



# Position of oral cephalosporins and its fixed-dose combinations in the guideline recommendations for the management of community-acquired infections

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## ABSTRACT

Community-acquired infections (CAIs) represent a major burden for health-care system. This directly aids the emergence of antibiotic-resistant organisms. India is not immune to it. This review assessed the current guideline recommendations for the usage of oral cephalosporins in the management of common CAIs. The researchers conducted iterative searches in PubMed, SCOPUS, and Google Scholar for published articles using various keywords. The search was conducted in November 2022 and considered articles published till date. Different CAIs are caused by similar organisms, susceptible to first-line antibiotics such as penicillin and cephalosporins. Most of the guidelines recommend the use of oral cephalosporins for the management of the commonly prevalent CAIs. These antibiotics however should be used as a monotherapy and not as fixed-dose combinations (FDCs), as FDCs with oral cephalosporins lack scientific basis and may be detrimental. For burden of CAIs intensified by anti-microbial resistance, guidelines are useful for the management of CAIs to educate the prescribers and preserve currently available antibiotics.

**Key words:** Anti-microbial resistance, Cephalosporins, Community-acquired infections, Fixed-dose combination, India

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## INTRODUCTION

### Rising burden of anti-microbial resistance (AMR) in India: An alarming situation

Community-acquired infections (CAIs), such as respiratory tract infections (RTIs), urinary tract infections (UTIs) and skin soft-tissue infections (SSTI), represent a major burden for every healthcare system, compounded by clinical failure due to ineffective and inappropriate antibiotic therapy.<sup>1-4</sup> This rising burden of infections

is aggravated by the emergence of antibiotic-resistant strains of the implicated pathogens, hindering their effective management.<sup>5</sup> According to a recent analysis, antimicrobial-resistant *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* predominantly contribute to the highest share of the bacterial causes of CAIs and also responsible for the majority of mortalities in these patients.

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The prevalence of AMR in CAIs has reached a critical level worldwide.<sup>6</sup> There is a clear direct association between inappropriate and irrational use of antimicrobials and rising AMR.<sup>7</sup> Largely unrestricted over-the-counter sales of antibiotics, manufacturing and marketing of many inappropriate fixed-dose combinations (FDCs) in India are some of the many contributing factors toward the development of AMR.<sup>8</sup> The World Health Organization's (WHO) AWaRe classification framework categorizes antibiotics into *Access* (antibiotics that are essential, widely available, affordable and quality assured with select few recommended as first-line or second-line antibiotics), *Watch* (broad-spectrum antibiotics with a high chance of resistance to be used only for specific indications), and *Reserve* (antibiotics to be used only as a last resort) groups. It also provides a list of antibiotic FDCs currently in the market, that are not "recommended" or "discouraged" since the combinations are not evidence-based, nor recommended in internationally accepted management guidelines.<sup>9</sup>

India is the largest antibiotic consumer in the world in absolute volumes.<sup>8,10</sup> It has been demonstrated that in countries where antibiotic prescription rates are very high, the level of antibiotic resistance has also reached an unacceptable level making most drugs ineffective.<sup>11</sup> FDCs are a hallmark of drug consumption in India. It is noteworthy that 71.4% of FDCs containing antibiotics are not listed in the national list of essential medicines and 48.5% belong to WHO-discouraged formulations.<sup>8</sup>

A drug technical advisory board (DTAB) subcommittee report of 2018 highlighted the growing number of "irrational" FDCs as a public health issue.<sup>12</sup> In the case of anti-microbial FDCs, the subcommittee report mentions an irrational combination of two or more anti-microbial agents or a combination of one or more anti-microbial agents with one or more non-antimicrobial agents raising the possibility of unnecessary overuse of one agent.<sup>12</sup> For an FDC to be considered rational, the drugs in the combination should act by different mechanisms, with closely related pharmacokinetics and the combination should not have supra-additive toxicity of the ingredients.<sup>13</sup> One of the common groups of antibiotics that is an integral part of management of CAIs as well as an important component in FDCs is Cephalosporins.

Cephalosporins are a large group of beta-lactam antibiotics, used in the management of a wide range of infections caused by Gram-positive and Gram-negative bacteria. They are generally well-tolerated, easy to administer, and are thus the most frequently used antibiotic class in India.<sup>8,14</sup> This narrative review was conducted with an objective to assess the current recommendation and rationale for the usage of oral cephalosporins in the management of common CAI and to determine the role of inappropriate FDCs of

oral cephalosporins and their potential to contribute to the rising AMR.

The researchers conducted iterative searches in electronic databases, such as PubMed, SCOPUS, and Google Scholar for publicly available scientific articles using various combinations of the keywords such as cephalosporin, treatment, management, "CAIs," rational, "FDCs" (non-exhaustive) in titles and abstract. The search was conducted in November 2022 and the review considered all articles published till November 2022.

## RECOMMENDATIONS ON MANAGEMENT OF COMMUNITY ACQUIRED INFECTIONS

The management of CAIs is steered by a range of national and international guidelines that are used by clinicians in India. These guidelines provide support for proper decision-making based on evidence regarding management and practical strategies for prescribing antibiotics including advice on whether a patient needs antimicrobial treatment and which antibiotic should be prescribed. Adhering to guidelines can help to improve prescription quality and to reduce antibiotic misuse in general.<sup>15</sup>

### UPPER RESPIRATORY TRACT INFECTIONS (URTI)

The current recommendations of various national and international guidelines on treatment options of URTI are shown in Table 1.

#### Acute otitis media

AOM is a frequent RTI in infancy and early childhood that is treated with antimicrobial agents. The commonly isolated organisms responsible for AOM are *S. pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pyogenes*.<sup>24,25</sup> The selection of the most effective antimicrobial to treat AOM has become more difficult in recent years because of increasing antibiotic resistance among all AOM pathogens.<sup>26</sup> The utilization of antimicrobial therapy is especially important in the treatment of AOM due to *S. pneumoniae*, as spontaneous resolution is observed only in 16% of the patients while the rates are higher for *H. influenzae* and *M. catarrhalis* at 48% and 85% of cases respectively.<sup>26-28</sup> It is imperative to consider the ability of an antibiotic to concentrate in the middle-ear fluid (MEF) in strengths high enough to eradicate the bacterial pathogens while choosing the drug to treat the condition.<sup>26</sup>

Beta-lactam antibiotics including cephalosporins, have a higher likelihood of successful treatment of AOM as they achieve a concentration of the antibiotic in MEF exceeding the minimum inhibitory concentration (MIC)<sub>90</sub>

**Table 1: Treatment options of URTI as per various guidelines<sup>16-23\*</sup>**

Condition	Guideline	First line antibiotic	Alternative antibiotics
AOM	ICMR (2022)	Amoxicillin-clavulanate/Amoxicillin	Cefpodoxime/Cefuroxime axetil/Cefdinir
	NTG (2016)	Amoxicillin-clavulanate/Cefpodoxime/ Cefuroxime axetil	-----
	AAP (2013)	Amoxicillin/Amoxicillin-clavulanate	Cefpodoxime/Cefuroxime axetil/Cefdinir
Acute pharyngitis/ tonsillitis	ICMR (2022)	Amoxicillin/Amoxicillin-clavulanate	----
	NTG (2016)	Penicillin V/Cefdinir/Cefpodoxime	----
Acute rhinosinusitis	ICMR (2022)	Amoxicillin-clavulanate	Cefpodoxime
	NTG (2016)	Amoxicillin-clavulanate	Moxifloxacin
	IDSA (2012)	Amoxicillin-clavulanate>Amoxicillin	----
	AAO-HNS (2015)	Amoxicillin/Amoxicillin-clavulanate	----
	ICAR-RS (2021) Sanford (2021)	Amoxicillin-clavulanate>Amoxicillin Amoxicillin-clavulanate/Cefpodoxime/ Cefuroxime axetil	Levofloxacin

AOM: Acute otitis media, NTG: National treatment guidelines, ICMR: Indian Council of medical research, AAP: American Academy of Pediatrics, IDSA: Infectious diseases society of America, AAO-HNS: American Academy of Otolaryngology-head-and-neck surgery foundation, ICAR-RS: International consensus statement on allergy and rhinology: rhinosinusitis. \*Only oral antibiotic treatment options are captured in the table, URTI: Upper respiratory tract infection

for common middle-ear pathogens for a time >40% of the dosing interval. Among cephalosporins, the order of the highest MEF/serum concentration ratio is cefprozil > cefuroxime > cefpodoxime > cefdinir. While all have MEF concentrations that is higher than the MIC<sub>50</sub> of penicillin-susceptible *S. pneumoniae*, only cefprozil {MIC<sub>50</sub>/MIC<sub>90</sub> (mg/L)=0.25/0.25} and cefuroxime {MIC<sub>50</sub>/MIC<sub>90</sub> (mg/L)≤0.06/0.12} attain concentrations that exceed the MIC<sub>90</sub>.<sup>29</sup> These aspects have been considered during drafting the guidelines for the management of the condition and antibiotics recommended based on these criteria.

Each organism exhibits varied susceptibility to different antibiotics as assessed in the survey of AMR (SOAR) study in India (2012-14) using the CLSI breakpoints as depicted in Figure 1.<sup>30</sup> It is another important aspect to be considered while selecting an antibiotic for use.

Apart from cephalosporins, macrolides are also used by clinicians for the management of URTIs. These are clinically less reliable against *H. influenzae*, which has a higher MIC than the achievable MEF concentrations and *S. pneumoniae*, that exhibit high rates of resistance to macrolides.<sup>29,32</sup> First-line agents, amoxicillin and amoxicillin-clavulanic acid (CA) combination may be associated with adverse events like gastrointestinal side effects. Second and third-generation cephalosporins are commonly prescribed alternatives to these drugs.<sup>33</sup>

### Tonsillopharyngitis

Viruses are the common cause of tonsillopharyngitis (40–60% cases). Bacteria are responsible for <30% and 10% of cases in pediatric and adult population, respectively. Most of these bacterial infections are attributed to group A beta-hemolytic streptococci (GABHS).<sup>34</sup> The treatment recommended by the guidelines includes, penicillin, amoxicillin, amoxicillin-CA combination, and

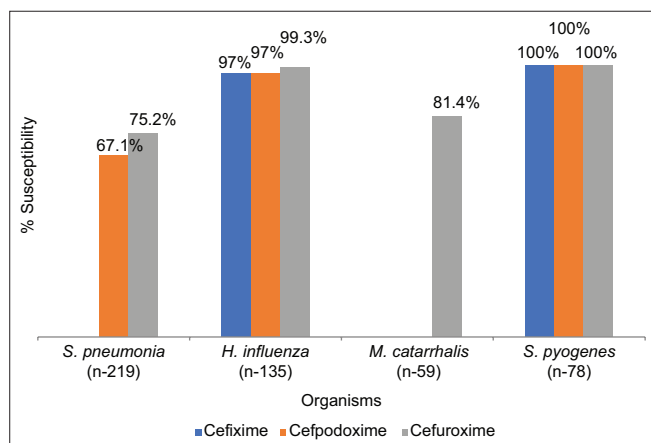
cephalosporins. A meta-analysis of randomized, controlled trials of cephalosporin versus penicillin treatment of GABHS tonsillopharyngitis in children and adults has indicated that the likelihood of bacteriologic and clinical failure of GABHS tonsillopharyngitis is significantly less if an oral cephalosporin is prescribed, compared with oral penicillin in both children and adults.<sup>35,36</sup> This change in the treatment response in contrast to the guidelines may be traced to the varying susceptibility trends arising due to inappropriate use of antibiotics leading to AMR.

### Acute bacterial rhinosinusitis

In the case of acute rhinosinusitis in adults, most (90–98%) cases in the ambulatory setting are due to a self-resolving viral infection. Guidelines recommend against the use of antibiotics in the 1<sup>st</sup> week of symptoms for patients with mild-moderate sinusitis. Antibiotics are indicated if the patient has a triad of temperature ≥39°C (102°F), presence of facial pain/pressure, and purulent discharge for >3 consecutive days.<sup>16</sup> Amoxicillin-CA is recommended as the first-line agent by national and international guidelines alike.<sup>16,17,22</sup> Among cephalosporins, cefuroxime (second-generation) and cefpodoxime (third-generation) can also be used for the management of rhinosinusitis.<sup>16,22</sup>

## CURRENT USAGE OF ANTIBIOTICS IN URTI: ARE WE FOLLOWING THE RECOMMENDATIONS?

Although most of the recommendations advocate for the use of beta-lactams (Amoxicillin, Amoxicillin-clavulanate, and Cephalosporins) for URTIs, the studies assessing the prescription practices in India portray a different picture. A study in Delhi that assessed the patterns of antibiotic use for URTIs in both public and private healthcare facilities showed that macrolides contributed to 25% of prescriptions followed by 20% (fluoroquinolones)



**Figure 1:** Percentage susceptibility rates based on CLSI breakpoints for cefuroxime, cefixime, and cefpodoxime as per SOAR study in India (2012–14).<sup>30,31</sup> Information not available for susceptibility of *S. pneumoniae* to Cefixime; Information not available for susceptibility of *M. catarrhalis* to Cefixime and Cefpodoxime; Susceptibility patterns may vary with geography and time

while cephalosporins were utilized for only 10% of the cases with URTIs.<sup>37</sup> This is in contrast to the guideline recommendations.

Among cephalosporin, cefixime (31%) was predominantly used although it is not recommended in the guidelines.<sup>38</sup> This shows a disparity in the real-world practice of antibiotic prescription as compared to the guideline recommendations.

## LOWER RESPIRATORY TRACT INFECTIONS (LRTI)

National and international guidelines predominantly suggest the usage of amoxicillin (and/or) Clavulanate (first line) and cefuroxime axetil/cefpodoxime (second line) for treating CAP with no comorbidities or risk factors. The presence of co-morbidities warrants an addition of a macrolide or doxycycline as elaborated in Table 2.

### Community-acquired pneumonia

The organisms responsible for URTIs are also responsible for CAP i.e., *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.<sup>40</sup> In addition, *Legionella*, *E. coli*, *Klebsiella*, and *S. aureus* are also commonly obtained isolates.<sup>18</sup> The choice of antibiotics depends on severity of disease, presence or absence of comorbidities, likely pathogen, likely resistance pattern and previous antibiotic use.<sup>17</sup>

### CAP without comorbidity

Amoxicillin was recommended based on several studies demonstrating good efficacy for outpatient CAP despite the presumed lack of coverage for atypical organisms. It also has a long track record of safety. Doxycycline recommendation was based on the broad-spectrum activity of the drug covering

the relevant organisms, even though it was supported by limited clinical trial data. Routine use of a macrolide antibiotic as monotherapy for CAP patients without comorbidities in an outpatient basis, due to rising resistance but may be considered in settings with documented “low macrolide resistance” (if local pneumococcal resistance is <25%) or contraindications to alternative therapies.<sup>40</sup> The role of fluoroquinolones is well established in CAP and all Western guidelines where the baseline prevalence of tuberculosis (TB) is low endorse them. However, in India where there is a high burden of TB and where TB may present as CAP, the use of empiric fluoroquinolone therapy may lead to masking and delayed diagnosis of TB and promotion of drug resistance. Therefore, fluoroquinolones are better avoided.<sup>17</sup>

### CAP with comorbidity

Patients with comorbidities should receive broad-spectrum antibiotics for adequate coverage, for two reasons. First, patients are more likely to experience unfavorable outcomes due to inadequate initial empiric antibiotic regimen. Second, the probability of increased risk of antibiotic resistance by virtue of previous contact with the healthcare system and/or prior antibiotic exposure. In patients with comorbidities like COPD, in addition to *H. influenzae* and *M. catarrhalis* (both of which frequently produce  $\beta$ -lactamase), *S. aureus* and gram-negative bacilli also cause CAP. For patients with co-morbidities, recommended regimens include a b-lactam or cephalosporin in combination with either a macrolide or doxycycline. These combinations should effectively target macrolide- and doxycycline-resistant *S. pneumoniae* (as b-lactam resistance in *S. pneumoniae* remains less common), in addition to b-lactamase-producing strains of *H. influenzae*, many enteric gram-negative bacilli, most methicillin susceptible *S. aureus*, and *M. pneumoniae* and *C. pneumoniae*.<sup>17,40,41</sup>

### Acute exacerbation of COPD

Infections are common in case of AECOPD, with bacterial infections responsible for approximately 50% of the cases. The most frequently isolated organisms are the same as those causing CAP.<sup>42</sup> Antibiotics are recommended for patients with exacerbation of COPD with two of the three cardinal symptoms: increase in dyspnea, sputum volume, and sputum purulence; have two of the cardinal symptoms in the presence of purulent sputum; or require mechanical ventilation. Antibiotic therapy can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. The duration of therapy should be 5–7 days. Usually, the initial empirical treatment is an aminopenicillin with CA, macrolide or tetracycline, second or third-generation cephalosporin.<sup>42,43</sup>

The GOLD report of 2023 in contrast does not advocate the use of azithromycin in patients prone to exacerbations due to its evidenced association with an increased incidence



**Table 2: Treatment options for LRTI in adults as per various guideline<sup>17,18,39,40\*</sup>**

Condition	Guidelines	First line antibiotic	Alternative antibiotics
No comorbidities or risk factors for MRSA or <i>Pseudomonas aeruginosa</i>	ICMR (2022)	Amoxicillin-clavulanic acid	Cefuroxime axetil
	IDSA (2019)	Amoxicillin/Doxycycline/Macrolide	----
	Stanford (2019)	Amoxicillin	Cefpodoxime/Levofloxacin
CAP with co-morbidities**	ICMR (2022)	Amoxicillin/clavulanic acid + macrolide or doxycycline	Cefuroxime axetil/ cefpodoxime and macrolide/ doxycycline
	IDSA (2019)	- Amoxicillin/clavulanic acid + macrolide or doxycycline - Cephalosporin (cefpodoxime or cefuroxime axetil) + macrolide or doxycycline - Monotherapy with respiratory fluoroquinolone	----
	Stanford (2019)	- Amoxicillin/clavulanic acid + macrolide or doxycycline - Cephalosporin (cefpodoxime or cefuroxime axetil) + macrolide or doxycycline	Levofloxacin
AECOPD	NTG (2016)	Amoxicillin-clavulanate	Azithromycin

CAP: Community-acquired pneumonia, AECOPD: Acute exacerbation of chronic obstructive pulmonary disease, NTG: National Treatment Guidelines, ICMR: Indian Council of Medical Research, IDSA: Infectious Diseases Society of America. \*Only oral antibiotic treatment options are captured in the table. \*\*Chronic heart, lung, liver, or renal disease, diabetes, alcoholism, malignancy, asplenia, MRSA: Methicillin-resistant *S. aureus*

of bacterial resistance, prolongation of QTc interval, and impaired hearing.<sup>43</sup>

## PRESCRIPTION TRENDS FOR LRTI MANAGEMENT IN INDIA

URTIs and LRTIs have a similar causative organism profile providing clarity on the similarity of the antibiotics that can be prescribed for both the conditions. This does not reflect in the real-world prescription practices study from North India, reporting an inclination toward a preference for cefixime (40%) and azithromycin (30%) to treat LRTIs.<sup>38</sup> Another retrospective study to look at 5-year prescription trend for CAP showed beta-lactams and macrolides were the two most frequently prescribed antimicrobials (34.1%) which are in accordance with the guidelines. However, newer-generation beta-lactams and reserve antibiotics were prescribed which need to be used with caution. The trend analysis also showed a significant increase in cephalosporin prescriptions ( $P < 0.01$ ) and a significantly decreased in penicillin prescriptions. The prescription of fluoroquinolones also decreased over the study period. The department-surveyed hospital did not have any antimicrobial stewardship program or written guidelines for doctors to follow for the treatment of CAP.<sup>44</sup> The findings of these prescription studies suggest the need for implementing antimicrobial treatment guidelines.

### Urinary tract infections (UTI)

The current recommendations of various national and international guidelines on treatment options for UTI are shown in Table 3 below.

UTIs are common bacterial infections, particularly in women.<sup>47</sup> The bacterial pathogens responsible for UTI have remained consistent for many years. Gram-negative bacilli are mainly causative in most cases. *E. coli* continues to be the primary offender, causing 75–90% of episodes of acute uncomplicated cystitis, most episodes of complicated UTI, and pyelonephritis. Gram-positive organisms are relatively less common; however, *Staphylococcus saprophyticus* accounts for 5–15% of UTI, mainly affecting younger women, and is generally confined to cystitis. The response of some pathogens to common antimicrobials has gradually evolved in the past two decades.<sup>48</sup>

Among the cephalosporins, second- and third-generation cephalosporins are most commonly recommended by the guidelines for the management of UTI.<sup>18,49</sup> Second-generation cephalosporins have less activity against Gram-positive cocci than first-generation cephalosporins but have enhanced activity against Gram-negative bacilli. Third generation cephalosporins have extended gram-negative bacteria coverage.<sup>14</sup>

Although third-generation cephalosporins are attractive options to cover a broad range of urinary pathogens for empiric UTI therapy, they have been associated with increased rates of *Clostridioides difficile* infections and selection of extended-spectrum  $\beta$ -lactamase expressing pathogens.<sup>50</sup> Few prescription pattern studies have shown higher usage of third-generation cephalosporin as a first-line agent irrespective of the causative agent for UTI which should ideally be reserved for complicated UTIs.<sup>51,52</sup>

From a pharmacokinetic standpoint, cefpodoxime (third-generation cephalosporin) has been reported to minimally concentrate in the urine with a peak of 20 mg/L, compared

**Table 3: Treatment options for UTI as per various guidelines<sup>18,45,46\*</sup>**

Condition	Guideline	First-line antibiotic	Alternative antibiotics
Acute uncomplicated Cystitis	NTG (2016)	Nitrofurantoin	Cefuroxime axetil
	AAP (2011)	Cotrimoxazole	NA
		Ciprofloxacin	
		Cotrimoxazole	
EAU (2022)	Amoxicillin-clavulanate	Cefadroxil/Cotrimoxazole ( <i>Escherichia coli</i> resistance <20%)	
	Sulfisoxazole		
Acute uncomplicated Pyelonephritis	NTG (2016)	Cefixime	NA
		Cefpodoxime	NA
	AAP (2011)	Cefprozil	NA
		Cefuroxime axetil	
		Cephalexin	
	EAU/ESPU 2022	(Without dilatation or known reflux, after 6 months of age) Cefpodoxime proxetil, Cefibuten, Cefixime	
		(For children up to 12 years of age)	
Cefaclor, Cephalexin, Cefuroxime axetil			
Cefpodoxime proxetil			

NTG: National Treatment Guidelines, ICMR: Indian Council of Medical Research, AAP: American Academy of Pediatrics, EAU: European Association of Urology, EAU/ESPU: European Association of Urology, EAU: European Society for Paediatric urology. \*Only oral antibiotic treatment options are captured in the table

with oral cefuroxime (second-generation cephalosporin), which achieves urinary peak concentrations ranging from 1000 to 7000 mg/L. In addition, only 29–33% of a single dose of cefpodoxime is excreted unchanged in the urine, whereas 50% or more of an oral dose of cefuroxime is excreted unchanged.<sup>50</sup>

As per EAU 2022 guidelines, the choice of antimicrobials for recurrent UTIs is the same as for sporadic acute uncomplicated UTI. The first-line treatment suggested is fosfomycin trometamol, pivmecillinam, or nitrofurantoin. Aminopenicillins are no longer suitable for antimicrobial therapy in uncomplicated cystitis due to negative ecological effects, high resistance rates, and their increased selection for extended-spectrum beta-lactamase (ESBL)-producing bacteria. Cephalosporins such as cefadroxil or comparable cephalosporins are recommended as alternatives.<sup>49</sup>

Fluoroquinolones and cephalosporins are the only antimicrobial agents that can be recommended for oral empirical treatment for uncomplicated pyelonephritis. Other agents such as nitrofurantoin, oral fosfomycin, and pivmecillinam should be avoided as there is insufficient data regarding their efficacy.<sup>49</sup>

When treating UTIs during pregnancy, not all antimicrobials are suitable for the treatment. Penicillin and cephalosporins should be considered for management in this group. Antibiotics contraindicated/avoided during pregnancy for the management of UTI include:<sup>49,53</sup>

- Fluoroquinolones
- Nitrofurantoin – third trimester and presence of G6PD deficiency
- Trimethoprim – first trimester
- Sulphonamides – third trimester.

### Skin and Soft Tissue Infections (SSTI)

The current recommendations of various national and international guidelines on treatment options for SSTI are shown in Table 4 below.

SSTIs have a variable presentation, etiology, and severity. Among culture-confirmed SSTIs, *S. aureus* and beta-hemolytic Streptococci are often suggested as being the most important.<sup>16</sup> methicillin-sensitive *S. aureus* is found to have a higher prevalence in patients and carriers compared to methicillin-resistant *S. aureus*, although the prevalence rate varies worldwide.<sup>56</sup>

**Table 4: Treatment options for SSTI as per various guidelines<sup>17,18,54,55\*</sup>**

Condition	Organism	First line antibiotic
Impetigo	<i>S. aureus</i> and GABHS	Penicillinase-resistant penicillins or first-generation cephalosporins
Cellulitis	<i>S. pyogenes</i> , <i>S. aureus</i>	Cephalexin (ICMR 2022) Or Amoxicillin-clavulanic acid (NTG 2016) ±Clindamycin (ICMR 2022) or Cephalosporins (IDSA 2014*)
Erysipelas	<i>cutibacterium acnes</i> , MSSA, streptococci	Amoxicillin-clavulanic acid (ICMR 2022) or Cephalosporins (IDSA 2014) or Dicloxacillin (IDSA 2014) or Clindamycin (IDSA 2014)
Furunculosis	<i>S. aureus</i>	Amoxicillin-clavulanic acid (NTG 2016)

GABHS: Group A beta-hemolytic streptococci. \*IDSA 2014 guidelines have recommended oral cephalosporins for mild non-purulent necrotizing infection, Cellulitis, and Erysipelas, MSSA: Methicillin-sensitive *S. aureus*

First-generation cephalosporins have active coverage against most gram-positive cocci, such as *Staphylococci* spp. and *Streptococci* spp., while having minimal coverage against gram-negative bacteria. Oral first-generation cephalosporins are commonly prescribed for the treatment of uncomplicated SSTI such as cellulitis and abscesses due to *Staphylococci* spp. or *Streptococci* spp. infection.<sup>14</sup>

Second-generation cephalosporin like cefuroxime can also be used in the management of SSTIs such as furunculosis, pyoderma, and impetigo as it is extensively distributed in tissues. The concentration of cefuroxime achieved in skin and soft tissue exceeds the MIC for methicillin-sensitive staphylococci and facilitates its eradication.<sup>57</sup> In a cross-sectional study in India, *S. aureus* demonstrated 85.7% susceptibility (n=12) to cefuroxime.<sup>58</sup> However, it is important to remember that susceptibility patterns may vary with geography and time.

## EVALUATING THE COMMONLY USED ORAL CEPHALOSPORIN FDCs IN INDIA

Although there are many different CAIs that require focus due to their high prevalence and difficulty in management because of a multitude of factors, they all are usually caused by a common group of bacteria. These organisms are usually susceptible to first-line antibiotics such as the Penicillin group or Cephalosporins. The efficacy of these antibiotics is documented when used as monotherapy or in combination with other groups of antibiotics (for complicated cases).

Among the various antibiotics from the above-mentioned national and international guidelines, only two FDCs antibiotics, namely Amoxicillin- CA and Trimethoprim-sulfamethoxazole are recommended. However, in India, Fluoroquinolones and CA in combination with Cephalosporin that are listed as “discouraged FDCs” by the WHO and are also commonly consumed. These discouraged FDCs were consumed by 16.5% of patients in India in 2019.<sup>8</sup> As per the same study, amongst the cephalosporin-fluoroquinolone combinations, Cefixime-ofloxacin was the most consumed discouraged FDC in India.<sup>8</sup>

The DTAB subcommittee report has suggested against the use of a combination of Cefixime-levofloxacin as this combination is not as per standard therapeutic guidelines for the treatment of RTI and UTI. Moreover, fluoroquinolones should not be used for empirical treatment of outpatient management of CAP unless tuberculosis is ruled out and no alternative antibiotic is available. Another FDC of Cefpodoxime-levofloxacin is also available in the Indian market. This is again considered inappropriate as levofloxacin is an integral part of MDR-TB therapy and should not be used singly or in combinations for other indications as a first line of management. Furthermore, there is a dosage frequency mismatch, for RTI levofloxacin is given 500 mg/750 mg once daily where cefpodoxime is 200 mg given twice a day. The subcommittee report concluded that there is no convincing scientific evidence or justification for use of such combinations.<sup>12</sup>

## ORAL CEPHALOSPORIN - CLAVULANIC ACID-CA FDCs: ARE THEY EVIDENCE BASED?

In general, the FDCs of oral cephalosporins and CA are considered inappropriate. Even though three Cephalosporin- CA (CA) combinations, i.e., Cefpodoxime + CA, Cefuroxime + CA, and Cefixime + CA are amongst the top 10 consumed FDCs in India. All three combinations are discouraged by WHO.<sup>8</sup>

Although the combination of Cefuroxime axetil and CA is not approved by the USFDA, it still is available in India for the management of CAIs.<sup>8,59</sup> Cefuroxime is a beta-lactam antibiotic with a higher stability to beta-lactamase hydrolysis due to its methoxy-imino side chain in position 7 of the Cephem nucleus.<sup>60</sup> The hydrolysis (%) of cefuroxime and other oral beta-lactams relative to cephaloridine 100% is shown in Table 5.<sup>61</sup> Cefuroxime has shown stability to the most common plasmid-mediated beta-lactamases; TEM-1, TEM-2, OXA-1, and OXA-2 produced by *E. coli*, and to SHV-1-producing *K. pneumoniae*.<sup>62</sup> Many of the clinically significant bacterial species producing beta-lactamases such as *Haemophilus*, *Moraxella*, *Staphylococci* and most *Enterobacteriaceae* remain susceptible to Cefuroxime although

**Table 5: Hydrolysis (%) of cefuroxime and other oral  $\beta$  lactams relative to cephaloridine 100%**

	Source and type of $\beta$ -lactamase	Cefuroxime	Cefaclor	Cephalexin	Ampicillin	Amoxicillin
Plasmid-mediated enzymes	<i>E. coli</i> TEM-1	<1	39	7	1124	252
	<i>E. coli</i> TEM-2	<1	20	<1	1037	455
	<i>E. coli</i> OXA-1	15	-	65	1811	<1
	<i>E. coli</i> OXA-2	<1	100	9	1564	290
	<i>K. pneumoniae</i> SHV-1	<1	183	8	1263	61
Chromosomally mediated enzymes	<i>K. pneumoniae</i> 1082E	36	134	<1	572	273
	<i>Enterobacter cloacae</i> P99	<1	106	24	<1	<1
	<i>Staphylococcus aureus</i> PC1	35	395	99	20000	382

*E. coli*: Escherichia coli, *K. pneumoniae*: Klebsiella pneumonia,

the susceptibility may vary across geographies.<sup>60</sup> CA, a beta-lactamase inhibitor (BLI), inhibits these class A beta-lactamases including TEM-1, TEM-2, and SHV1. However, most OXA-type ESBLs are relatively resistant to inhibition by CA. CA is less or not at all effective against molecular class B metallo beta-lactamases, molecular class C (AmpC) beta-lactamases, and molecular class D beta-lactamases.<sup>63</sup>

Hence, combining Cefuroxime with CA lacks a scientific and rational explanation. Thus, theoretically, the addition of BLI such as CA to Cefuroxime will provide no added advantage.<sup>59</sup> In a study by Sawant and Pandit it was observed that there was no reduction in MIC of Cefuroxime after the addition of CA against *S. aureus*, *K. pneumoniae*, *H. influenzae*, *E. coli*, or *S. pneumoniae*. The same study also confirmed that there is no decrease observed in MICs of cefixime within the CA combination compared to cefixime alone against *S. aureus*, *E. coli*, *H. influenzae* and it *M. catarrhalis*.<sup>64</sup>

In addition, CA, which has a little inhibitory effect on AmpC beta-lactamase activity, can function as an inducer and paradoxically increase AmpC-mediated resistance in an inducible organism to cephalosporins like Cefuroxime. These AmpC  $\beta$ -lactamases enzymes, besides being resistant to CA, are also resistant to other BLIs, including tazobactam and sulbactam.<sup>59,63,64</sup>

Thus, it is not only an inappropriate but also an antagonistic combination.<sup>59,63</sup> The Cefuroxime and CA combination is also not recommended by the WHO 2021 AWaRe classification.<sup>9</sup>

Although the BLI component is devoid of clinically useful intrinsic antibacterial activity, the dose ratio in which it is combined with beta-lactam antibiotic is significant. The percentage of time for which the free drug concentration of BLI remains above the critical threshold concentration for a particular pathogen affects MIC of BL-BLI combination. Thus, combining BLIs in arbitrary dose ratios is unjustified.<sup>65</sup> The assessment of the probability of joint target attainment to validate optimal combination

dose ratios and dosing regimens should be done using systematic PK/PD or simulation studies. The majority of the data available for BL-BLI combinations are available as *in-vitro* studies which are not adequate for establishing clinical efficacy or safety in target population.<sup>66</sup>

It is essential to ensure that this as well as similar other FDC antibiotics undergo adequate *in vitro* as well as clinical testing. Convincing scientific evidence or justification for the use of such combinations is needed before being marketed. Thus, discouraged FDCs may not only add to treatment costs and toxicity but, more importantly, lead to increasing AMR.<sup>59</sup>

## CONCLUSION

CAIs have a major social and economic burden on the nation. Inappropriate and irrational use of antimicrobial agents has led to a rise in not only AMR but the cost of treatment as well. Different CAIs have an underlying similar causative agent susceptible to first-line antibiotics such as aminopenicillins and cephalosporins. Most of the guidelines in India and the world over recommend the use of cephalosporins for the management of the commonly prevalent CAIs but multiple studies from India indicate a deviation in prescriptions from the guideline recommendations. There can be many factors responsible for this that needs to be explored.

Cephalosporins have a broad spectrum of activity that allows for their varied use in multiple medical specialties.<sup>14</sup> The analysis of consumption of systemic antibiotics in India has shown high usage of broad-spectrum third-generation cephalosporins.<sup>8</sup> Apart from the usage by doctors, the percentage consumption may also reflect inappropriate prescription or over-the-counter antibiotic dispensing. This necessitates the need for stricter regulations and stewardship programs.<sup>8</sup> To ensure appropriate prescription and dispensing practices, it is important to understand considerations and general clinical principles while prescribing oral cephalosporins.



These oral cephalosporin antibiotics should be used individually and not as part of the different FDCs, for example, oral cephalosporin + CA that are currently available in the market. Additionally, these oral cephalosporin plus CA combinations are not recommended by any national or international guidelines for the management of CAIs and are rather discouraged by the WHO.<sup>9</sup> These FDCs lack scientific basis and may be detrimental rather than beneficial. There is a requirement to enforce strict regulatory checkpoints to prevent the manufacturing, approval, and marketing of such inappropriate combinations. There is also a need to educate the prescribers on rational combinations and the use of various guidelines for the prescribing of antibiotics after consideration of the local resistance patterns.

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