A Relook of Cefuroxime in Community Infections: An Option Still Beneficial

VR Badhwar¹, S Ganapathy², PP Prabhudesai³, NK Tulara⁴, AY Varaiya⁵, D Vyas⁶

Abstract

In community and family practice, infections are a common OPD presentation. In the management of common bacterial infections seen in community especially RTI, UTI, SSTI; cefuroxime a second generation cephalosporin with a broad spectrum of activity can be used for empirical treatment. To know current place of cefuroxime in the management of infections, physicians, surgeons, microbiologist, chest physician, gynecologist and pediatrician came together to discuss and debate their experience with cefuroxime and its place in today’s world.

Cefuroxime is a drug which balances efficacy with safety. Several international bodies and guidelines including the US FDA and The British Thoracic Society, the World Society of Emergency Surgery (WSES) have recommended cefuroxime for the management of community acquired pneumonia and skin and soft tissue infection respectively. Cefuroxime has been recommended in the 2015 list of the US FDA list of drugs which can be used safely during pregnancy.

Cefuroxime can become a useful empiric choice antibiotic for the Indian physicians treating urinary tract infections, respiratory tract infections and skin and soft tissue infections in their outpatient departments.

Introduction

The understanding of the prevailing infections in the community and health care infrastructure aids in developing better practices for common community infections.

Other than gastrointestinal infections; respiratory tract infections, urinary tract infections and skin and soft tissue infections are the most commonly encountered infections in the outpatient department setting in India. The challenge is to make a probable diagnosis of the possible pathogens involved and to choose the proper antibiotic to which pathogens are susceptible.

Rapid resolution of symptoms is common expectation of patient in any infection. However challenges posed by pathogens such as presence of mixed pathogens, infections cause by beta-lactamase secreting pathogens and increased prevalence of antibiotic resistance adversely affect outcomes of antibiotic therapy.

Cefuroxime axetil is a prodrug of the cefuroxime. It has demonstrated in vitro antibacterial activity against several gram-positive and gram-negative organisms, which are commonly implicated in causing community-acquired infections.

Cefuroxime axetil is an effective treatment in patients with respiratory tract infections (otitis media, pharyngitis, sinusitis, CAP and acute exacerbations of chronic bronchitis), genitourinary infections and skin and soft-tissue infections. Cefuroxime axetil can be considered to be an empirical therapy for community-acquired infections, including those caused by beta-lactamase producing strains of common respiratory pathogens.

Cefuroxime is well tolerated by adult and pediatric patients. The majority of adverse events are mild to moderate in intensity and reversible upon discontinuation of treatment. The role of cefuroxime in the management of these common infections in the family practice must be evaluated to ensure improved outcomes in patients with these infections.

Respiratory Tract Infection in Clinics

In spite of an improved understanding of the pathophysiology of respiratory tract infections, the prevalence of these infections continues to rise. This disease burden is further
increased by the periodic outbreaks of acute infectious respiratory diseases.¹

In respiratory tract infections diverse challenges are present which must be addressed in order to resolve the infections. The distinction of bacterial infection from viral infections is a dilemma that often vexes the physician and makes him ponder whether he should initiate treatment with antibiotics.

Secondly, the presence of viscid mucus may hamper the penetration of antibiotics. Impaired innate defense barriers such as reduced ciliary motility pose an additional dilemma in the management of respiratory tract infections. Patients at extremes of age, and patients with co-morbid diseases such as diabetes, ischemic heart disease, hepatic and renal compromise are a challenging subset of patients. Balancing antibiotic efficacy with safety is often difficult in these patients.

Making an informed decision regarding the choice of an antibiotic plays a critical role in ensuring positive outcomes (Table 1)

### Pathogens Implicated in Respiratory Illness

Respiratory tract infections may be caused by viruses or bacteria that often interact with each other. Diverse pathogens are implicated in upper and lower respiratory tract infections (Table 2).

#### Cefuroxime Axetil in Upper and Lower Respiratory Tract Infections

Cefuroxime has several pharmacokinetic features which help it to effectively address few of the challenges posed by respiratory tract infections. Cefuroxime achieves high concentrations in respiratory tissues and fluids. High concentrations of cefuroxime have been observed in human alveolar macrophages (AM), epithelial lining fluid (ELF), bronchial mucosal biopsies and serum after a single dose, equivalent to 500 mg of oral cefuroxime base (Table 3).

Levels of cefuroxime achieved after administration of all dosages were found to exceed the MIC values for the major chest pathogens. Penetration of cefuroxime into bronchial secretion was also found to be dose-related.⁴

Cefuroxime is effective against common bacterial pathogens implicated in respiratory tract infections.⁵

ELF and mucosal site concentrations of cefuroxime are found to be effective against S. pneumonia and H. influenzae. Cefuroxime has been reported to be effective even against M. catarrhalis which commonly inhabits the upper respiratory tract and causes acute otitis media and sinusitis in children.⁶

Cefuroxime-axetil is the first oral broad spectrum cephalosporin found to be naturally stable in the presence of beta-lactamases.

### Rapid Symptom Resolution with Cefuroxime

Treatment with cefuroxime in Acute Exacerbation of Chronic Bronchitis patients with mucoid and purulent sputum was observed to cause rapid onset of symptom resolution from day 2 onwards.

A mere 4 days course of cefuroxime axetil is was found to be effective in treatment of acute bacterial infections of maxillary sinuses and otitis media. It was also observed that 5 days of cefuroxime axetil therapy or s 10 days of amoxicillin/clavulanate was similar in terms of rates of clinical cure, bacteriological eradication and recurrence in paediatric patients with either acute otitis media or sinusitis.⁸

The Shortened-course therapy with agents such as cefuroxime axetil has the potential to improve patient compliance and so also to reduce the rate of clinical failure and the emergence of resistant strains.⁸

Cefuroxime treatment caused improvement in all clinical parameters like fever and signs and symptoms of infection such as pain, sinus tenderness and reddening of the eardrum with most patients being symptom-free after treatment.⁹

Clinical success was observed in
Regimens

Antimicrobial Resistance and Cefuroxime

Asian countries are considered epicenters of resistance, due to the rampant use of antibiotics in the real life setting. Several upper respiratory organisms have been reported to be resistant to penicillins either through the production of beta-lactamase (H. influenzae, M. catarrhalis, S. aureus, Fusobacterium spp., and Prevotella spp.) or through changes in the penicillin-binding protein (S. pneumoniae).

Cefuroxime has been reported to retain efficacy against these bacterial pathogens.12

Patient Compliance to Cefuroxime Regimens

A short course of antibiotics is more likely to have patient acceptance and compliance to the treatment regimen. Often when a feeling of wellbeing occurs with defervescence of fever, the patient compliance to the treatment regimen of antibiotics drops, more so if the treatment duration is prolonged. The poor compliance with standard antibiotic regimens of 7 - 10 days’ duration may be responsible for the reported treatment failure. This interrupted treatment regimen also increases the risk of emergence of resistant pathogens.

In acute otitis media or sinusitis, shortened-course of therapy with cefuroxime axetil improves patient compliance and may help reduce the rate of clinical failure and the emergence of resistant strains.8

Urinary Tract Infections

Urinary tract infections are commonly encountered in clinical practice especially in women. The short urethra in women predisposes them to a higher prevalence of urinary tract infections. Occurrence of UTI in women increases during pregnancy.

The diagnosis of UTI is microbiological and it is based on two urine cultures presenting more than 105 colonies/mL urine of the same germ.13

Asymptomatic bacteriuria has been reported in 2 to 10% of all pregnant women and almost 30% of these women may develop pyelonephritis if not adequately treated.14

Recurrent lower urinary tract infections (UTIs) are usually defined as two or more episodes of urinary tract infection occurring in the preceding 12 months. Untreated UTI in pregnant women can lead to increased maternal and perinatal morbidity and mortality and low birth-weight and premature delivery.15

Urinary tract infections are a common diagnosis in older men with prostatic disease, outlet obstruction or urinary tract instrumentation. These infections may also occur in young men who are not circumcised (increased E. coli colonization of the glans and prepuce), men who engage in anal sex (exposure to E. coli in the rectum), or in men whose sexual partner has colonization with uropathogens. In men, a urine culture growing more than 1,000 CFU of a pathogen per mL of urine is considered to be the best indicator of a urinary tract infection, with a sensitivity and specificity of 97 percent.

Escherichia coli are a common cause of uncomplicated UTI and accounts for about 75 to 95 percent of all infections. Almost fifty percent of patients infected with S. saprophyticus present with upper urinary tract involvement, and these patients may have recurrent infection.16

Urinary tract infections in children are a distinct challenging clinical entity. Diagnosis and management of UTI continue to be a controversial issue with many challenges for the clinician. UTI may often be missed on history and physical examination, and the decision to screen for UTI must balance the risk for missed infections.

Role of Cefuroxime in the Management of Urinary Tract Infections

Cefuroxime is a second generation cephalosporin. It has a broad spectrum of antimicrobial activity against both Gram-positive and Gram-negative organisms. It has demonstrated excellent in vitro activity against staphylococcal strains, streptococcal strains (other than enterococci), N. gonorrhoeae, H. influenzae and N meningitidis, members of the Enterobacteriaceae

Table 4: Clinical response with cefuroxime

<table>
<thead>
<tr>
<th>Respiratory tract infection</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchopneumonia</td>
<td>90% responders</td>
</tr>
<tr>
<td>Post-operative pneumonia</td>
<td>91% responders</td>
</tr>
<tr>
<td>Chronic bronchitis, bronchiectasis</td>
<td>91% responders</td>
</tr>
<tr>
<td>Tonsillitis and pharyngitis</td>
<td>Complete resolution of infection</td>
</tr>
</tbody>
</table>

94.3% of the patients. High clinical cure rates and response rates have been documented after treatment with cefuroxime in both upper and lower respiratory tract infections.10

Table 5: Pathogens implicated in urinary tract infections

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute uncomplicated cystitis</td>
<td>E. coli, S. saprophyticus, P. mirabilis, K. pneumonia</td>
</tr>
<tr>
<td>Recurrent cystitis in young women and men</td>
<td>E. coli, S. saprophyticus, P. mirabilis, K. pneumonia</td>
</tr>
<tr>
<td>Asymptomatic bacteriuria in pregnancy</td>
<td>E. coli, S. saprophyticus, P. mirabilis, K. pneumonia</td>
</tr>
<tr>
<td>Complicated urinary tract infection</td>
<td>E. coli, K. Pneumoniae, P. mirabilis, Enterococcus species, Pseudomonas species</td>
</tr>
<tr>
<td>UTI in pregnant women</td>
<td>E. coli, K. Pneumoniae and Enterobacter spp., other gram negatives pathogens (P. mirabilis, Pseudomonas, Citrobacter), gram positive bacteria (S. aureus, Group B Streptococcus) and others (G. vaginalis, U. urealyticum)</td>
</tr>
</tbody>
</table>
Patients Treated with Cefuroxime

Outcomes of Urinary Tract Infections in adults (Tables 6 and 7).

Postmenopausal women, children patient populations including, pregnant women but also in other

For the management of urinary

Make it a well accepted drug

Pharmacodynamics features that

Both pharmacokinetic and

Cefuroxime exhibits both pharmacokinetic and pharmacodynamics features that make it a well accepted drug for the management of urinary tract infections not only in pregnant women but also in other patient populations including, postmenopausal women, children and adults (Tables 6 and 7).

Outcomes of Urinary Tract Infections in Patients Treated with Cefuroxime

87.3% of beta lactamase secreting against E. coli were susceptible to cefuroxime.

Cefuroxime retained sensitivity against uropathogens resistant to other antibiotics. Cefuroxime exhibited high efficacy rates (96%) in pregnant women with pyelonephritis.

Cefuroxime has been found to be effective against E. coli isolates from patients with urinary infections and glycosuria.

Recurrent urinary tract infections (UTI) is often associated with underlying urinary tract anomalies. They are also associated with higher antibiotic resistance of uropathogens.

The majority of E. coli strains from consecutive episodes have a unique characteristic persisting

clones resulting in recurrent episode of UTI. Recurrent UTI are also strongly associated with Trimethoprim/sulfamethoxazole resistant pathogens.

In a Cochrane database analysis of 10 studies, recruiting a total of 1125 pregnant women Cefuroxime was rated as an effective antibiotic with good cure rates and low recurrence rates.

The American Academy of Pediatrics recommends a 7 to 14-day course for all children 2 months to 2 years of age with UTI. Cefuroxime has been found to be effective and safe in the management of urinary tract infections in children.

Skin and Soft Tissue Infection

SSTIs are a common diagnosis in the outpatient department. There is a higher prevalence among men (60% to 70% of all cases) and in patients aged between 45 and 64 years of age. Often SSTIs involve the lower leg region.

Skin and soft tissue infections (SSTIs) have variable presentation, etiology and severity that are associated with microbial invasion of the layers of the skin and underlying soft tissues.

Pathogens Implicated in SSTIs

The most common pathogens implicated in SSTIs are S. aureus, S. epidermidis, Streptococci, E. coli, Klebsiella, Proteus, Pasteurella, B. Fragilis, Eikenella corrodenus, Clostridium spp. These pathogens are implicated in impetigo, folliculitis, furuncles and carbuncles, erysipelas, cellulites, diabetic foot infections and recurrent abscess.

Challenges in Management of SSTIs

Current challenges in the management of SSTIs include the rapid emergence of community-acquired methicillin-resistant Staphylococcus Aureus (CA-MRSA), cotrimoxazole resistant Staphylococcus the emergence of macrolide-resistant streptococci within the past ten years, and the absence of a good diagnostic algorithm to help the clinician differentiate life-threatening SSTIs that may require prompt hospitalization and aggressive interventions from those that can be effectively managed in an outpatient setting.

Other factors which may have an adverse impact on outcomes in SSTIs include impaired integrity of skin, diabetes, obesity, reduced blood supply, and alcohol abuse.

Role of Cefuroxime in Diabetic Foot Infections

The Critical triad of neuropathy, minor foot trauma, foot deformity was present in > 63% of patient’s causal pathways to foot ulcers.

Diabetic foot infections (DFIs) present with an unique set of challenges in terms of low immunity, presence of biofilms, presence of polymicrobial organisms like anaerobes, along with gram negative and positive aerobic bacilli and reduced blood supply.

Cefuroxime is effective against polymicrobial infections present in diabetic foot infections.

Cefuroxime also has an ability to attain high and adequate concentrations in ischemic tissues and wound exudate.

Cefuroxime has an ability to easily penetrate through biofilms and reduces the number of bacteria in biofilms adherent to implants more than vancomycin, tobramycin or ciprofloxacin.
Infections Developing in Damaged Skin, Wounds and Bite Wounds

Infections in damaged skin include bite wounds (animal and human bites), burn wounds or in pressure or vascular ulcers. In case of animal bites, the organisms recovered often originate from the oral cavity of the animal biter and the victim’s skin flora. Anaerobes are commonly isolated from human and animal bite infections. Staphylococcus and Streptococcus are the organisms most frequently found in human bites, and in animal bites; Pasteurella multocida must be considered in dog and cat bite.28

The risk of infection depends on several factors including the type of bite; the site of injury, the time elapsed from the bite until presentation, host factors, and the management of the wound. Antibiotic prophylaxis is recommended for patients with high-risk wounds. A broad-spectrum antibiotic (with activity against anaerobes) must be prescribed for patients with signs of sepsis, compromised immune status, severe comorbidities, associated severe cellulitis, severe and deep wounds.29,30

If managed incorrectly, SSTIs can develop into more complicated soft tissue infections. Hospitalization, radiographs, and surgical debridement are essential for most of the hand wounds contaminated by human saliva or animal saliva.

In addition to local wound infection, complications include lymphangitis, local abscess, septic arthritis, tenosynovitis, and osteomyelitis. Uncommon complications include endocarditis, meningitis, brain abscess, and sepsis with disseminated intravascular coagulation especially in immunocompromised individuals. Wound management includes administering local care and using proper antimicrobial therapy when needed.31

Role of Cefuroxime in SSTIs

Cefuroxime in the real-life setting is used for diverse SSTIs such as i) Orbital cellulitis in children ii) Prophylaxis prior to surgery where cefuroxime is used as a prophylactic antibiotic, administration 59 to 30 minutes before incision is more effective than administration during the last half hour iii) Common general bacterial skin and soft tissue infections (e.g., furunculosis, pyoderma and impetigo) iv) Diabetic foot infections which are polymicrobial.32-34

Cefuroxime is extensively distributed in tissues. Cefuroxime demonstrates concentration dependent killing. The concentrations of cefuroxime achieved in skin and soft tissues exceed the MIC for Methicillin sensitive staphylococci and this facilitate the killing of staphylococci.35

Mean cefuroxime levels in the tissues were in the range of 39-58 micrograms/g, these concentrations are well above the MIC values of the most common bacteria causing wound infections.

Cefuroxime has a low MICs against pathogens isolated from wounds (Table 8).36

Cefuroxime has also demonstrated high beta-lactamase stability. Its beta-lactamase stability makes it effective in the management of a variety of infections caused by beta-lactamase-producing strains of H. influenzae, B. catarrhalis, and S. aureus.

Cefuroxime in Children with SSTIs

Pyoderma in children is one of the most common cutaneous diseases encountered in pediatric practice.

Impetigo (bullous and non-bullous), superficial folliculitis and ecthyma are the three important patterns of primary pyodermas. Eczema with secondary infection (including atopic dermatitis), scabies, popular urticaria with secondary infection are the common secondary pyodermas.37

The difficulty in treating these cases may be due to two factors i). Increased antimicrobial resistance. II) Changing pattern of microbiology of pyoderma, including community-acquired methicillin-resistant Staphylococcus Aureus (MRSA). Cefuroxime has excellent in vitro activity against staphylococcal strains, streptococcal strains (other than enterococci).38

Cefuroxime is metabolically stable. Three fourths of cefuroxime is distributed in the extravascular compartment. Cefuroxime therapy is well tolerated in both adults and children.39

Post-operative Infections and Role of Cefuroxime

Diabetes, obesity, older age, emergency operations and obvious contamination (with debris, pus, stool, or other substances) of the injury or the surgical area are considered as the major risk factors for postoperative infections.40

Infections after surgical procedures (operations) can cause pain, poor wound healing, need for further treatment including antibiotics, longer hospital stays, and increased health care costs.

Antibiotic prophylaxis is intended to prevent postoperative wound infections, a major source of morbidity and mortality in surgical patients. Cefuroxime is a well-established second-generation cephalosporin that is given pre-operatively in surgery units at a standard dose of 1.5 g.41

Extensive Tissue Distribution of Cefuroxime and Positive Outcomes Post-cefuroxime Treatment

Cefuroxime is detectable in therapeutic concentrations in
plasma (66.8±18.9 mcg/mL) muscle (60.1±15.2 mcg/mL), such adipose tissue (39.2±26.4 mcg/mL).

Cefuroxime distributes into the interstitial fluid space (ISF) of subcutaneous adipose tissue or morbidly obese patients of the interstitial space fluid (ISF).

Cefuroxime has been demonstrated to be effective in the reduction of wound sepsis following biliary surgery. Cefuroxime can be an effective component of sequential therapy of SSTI post operatively as it is associated with high clinical cure rates (88%).

Safety Profile of Cefuroxime

Cefuroxime axetil is well tolerated by adult and paediatric patients. The majorities of adverse events (primarily gastrointestinal disturbances) are mild to moderate in intensity and are reversible upon discontinuation of treatment, with very few serious adverse events reported.

Florquinolones and Macrolide group of antibiotics are associated with QT prolongation especially in patients with underlying heart disease. Cefuroxime can be safely used in cardiac patients. Cefuroxime has been used in cardiac and medical-surgical critical care units for prevention and treatment of pneumonia.

Fluroquinolones have also been given a Boxed warning by the US FDA regarding the increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs. Cefuroxime is not known to cause tendinitis.

The US FDA and The British Thoracic Society have recommended cefuroxime for community acquired pneumonia.

Safety in Pregnancy

Cefuroxime is a pregnancy category B drug. Pregnant women across the three trimesters have safely been treated with cefuroxime. Cefuroxime has featured in the US FDA 2015 list of recommended drugs safe for management of pregnancy related infections.

The US FDA recommended dose of cefuroxime in pregnant women is 250 mg, every 12 hours for 3–7 days. No teratogenic effects were observed. Subsequent follow up indicated no cause of concern in terms of physical or mental development in any of the children.

Cefuroxime is approved by the US FDA and has been recommended in the 2015 list of the US FDA of drugs which can be used safely during pregnancy.

Cefuroxime does not cause photosensitivity reactions which are seen with some of the fluoroquinolones. Secondly it has a low risk of drug interactions since it is not metabolized by the CYP 450 enzyme system.

Conclusions

Cefuroxime axetil is a broad spectrum antibacterial agent which shows with a pharmacokinetic profile that permits convenient twice-daily administration. Cefuroxime is stable against beta lactamase enzymes and it has ability to eradicating beta lactam producing bacteria make it effective in today’s emerging trend of antibiotic resistance.

Several international bodies and guidelines have recommended cefuroxime. The US FDA and The British Thoracic Society have recommended cefuroxime for community acquired pneumonia. Cefuroxime features in the Recommendations of World Society of Emergency Surgery guidelines for management of skin and soft tissue infections.

The views of the experts and the recommendations from the various guidelines indicate that cefuroxime continues to have an important place in the management of community infections in the real life setting in India. However, considering the resistance pattern it should be avoided for management of serious hospital infection.

Disclaimer

The initiative of bringing together experts from different specialities on one platform was supported by Abbott Healthcare Private Limited (through its Restora division) in the quest of widening therapy knowledge of Cefuroxime in common community infection for the benefit of medical fraternity. The views expressed in this article are for educational purpose only and constitute the views of the authors solely. Medical practitioners are advised to take decisions based on their own clinical judgment.

References


3. Dasaraju PV, Liu C, et al. Chapter 93,
Infections of the Respiratory System
Medical Microbiology. 4th edition., Baron S, editor.


