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CEFTAROLINE: A NEW CEPHALOSPORIN WITH ACTIVITY AGAINST METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

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Abstract:

Superbug infection is caused by multi resistant staphylococcus aureus and belongs to the family staphylococcaceae. A common cause of infection in hospitals and community, it is becoming virulent and resistant to antibiotics. Staphylococcus aureus, a known pathogen for nosocomial infections, has developed resistance towards methicillin and related drugs. There are very few options available like Vancomycin, Linezolid, Daptomycin etc. for the treatment of MRSA infections which are associated toxicity and high costs. However, none of the beta-lactam antibiotic was effective against MRSA. Once methicillin resistance is developed by the bacteria, it is considered as resistant to many other Beta lactams including Cephems and Beta lactamase inhibitor combinations. Recent introduction of 'Ceftaroline fosamil' a new broad-spectrum cephalosporin often described as a 'Fifth Generation' cephalosporin, has created a considerable amount of expectation as an alternative for infections due to MRSA. Ceftaroline is used for the treatment of community acquired pneumonia and acute skin and skin structure infection caused by susceptible organisms in adults >18 years of age. The safety of ceftaroline in paediatric population is not yet established. It is primarily eliminated by kidney and requires dose reduction in patients with renal impairment. It is approved by DCGI May 2016 for marketing in India.

Key words: *Ceftaroline, 'Fifth Generation' cephalosporin, MRSA, Community-acquired pneumonia, acute skin and skin structure infection*

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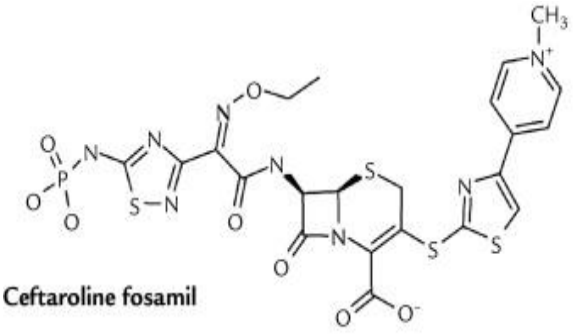
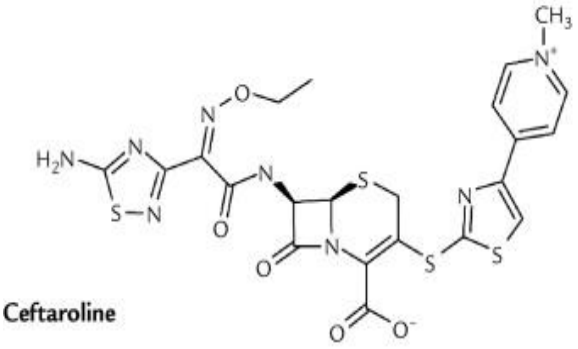
INTRODUCTION:

Methicillin-resistant *Staphylococcus aureus* (MRSA) have been on the increase during the past decade, due to the steady growth of the elderly population and immunocompromised patients, and the emergence of multidrug resistant (MDR) bacterial strains. Although, only a limited number of anti-MRSA drugs are available, a number of different combination antimicrobial drug regimens have been used to treat serious MRSA infections. The increasing drug resistance among Gram-positive bacteria is a significant problem because they are responsible for one third of nosocomial infections. Drug resistance in Gram-positive organisms (i.e. Staphylococci, pneumococci) vancomycin resistance in enterococci, and mycobacteria have achieved prominence in last 15 years. Methicillin-resistant *S. aureus* (MRSA) is one of most frequently reported nosocomial pathogen in developed countries. *S. aureus* commonly colonizes the external portion of nose (anterior nares), throat, respiratory tract, urinary tract, and soft skin tissues. Most often, *S. aureus* infections are associated with medical insertion of foreign metals, plastic or vascular devices such as those used for hemodialysis, venous catheterization, or artificial prostheses. *S.aureus* also cause wound infections and has the potential to induce osteomyelitis, endocarditis and bacteremia, leading to infections in any of the major organs of the body. Some CAMRSA (community-associated methicillin resistant *S. aureus*) strains can affect vital organs and lead to widespread infection (sepsis), toxic shock syndrome, and necrotizing pneumonia. These life-threatening medical conditions are believed to be due to toxins carried by CA-MRSA strains, such as Panton-Valentine leukocidin (PVL) and phenol-soluble modulins (PSM). Penicillin, once an effective antimicrobial against *Staphylococcus aureus* has no place in the treatment of staphylococcal infections in today's era. This is because of increased encounters with penicillinase producing strains of *S.aureus* in more than 90% of cases regardless of the clinical setting. This brought penicillinase stable penicillins like Methicillin, Oxacillin, Cloxacillin, Nafcillin. However, as rapidly as new antibiotics were introduced, *Staphylococci* have developed efficient mechanisms to neutralize them.

CHEMISTRY:

Ceftaroline fosamil is a N –phosphono prodrug of the fifth-generation cephalosporin derivative ceftaroline with antibacterial activity. It is hydrolyzed to the active form ceftaroline in vivo. Ceftaroline binds to and inactivates pencillin binding proteins located on the inner membrane of the bacterial cell wall. BPS are enzymes involved in the terminal stages of assembling the bacterial cell wall and in reshaping the cell wall during growth and division. Inactivation of PBPs interferes with the cross linkage of peptidoglycan chains necessary for bacterial cell wall strength and rigidity.This results in the weakening of the bacterial cell wall and causes cell lysis.

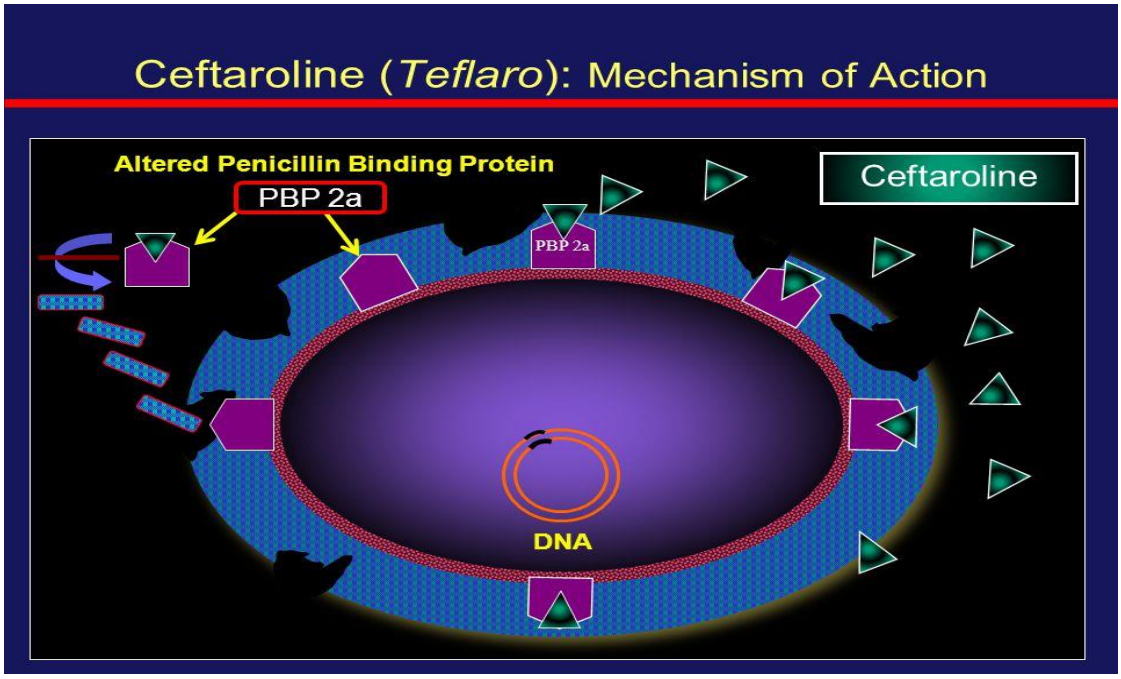




(Fig 1) Ceftaroline fosamil is a N –phosphono prodrug of the fifth-generation cephalosporin derivative ceftaroline with antibacterial activity.

MECHANISM OF ACTION

Ceftaroline is a bactericidal drug. Its bactericidal action is similar to other cephalosporin and mediated through binding to essential penicillin binding protein. Ceftaroline binds to PBP 1–4 and has an especially high affinity for PBP2a (mecA), which is associated with methicillin resistance. This unique affinity for PBP2a distinguishes ceftaroline from other cephalosporins. Ceftaroline binds to all 6 PBPs that have been identified in S. pneumoniae (PBP1A, 1B, 2x, 2A/B and 3).



(fig:2) Ceftaroline binds to PBP 1–4 and has an especially high affinity for PBP2a (mecA), which is associated with methicillin resistance.

ANTIMICROBIAL ACTIVITY

Ceftaroline is a broad-spectrum cephalosporin with bactericidal activity against gram-positive bacteria, including methicillin- resistant S. aureus (MRSA), vancomycin-intermediate S. aureus (VISA), vancomycin-resistant S. aureus (VRSA), Staphylococcus epidermidis (both methicillin sensitive and resistant), and other coagulase negative staphylococci, including Staphylococcus lug- dunensi, Staphylococcus hominis and Staphylococcus hemolyticus.

Ceftaroline is active against MRSA strains, including Panton Valentine-leukocidin (PVL)-producing strains, as well as strains that are resistant to other classes of antimicrobial agents, such as glycopeptides, daptomycin, clindamycin, sulfamethoxazole-trimethoprim, and linezolid.

Although, Ceftaroline has good activity against many Gram-negative organisms, Pseudomonas aeruginosa, Acinetobacter spp. and Stenotrophomonasmaltophilia have decreased susceptibility. Ceftaroline is not active against Gram-negative bacteria producing extended spectrum beta-lactamases (ESBLs). Ceftaroline has poor activity against Gram-negative anaerobes such as Bacteroides fragilis and Prevotella spp. however, Gram-positive anaerobes such as Propionibacterium spp. And Peptostreptococcus spp. are highly susceptible.

PHARMACOKINETICS

Ceftaroline fosamil is a water-soluble prodrug. It rapidly gets converted to its active biologic form ceftaroline after intravenous infusion. Mean peak plasma concentration of 19 µg/ml can be achieved in1 hour after intravenous infusion of ceftaroline in a dose of 600 mg. This cephalosporin exhibits linear pharmacokinetics and has a serum half-life (t½) of 1.6 h (for a single dose) to 2.7 h (following multiple doses). Ceftaroline has a volume of distribution (Vd 20 L) that is similar to that of other parenteral cephalosporins. Plasma protein binding is 20%. It gets metabolized to its metabolite, Ceftaroline M1, which is microbiologically inactive and both parent compound and its metabolite excreted mainly through kidney and very less through feces. The elimination half-life of ceftaroline is about 2.66 hours. The elimination of ceftaroline is altered in patients with diminished renal function, and dosage adjustments are recommended when the patient's creatinine clearance level is 50 mL/min. Patients undergoing hemodialysis exhibit significantly increased serum concentrations of ceftaroline, compared with those in patients with healthy renal function.

The systemic clearance of ceftaroline is not expected to be significantly affected by hepatic impairmen

PHARMACODYNAMICS

The duration of exposure (ie, the duration that the serum concentration is >MIC) determines the degree of antimicrobial activity for time-dependent (concentration-independent) agents. In an invitro hollow-fiber model, concentrations of ceftaroline were compared with those of vancomycin for activity against strains of heterogeneous vancomycin-intermediate S. aureus. In this model, ceftaroline exhibited superior killing, compared with that of vancomycin, and no difference in antimicrobial activity was observed between 2 ceftaroline dosing intervals (every 8 h vs every 12 h). Moreover, emergence of drug-resistant isolates was not observed following ceftaroline exposure. Ceftaroline has been compared with ceftriaxone and vancomycin against strains of S. pneumoniae in a rabbit meningitis model. Peak ceftaroline levels in the cerebral spinal fluid (CSF) were 3.2 mg/L after the first dose (40 mg/kg), and its CSF penetration was 14% -65%. Treatment with ceftaroline produced greater reduction in counts of penicillin susceptible S. pneumoniae compared to ceftriaxone and ceftaroline was superior to vancomycin against penicillin resistant S. pneumoniae.

PREPARATION

Ceftaroline fosamil is available as acetate salt for intravenous infusion to be given over a period of 1hour. Doses are expressed in terms of equivalent amount of Ceftaroline fosamil. 1.11 gm of Ceftaroline fosamil acetate is equivalent to about 1 gm of Ceftaroline fosamil. Ceftaroline fosamil is available in 600 mg single use vial of sterile powder. The vial contents should be reconstituted with 20mL of sterile water and further diluted in 250 mL of normal saline, 5% dextrose solution, 2.5% dextrose and 0.45% sodium chloride solution, or Lactated Ringer's Injection. The resulting solution should be used within 6h if stored at room temperature or within 24 h if refrigerated.

USES AND ADMINISTRATION

Ceftaroline is used for the treatment of community-acquired pneumonia and acute skin and skin Structure infection caused by susceptible organisms in adults >18 years of age. It may be of particular use for skin infection caused by MRSA. The usual dose is 600 mg every 12 hour. However, the duration of therapy should be guided by the severity and site of infection and the patient's clinical and bacteriological progress.

DOSAGE REGIMEN IN PATIENTS WITH RENAL IMPAIRMENT

In patients with renal impairment, the following intravenous doses of Ceftaroline fosamil are recommended, according to creatinine clearance.

Creatinine clearance (ml/min)	**Dosage regimen**
> 50	No dosage adjustment necessary
> 30 and = 50	400 mg every 12 hours
15 and = 30	300 mg every 12 hours
< 15 (End-stage renal disease), including Haemodialysis#	200 mg every 12 hours

#For patients on haemodialysis, the doses should be given after the dialysis run.

USE IN PAEDIATRIC POPULATION AND PREGNANCY

Ceftaroline is approved only for use in adult population (>18 years of age). The Safety and Effectiveness of this drug in paediatric population has not yet been established. Ceftaroline fosamil has been classified as pregnancy category B.

ADVERSE EFFECTS AND PRECAUTIONS

It promotes colonization and super infection with resistant organism. *Clostridium difficile* associated diarrhoea (CDAD), ranging in severity from mild diarrhoea to fatal colitis, has been reported. Therefore, careful evaluation is warranted if diarrhea occurs.

Severe hypersensitivity is reported with Ceftaroline. Hence, it is cautioned to use Ceftaroline with all precaution in the similar line with other cephalosporin, especially in patients with known hypersensitivity. Direct Coombs' test seroconversion has been reported with Ceftaroline. If anaemia develops during or after therapy, a diagnostic workup for drug-induced haemolytic anaemia should be performed and consider discontinuation of Ceftaroline.

DRUG INTERACTIONS:

Ceftaroline+warfarin

Severity:major

Onset:delayed

Concurrent use of CEFTAROLINE &WARFARIN may result in an increased risk of INR elevation and increased risk of bleeding.

MANAGEMENT: Consider close monitoring of degree of anticoagulation with concomitant ceftaroline and warfarin.

Cholera vaccine+ceftaroline
Severity: major
Onset: not specified
Concurrent use of CHOLERA VACCINE, LIVE &SYSTEMIC ANTIBIOTICS may result in reduced immune response to the cholera vaccine.
MANAGEMENT: Do not administer the live cholera vaccine and antibiotics concomitantly; do not administer the vaccine in patients who have received oral or parenteral antibiotics within 14 days prior to vaccination.

CEFTAROLINE VS OTHER ANTIMICROBIALS
The safety and efficacy of ceftaroline was compared with vancomycin in a Phase-III clinical trial in Skin and Skin Structure infections (CeftAroliNe Versus Vancomycin in Skin and Skin Structure Infections - CANVAS trial). It was a non inferiority double blind, randomized, active controlled design. Similarly, efficacy and safety of Ceftaroline was compared with Ceftriaxone in community acquired pneumonia (CAP) in a Phase III, double blinded, randomized, multinational, multicentertrial (ceFtarOline Community-acquired pneumonia trial versus ceftriaxone - FOCUS Trial).

These clinical trials showed that ceftaroline was non inferior to vancomycin plus aztreonam in the treatment of c SSTIs and to ceftriaxone in the treatment of CAP. Ceftaroline achieved demonstrated high bactericidal activity and substantiated clinical cure rates which are comparable with their respective controlled arm. The most potential advantage of Ceftaroline, over other Beta-lactam antibiotic, is its activity against MRSA. In addition, there are no reports on development of resistance in the FOCUS and CANVAS trials. One potential disadvantage of ceftaroline compared with other broad-spectrum antibacterial agents is its lack of coverage of Gram-negative organisms, particularly those producing âlactamases including AmpC, extended-spectrum beta lactamase (ESBL) and K. pneumonia carbapenemase (KPC). The disadvantage of FOCUS and CANVAS trial is that these trials showed only non-inferiority as opposed to superiority to its comparator. There is lack of clinical trial data as far as efficacy of Ceftaroline in patients with MRSA pneumonia. Hence, at present, superiority of Ceftaroline over other antimicrobial active against MRSA cannot be commented. However, it is definitely a new arrow in quiver against MRSA.

DRUG APPROVAL:
FDA Approved:29/10/2010
It is a cephalosporin antibacterial indicated for the treatment of acute bacterial skin and skin structure infections and community acquired bacterial pneumonia (CABP).

CONCLUSION:
MRSA infections remain a significant threat to human health into the second decade of the 21st century. Despite significant progress in understanding the pathogenesis of MRSA infection and the virulence mechanisms of MRSAstrains, daunting challenges remains. Ceftaroline is a novel, broad-spectrum cephalosporin, which exhibits bactericidal activity against Gram-positive bacteria, including MRSA and MDRSP. Ceftaroline offers an exciting addition to the antiMRSA armamentarium, including activity against VISA, hVISA, VRSA, and daptomycin and linezolid-resistant strains. Unique among many anti-MRSA agents, ceftaroline additionally provides activity against Gram-negative respiratory pathogens including *H. influenzae* and *M.catarrhalis*. Since ceftaroline is not effective against organisms with AmpC- or ESBLs, research investigating combination with β-lactamase inhibitors to provide potential activity against these Gram-negative organisms are underway. To date, ceftaroline has demonstrated an excellent safety profile comparable to contemporary cephalosporins and exhibits an inherently low propensity to inducing resistance, especially among Gram-positive organisms; however, long-term data and clinical experience with this novel agent are needed. Ceftaroline is currently FDA approved for the treatment of both STTIs and CAP.

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