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Review Article

# Production, Characterization and Clinical Applications of Third-generation Cephalosporins

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**Abstract:** Cephalosporin is one of most widely used drug in world wide. Cephalosporin mechanism of action is more resistant to other agents that have infections from these agents. Its classification ranking 4th generation cephalosporin is more critical than 3rd generation cephalosporin but both are critical in WHO criteria. In human medicines and all risk management factors used cephalosporin antibiotic as one of the major factor. Its production on large scale is very important. Cephalosporin produced from *Cephalosporium acremonium* which immobilized in agar or other agents and cephalosporin antibiotics produced under optimum and favorable conditions. Calcium alginate and glass wool also used for immobilization and repeated batch of shake flask fermentations used for its production. It was recently improved for the treatment of community acquired pneumonia. It has also broad spectrum activity against gram positive and gram negative bacteria. It is also used for the treatment of hospitalized patients. Cephalosporin shows low resistance ratio and safety measurements. It is mostly used for the treatment of skin complicated infections. It will evaluate the pharmacological characters, efficacy, safety, antimicrobial property and its application of cephalosporin in the treatment of community acquired pneumonia.
**Keywords:** cephalosporin, *Cephalosporium acremonium*, community acquired pneumonia.

## INTRODUCTION

Sea water was used first time by Brotzu to isolate *Cephalosporium acremonium* in 1945. Later many scientists worked on it in 1955-56 which was isolated cephalosporin in various forms like C and P and penicillin N also from culture of acremonium [1]. Acyl side chain linked with amino group so it resembles with penicillin. Its main disadvantage is low potency of cephalosporin C. Also some semi synthetic derivatives of cephalosporin are also produced like cephalothin and cephaloridine [2]. Modification of cephalosporin gives various compounds having different characteristics. The important broad spectrum antibiotic in international market and is more resistant to penicillin. Mostly cephalosporin C is mostly used for the synthesis of cephalosporins that produced by some other type of fermentation or by aerobic fermentation which are using different strains of *Cephalosporium acremonium* and many other species [3]. The CPC weak antibacterial activity but its modifications and its side chain create various cephalosporins which have diversified effects and antibacterial activity. The mold is renamed as acremonium chrysogenum. 65% of penicillin and cephalosporin share worldwide market of antibiotics [4]. Clinical uses of cephalosporins are drugs choice by dental treatment or odontogenic infection or who persons have allergic responses as alternative of this penicillin used for orodental therapy caused by aerobic bacteria. Adverse reactions of this drug are hypersensitivity reactions, cross reactivity with penicillin, diarrhea, alcohol problem and serious bleeding [5].

The production of cephalosporins in batch as well as continuous culture using free and immobilized cells of mold or any bacterial species reported in various reports having different aspects. The media optimization for production of antibiotic also reported by some authors and different thesis were present [6]. Some reported single constituent of the fermentation of CPC. In media optimization also optimize carbon nitrogen ratio for the synthesis of cephalosporins. By using immobilized cells during production of cephalosporins with various supports like polyacrylamide, calcium alginate and various other compounds. Cephalosporin production by using calcium alginate cells of fungus species. Using special conditions, production of cephalosporin is enhanced by immobilization [7]. Polyacrylamide gel also used for the inactivity of multi enzymes in the mycelium. This gel also entrapped various streptomyces species for

cephalosporin production. Agar immobilization is also used for cephalosporin production [8].

Cephalosporin with penicillin acts as strong antibiotic that inhibit and remove the growth of microorganism. Cephalosporin is more resistant than penicillin against any microbes. The production of cephalosporins in batch as well as continuous culture using free and immobilized cells of mold or any bacterial species reported in various reports having different aspects [9]. The media optimization for production of antibiotic also reported by some authors and different thesis were present. Influence of media constituent in production of cephalosporin and in batch process sucrose is rapidly consuming so such kind of studies very important for the production of antibiotic and good production performance. The present studies deal with the media component that improves the production of cephalosporins [10].

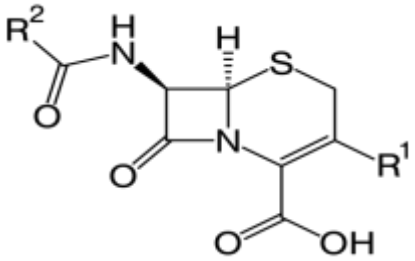


**Fig 1: Structure of cephalosporin**

Different generations of cephalosporins depend upon different antimicrobial spectrum. Antimicrobial properties are against gram positive decrease but against gram negative increase [11]. Mostly bacteria infections treated by using cephalosporin antibiotic like repiratory tract, infection of skin and infection of urinary tract. Different strains of cephalosporium species are used for the production of cephalosin are used in fermentation which are used as starting material and a process run which requires different factors for good production performance [12]. Submerged and solid state fermentation also used by immobilized cells or organisms. The maximum production of cephalosporin is by using wheat raw and sugar bagasse. As substrate optimization so different other conditions are also important as addition of yeast, soluble starch and pH control and other nutrients [13]. Inoculums level and incubation period also effect the production of cephalosporin by solid state fermentation. Shake flask fermentation best used for production of cephalosporins [14]. In immobilization *Cephalosporium acremonium* spores immobilized in gels and the production of secondary metabolties was higher for immobilized cells than other freely suspended cells. The cephalosporin production by these cells 3-4 times more and chooses entrapment method by immobilization which has good production and investigation of free susupended cells and confinement in immobilized cells [15]. The structure of cephalosporin is shown in fig 1 [16].

## ANTIBIOTIC PRODUCTION FROM MICROBES

*Acremonium chrysogenum* strain used in fermentation for high yielding to produce such broth has CPC. Purification of fermentation broth is by aqueous solution of CPC. Enzymatic activity is done by purification of such extract to produce aqueous solution of CPC. Precipitation is done of this broth and after this isolation of ACA of appropriate purity 98% for use in the cephalosporin production and intermediate and also active pharmaceutical ingredients [17]. In industrial scale production all ingredients added and it takes three weeks from which two weeks done fermentation and one week for down streaming processing. After down streaming process one day takes for purification, crystallization and drying. After that cephalosporin is crystallized, used and formulated for marketing [18].

Some steps from this outlined production can be changed. Some steps modified or changed such as ion exchange column and crystallization of CPC not require so some procedures will take these steps in already running process [19]. Crystallization of CPC is done in china to make supply easier. CPC are precipitated with zinc salt or any other sodium or potassium slat. Sodium or potassium slats are used for splitting into ACA. Other production methods are also used for the purification and crystallization of product. But cephalosporin also produced synthetically some reactions occur in our body as shown in fig 2 [20].

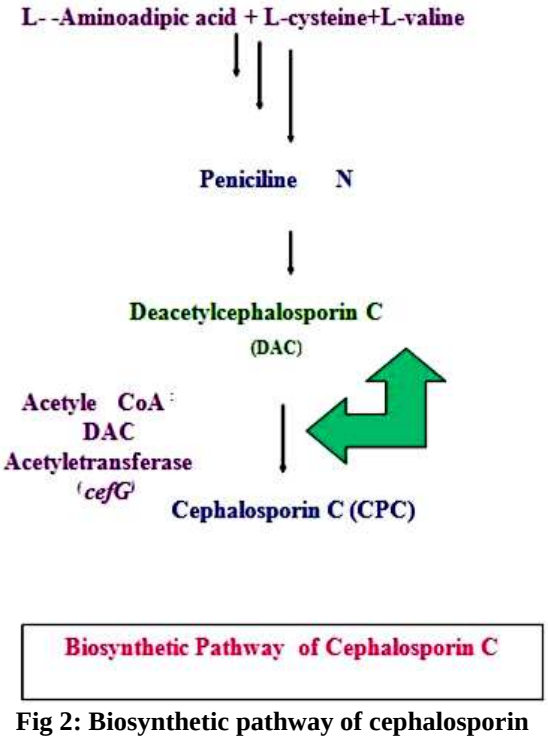


**Fig 2: Biosynthetic pathway of cephalosporin**

## MECHANISM OF ACTION

Cephalosporin is a fifth generation antibiotic and have similar action as other antibiotics. Cephalosporin binds with penicillin binding proteins and removes the growth of microbes and also prevents the growth of peptidoglycan essential component of bacterial cell wall. Streptococcus species caused those infections which have affinity for cephalosporins [21]. Cephalosporins bind with penicillin binding proteins which are primary target for bacteria and also resistant strains. The mechanism of action of cephalosporin C is shown in fig 3 [22].

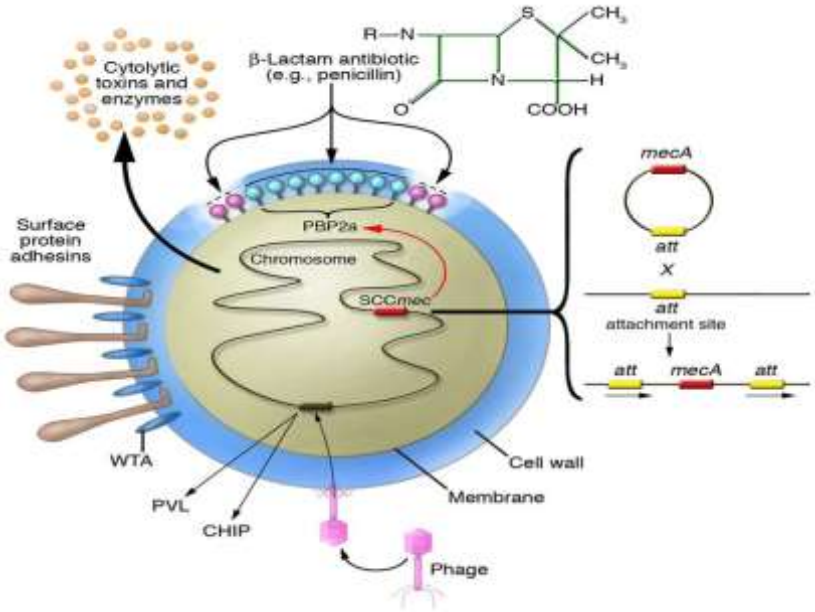


**Fig 3: Mechanism of action of antibiotics**

## MICROBIOLOGICAL ACTIVITY

Gram negative pathogens are treated by broad spectrum cephalosporin. Several studies in vitro activity of cephalosporins have been carried out. A study of such pathogens cephalosporins is to comparator agents [23]. Cephalosporin was found to be eights fold more effective against pneumonia strains than other generation cephalosporins. Cephalosporin show more activity against other pathogens. Another generation cephalosporin group found to be more resistant against 120 types of streptococcus species [24]. Mutations and other penicillin binding proteins have activity against these strains and resistance to beta lactams. In susceptibility study of 891 strains of bacterial species isolated in US which compared those antibiotics with current available cephalosporin antibiotic therapies [25]. Those strains which are resistant to penicillin but cephalosporin are more effective and have more activity against those strains. In some other studies cephalosporins have more activity against 548 strains of *Hemophilus influenza* and 377 strains of some other species, a degree of activity compared with cephalosporin [26]. In experimental pneumonia model rabbit were inoculated with different strains of bacterial species and in result to eradicate the infection caused by penicillin but some strains are more prior by the treatment of cephalosporins [27].

First generation cephalosporin antibiotic used against methicillin resistance *Staphylococcus aureus*, these characteristics more useful if pathogen continues to increase in frequency. Large series of antibiotics or isolates have bactericidal activity against different bacterial species. The activity of cephalosporins is against different four strains. The bactericidal activity against three strains and reduction in bacterial count is with respect to fourth [28]. Third generation cephalosporin used against gram negative microorganism. Different microbial species have potency against ceftaroline. Hence it is important that ceftaroline has similar function to third generation antibiotics and have not significant effect as beta lactamase producing organism or other microorganisms [29].

**Table-1: Spectrum of microbiological coverage**

| **Gram-positive bacteria** | **References** |
|---|---|
| *Staphylococcus aureus* (MSSA and MRSA) | [6] |
| *Streptococcus pyogenes* | [2] |
| *Streptococcus agalactiae* | [14] |
| *Streptococcus pneumoniae* | [32] |
| *Streptococcus dysgalactiae* | [15] |
| **Gram-negative bacteria** | |
| *Klebsiella pneumoniae* | [43] |
| *Klebsiella oxytoca* | [6] |
| *Escherichia coli* | [42] |
| *Citrobacter koseri* | [16] |
| *Citrobacter freundii* | [9] |
| *Enterobacter cloacae* | [18] |
| *Enterobacter aerogenes* | [4] |
| *Haemophilus influenza* | [10] |
| *Haemophilus parainfluenzae* | [23] |
| *Proteus mirabilis* | [34] |
| *Moraxella catarrhalis* | [6] |

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin susceptible *Staphylococcus aureus*.

## ADVANTAGES

As compared to other antibiotics used for clinical purposes, cephalosporins have low resistance and more activity against most pathogens. Its safety profile is similar to those currently available microbes to treat these infections. Some adverse effects of cephalosporins are also present such as vomiting, diarrhea, nausea but some serious effects anaphylaxis and respiratory failure also occur. The frequency of such antibiotics to develop resistant with major pathogens is low. Cephalosporins are used with more resistant and demonstrated with such pathogens and not used in the treatment of patients. These have activity also to treat bacterial isolates including various pathogens. Cephalosporin treat the most common pathogen with low propensity for drugs interactions and its good alternative agent for those who do not tolerate or respond to other antibacterial therapies [30].

## DISADVANTAGES

Cephalosporin has been tested on specific population of patients and not useful for skin and skin structure infections because it has adverse effects. Its use because various infections to treat one type of infection causes other risk factors. Cephalosporins are used intravenously. Intramuscular administration has been studied but not approved. There is no oral preparation of this antibiotic. Different generations of cephalosporins have various doses and have various reports against them. Currently there are no cost benefits by use of cephalosporins in the treatment of patients but the current cost of this medication higher. Intravenous formulation to treat various diseases increases the cost of this antibiotic. Vancomycin should be less expensive and it is the first generation cephalosporin [31]. Caution should be undertaken while using these antibiotics and it has same safety profile as other cephalosporins. Clinically cephalosporins used to treat complicated skin structure and skin infections with these pathogens. Studies on other bacterial species are lacking efficacy. Its uses limited to the population where it has shown clinical efficacy [32].

## CLINICAL USES

### Respiratory tract infections

Cephalosporins have advantage over other antibiotics or other generations of cephalosporins like ampicillin and amoxicillin in otitis media. Cephalosporin other generation antibiotics is more useful than other erythromycin antibiotics for penicillin allergic patients. Like cefaclor another cephalosporin more efficacious than other antibiotics likes erythromycin and sulphonamide to cure patients of otitis media of children which are developed. Amoxicillin more effective and must be 1$^{st}$ generation antibiotic. Oral or parenteral cephalosporin has no evidence to treat only chronic bronchitis [33]. It is possible that other antibiotics like cefotaxime or cefoperazone would be more beneficial in the 1$^{st}$ generation therapy of patients who have infectious by *Streptococcus pneumonia* and *Hemophilus influenza* require hospital treatment [34].

All cephalosporins cure *Pneumococcal pneumonia* because it will be present outside the boundary of hospital but benzylpencillin more effective used by intramuscular injection. When pneumonia caused by *Hemophillus pneumonia* then cephamandole used against that infection. Direct comparison of all that antibiotics discussed has not been reported. Cefuroxime

is more useful than antibacterially and pharmacologically to other antibiotics. Semi synthetic penicillin for staphylococcus species target but cephalosporins used and it should be older one than other antibiotics. Cephalosporins are now used to aminoglycides for the treatment of other diseases and other pneumonia agents treated by other cephalosporin generation antibiotics [35].

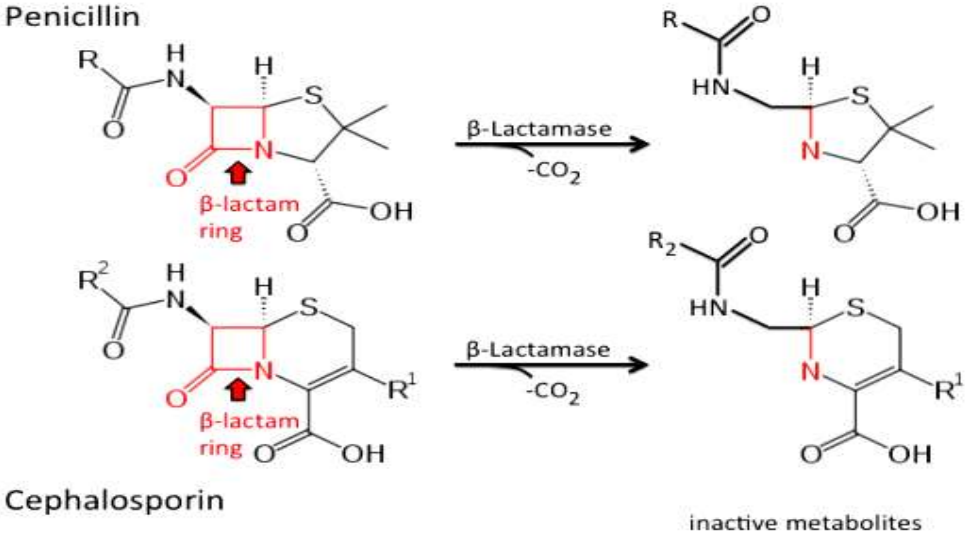


**Fig 4: cephalosporin converts to inactive metabolites**

Lungs or pulmonary infections mostly due to in hospital by organism like aeruginosa, *Enterobacter sp*., E. coli or often in combination with other mouth flora. Mostly mouth flora anaerobes and *Enterobacter sp*. treated by cefoxitin agent and other antibiotics. Some penicillin also used more useful for the cure of diseases infectious by pathogens. Pulmonary diseases due to anaerobic flora have been treated by old and new cephalosporins and there have been no other antibiotics which have been more choiceful in such infections [36]. Bacterial pulmonary diseases in children and adults with cystic fibrosis cured by cephalosporin antibiotics and these diseases caused by aeruginosa species. Tetracycline also remains the choice of drug for other group of organisms.

**Urinary tract infections**

Oral cephalosporins are mostly useful for the cure of urinary tract infections in domicile and hospital settings. For the cure of lower tract infections single dose of some antibiotics is mostly useful and preferred. In hospital urinary tract infections due to multiple pathogens agents cause non pathogenic alternative to the aminogylcosides.70% treatment rate with these new agents that have these activities in vitro. Pseudomonas such organism which are only cured by cephalosporins none other antibiotic that has more preferable activity against this organism. Upper urinary tract infection also treated by cephalosporins within 10-14 days [37].

**Intra abdominal infections**

Facultative bacilli and other anaerobic bacteria are caused by intestinal mucosa that results from breaches in intra abdominal infections. Cephalosporins have chemotherapeutic role in such infections. Cefoxitin have proved as effective as amino glycosides. If pseudomonas like other organism present and infectious caused by in case of hospital cure or after use of these antibiotics, cephalosporins antibiotics used until culture results known. Single therapy is more effective than combined antibiotics equal to or more effectively used. The doses of some antibiotics were lower than favored by most physicians [38]. So, third generation cephalosporin is more effective for the treatment of intra abdominal infections mostly when there is concerned with renal toxicity. Some antibiotics most actively used agent and should be main component of infections.

**Gastrointestinal infections**

Salmonella and shigella species disapproved the oral and parenteral cephalosporins. Cefotoxime more effective with salmonella infections but other antibiotics used as next base choice foe the treatment of this disease. Some bacterial species have no effects and no reports of infections occurred by this organism. Any of all those of cephalosporins can be used to cure diarrhea. Some membranous infections have occurred with many of cephalosporins [39].

**Hepatobiliary infections**

Enterobacter species, E. coli caused infection in biliary tract. Anaerobes are most useful when there has been operate or in special case diabetes in who spore forming bacteria may be the pathogen. Cephalosporin antibiotics all proved useful in such

infections. When there has been infection due to these bacteria agents such as preferred agent would be piperacillin. Liver diseases are due to anaerobic species in which aforementioned penicillins may give better results [40].

**Gynaecological infections**

Cephalosporin antibiotics have no role in treatment of inflammatory disease. Oral cephalosporin also used in such infections. Bacteria cause infections in the patient who treated by radiation therapy or cytotoxic. E. coli and other bacteria are the important pathogens. Cephalosporin has proved excellent therapy. Third generation cephalosporins and cefoxitin should be gynecological infections and prevent formation and surgical invention [41].

**Sexually transmitted diseases**

Penicillinase producing bacteria provide an important area for cephalosporin antibiotics. The best agent maybe antibiotic and have 8 hours serum half life and have dose as low as 250 mg in intramuscular injection. It also resulted more reacted against man as well as rabbit and it will be important for the treatment of sexually transmitted diseases. One drawback of these new agents is their deficiency of inhibitory activity against some species [42].

**Skin and soft tissue infections**

Streptococcus species and other bacterial species cause skin and soft tissue infections are best treated by benzyl penicillin and other antibiotics. Cephalosporin with penicillin is therapeutic agent possibility in adults and erythromycin in children. Infections by bites or closed injuries are when responsible organism bacteria treated with penicillin. Gram negative bacilli and anaerobic bacteria cause ulcers and peripheral vascular diseases are associated with cephalosporins. Third generation cephalosporin is most useful and active related to all these infections. But most other agents are associated when pseudomonas has been present [43, 44].

**Bone and joint infections**

Bacterial species are treated by earlier cephalosporins and have resulted best treatment against these antibiotics. In the patient with penicillin allergy with pencillinase producing bacteria now give cured by antibiotics. The total number of patients which have this disease tested with new cephalosporin has been small. All cephalosporin antibiotics are effective and no one regarded as first choice. The efficacy of new cephalosporins is not well established. While other generations of cephalosporins was undecided. These agents now used for the treatment of these diseases [45].

**Cardiovascular infections**

Penicillin alternative is first generation cephalosporin have been used due to bacterial species remain the first choice. Gram negative on the left side of heart is a disease cured by surgery and has cured with any of the new agents [46].

**Central nervous system infections**

First and second generation cephalosporin have been used for the therapy of central infections. Chemotherapy results are available of new cephalosporin and some antibiotics are used as first initial therapy of this infection which caused by some bacterial species. In some countries Listeria and other species are also important. Mortality rate was also reduced by these cephalosporins. None of these agents is satisfactory and superior to these kinds of bacteria. Cefotaxime has proved to be excellent therapy of such infections and single agent can not be used or effective in other species. Cephalosporins old and new have no role but it have minor role in the therapy of brain and other bacterial species are the important pathogens [47-50].

## FUTURE INVESTIGATIONS

The studies of antimicrobial resistance remain concern for the development of novel agents. Future studies on drugs clinical impact on pneumonia should be explored in species and other infections caused by pathogens. The use of cephalosporin against pneumonia explored in other populations such patients in ICU or with septic shock or any other infecting organ and requiring renal replacement therapy. Cephalosporins wide coverage of gram positive and gram negative pathogens in combining this antibiotic with other pathogens to provide additional pathogen coverage. Preliminary models are promising. The clinical implications of this drug combination are encouraging in an era of increasing multi-resistant pathogen induced infections.

**Table-2: Indications for cephalosporin**

| Diseases | Antibiotics | References |
|---|---|---|
| **Respiratory tract infections** | | |
| Otitis media | Cefaclor | |
| *Streptococcus pneumonia* | 1st generation agent | |
| *Hemophilus influenza* | Cefotaxime | |
| *Staphylococcus aureus* | Cefazolin | |
| Klebsiella | Cefotaxime | [15] |
| Pseudomonas | Ceftazidime | |
| Anaerobic organisms | Cefoxitin | |
| **Urinary tract infections** | | |
| Enterobacteriaceae | Cefotaxime | [35] |
| Pseudomonas | Ceftazidime | |
| **Central nervous system infections** | | |
| Neonatal | Cefotaxime | |
| *Streptococcus pneumonia* | Cefotaxime | |
| *Hemophilus influenza* | Cefotaxime | [43] |
| Enterobacteriaceae | Cefotaxime | |
| **Bone and joint infections** | | |
| *Staphylococcus aureus* | Cefazolin | |
| Enterobacteriaceae | Cefotaxime | [22] |
| Pseudomonas | Ceftazidime | |
| **Diarrhoeal diseases** | | |
| Shigella | | |
| Salmonella | None | [10] |
| Campylobacter | | |
| **Sexually transmitted diseases** | | |
| Gonorrhoea | Cefoxitin | [28] |

## CONCLUSION

Cephalosporin, a fifth generation antibiotic used for the treatment of community acquired patients in hospitalized patients. But its high potency also caused various effects on human body and does not effect the bacterial infections. Even this antibiotic FDA approved but its high dosage also cause various side effects. Recent studies on cephalosporin to improve its efficiency and resistant to more pathogens when it used with other antibiotic it is more resistant and also resist gram negative bacteria. In appropriate use of cephalosporin cause various resistant strains to enter in hospital environment or community like various bacterial pathogens. In a time of enhancing resistant drug infections, provide the additional treatment of already antibiotics.

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