosporin is effective against pneumococci that are highly resistant to penicillin.

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