

REVIEW ARTICLE

Cefixime-ofloxacin Combination in the Management of Uncomplicated Typhoid Fever in the Indian Community Setting

Mangesh Tiwaskar

Abstract

Antimicrobial resistance is a global problem and is definitely a cause of concern in India too, in the context of typhoid fever. It is becoming clearer that monotherapy is not effective for typhoid fever and the option to be considered is combination therapy. There are very few antibiotic combinations that are approved and backed by clinical evidence, available in India for the treatment of typhoid fever. Cefixime-ofloxacin combination is approved by Indian Regulatory Authority and has a good body of clinical evidence in the current Indian context. In-silico studies have demonstrated positive rationale of combining these two drugs, while in-vitro studies have substantiated the same by showing a strain specific synergistic and or additive activity between the two drugs against *S. typhi*. Clinical studies in Indian patients have shown multiple benefits of using this combination in typhoid fever such as a quick time to defervescence (~3 days), complete clinical cure in ~7 days, effective symptomatic relief, efficacy in relapse cases and a reduced need for hospitalization. The drug combination also demonstrates a very good tolerability profile. Recommendations of the Association of physicians of India also back this combination in typhoid fever. Thus, in the current era of emerging antibiotic resistance, cefixime-ofloxacin is a safe, effective and reliable treatment option for clinicians to treat uncomplicated typhoid in the Indian community setting.

Introduction and Relevance in the Current Indian Context

Antimicrobial resistance is a burning problem and is definitely a cause of concern in India too, in the context of typhoid fever. The 2016 -National treatment guidelines for antimicrobial use in infectious diseases issued by the national centre for disease control (DGHS, MOHFW – Govt of India) indicate that majority of the strains of bacteria causing enteric fever are nalidixic acid resistant.¹ In 2017, ICMR released 'Treatment Guidelines for Antimicrobial Use in Common Syndromes' document. This report once again highlights that quinolone resistance is increasing and is as high as 69% for *Salmonella typhi* and 23% for *S. Paratyphi A*.²

It is becoming clearer that monotherapy is not effective for typhoid fever and the best option is considered to be combination therapy.³ The 2015, Association of Physicians of India (API) recommendations for the management of typhoid fever highlight the fact

that, a number of physicians currently use fixed-dose combinations in typhoid.⁴ In a recent (2016) knowledge, attitude, practices study with general practitioners in India for typhoid fever, the investigators reported that in 38% of typhoid cases combination therapy is used.⁵ This is in line with reports of Butler et al 2011, suggesting that the use of a combination of cephalosporin and fluoroquinolone is very common in the United states of America. WHO also supports the use of combination therapy for the treatment of typhoid fever.⁶

Of relevance, here, the NCDC Indian guidelines cited above suggest, that combination antimicrobial therapy can be considered in conditions¹

- i. Where synergism of antimicrobials established
- ii. When there is a need to extend the antimicrobial spectrum beyond a use of a single agent (treatment of poly microbial infections)
- iii. Where treatment is initiated for pan-resistant organisms and to prevent emergence of resistance

- iv. Where monotherapy is not recommended

As seen in the detailed review in subsequent sections, in the Indian context of enteric fever and the above recommendations for use of combination therapy, the combination of cefixime-ofloxacin ticks all the requirements of use of combination therapy i.e., it has a demonstrable synergistic and or additive effects against *S. typhi*, can extend the anti-microbial spectrum to fluoroquinolone non-susceptible *S. typhi* strains, has a role in preventing emergence of drug resistance and is also recommended by Association of Physicians of India (API) guidelines where fluoroquinolone monotherapy fails. There is also a good body of Indian evidence supporting the efficacy and tolerability of cefixime-ofloxacin combination in the management of typhoid fever. The combination has been approved the drug regulators in India for the treatment of typhoid fever.

In this backdrop, this review aims to elaborately present the following aspects related to cefixime-ofloxacin combination, with respect to typhoid fever in the Indian context:

1. Rationale for the combination.
2. Evidence for use of cefixime-ofloxacin combination in typhoid fever:
 - I. In-silico evidence
 - II. In-vitro evidence
 - III. Clinical study evidence
 - IV. Drug utilization patterns study evidence
3. Regulatory status in India
4. Guideline recommendations in the Indian context
5. Clinical evidence in the Indian context
6. Physician usage and prescription

Table 1: Key findings of the study

Investigation details	Methodology	Results
Drug-target identification	BalestraWeb server / MetaPocket server	Network analysis showed that the target of cefixime was found to be PBP2, and the targets of ofloxacin were found to be DNA gyrase subunit A (gyrA), DNA topoisomerase IV subunit A (parC) and DNA topoisomerase 2-alpha (TOP2A).
Drug-target interaction	Autodock 4.2 / PyMOL	The auto dock binding energies between PBP2 and cefixime was found to be -5.95 kcal/mol with the inhibitory constant of 43.69 uM The auto dock binding energies between DNA gyrase subunit A and DNA topoisomerase IV subunit A with ofloxacin were found to be -5.8 kcal/mol and -6.8 kcal/mol, with the inhibitory constants of 49.94 uM and 10.33 uM respectively Also, cefixime forms three hydrogen bonds with amino acid residues (LYS554, TYR559, and ASN556) and Ofloxacin forms two hydrogen bonds (ILE264 and PRO218). Comparatively highest numbers of hydrogen bonds (6 hydrogen bonds) were found to be involved in the interaction.
Drug-drug interaction	RxList server	No direct interaction between cefixime and ofloxacin
ADMET analysis	pkCSM server	
Absorption	Water solubility / Caco2 permeability	Overall, there was good absorption activity shown by both the drugs. Water solubility was -2.523 mol/L and -3.179 mol/L for cefixime and ofloxacin respectively. Caco2 permeability was observed to be -0.585 X 10 ⁻⁶ cm/s and 1.365 X 10 ⁻⁶ cm/s for cefixime and ofloxacin respectively. Both the drugs showed activity with P-glycoprotein substrate and P-glycoprotein I inhibitor / P-glycoprotein II inhibitor activity was absent for both the drugs.
Distribution	VDss (human)	Overall good distribution activity. The distribution property of the drug in the body, showed a lower value -1.737 and -0.028 log L/kg for cefixime and ofloxacin respectively. The cefixime and ofloxacin showed fraction unbound of 0.527 and 0.577 Fu. The Brain Blood Barrier (BBB) was found to be less in the case of cefixime with the value of -1.737 log BB, whereas ofloxacin showed higher BBB with -0.792 log BB.
Metabolism	CYP interaction	Both cefixime and ofloxacin do not have a substrate or inhibitor activity for any of the CYP family of proteins
Excretion	Total clearance and Renal OCT2 substrate activity	Overall good excretion. Total clearance activity of 0.85 log ml/min/kg for cefixime and 0.414 log ml/min/kg for ofloxacin was reported. No renal OCT2 substrate activity for both the drugs was seen.
Toxicity	Series toxicity assay	No AMES toxicity, hERG I inhibitor, hERG II inhibitor toxicity and skin sensitisation.

trends in the Indian context

7. Availability in India

8. Conclusion

1. Rationale for the combination: Studies indicate that emergence of resistance is less common when combination therapy is used. Improved efficacy of the combination compared with a fluoroquinolone alone is considered because of its synergistic effect; Cefixime inhibits bacterial cell wall synthesis & ofloxacin affects bacterial DNA gyrase. As both act on different target sites, combination provides synergistic effect against most of the pathogens. For the management of typhoid fever rapid cure is desirable to prevent the acute and chronic complications of salmonella infection.⁷

2. Evidence for use of cefixime-ofloxacin combination in typhoid fever:

I. In-Silico evidence:³ The testing of drug toxicity on the animals are constrained by ethical consideration, cost and time. To reduce this burden, the involvement of computing technology in drug discovery has become a better alternative. Bhaktavachalam et al, 2017 reported the results of an in-silico approach of study to understand the drug-drug interaction, toxicity, docking with receptors for binding affinity and

energy, for cefixime-ofloxacin combination.

The parameters studied and final observations for cefixime-ofloxacin combination are summarized in Table 1.

The investigators reported that cefixime-ofloxacin combination has no drug-drug interaction and is non-toxic as predicted through computational analysis. The administration of both these drugs in combination could be highly safe without cross reactions. Also, there is improved efficiency of the combination, as targets for both molecules are different i.e., cefixime binds with PBP2 (penicillin-binding protein 2) interfering with the cell wall synthesis and the binding of ofloxacin with gyrase subunit A (gyrA), DNA topoisomerase IV subunit A (parC) and DNA topoisomerase 2-alpha (TOP2A) can halt the DNA replication resulting in arresting further cell division. Overall, this combination of cefixime with ofloxacin improves the efficiency of treatment by acting and inhibiting two different targets, with a short course of therapy.

II. In-Vitro evidence^{3,8}

Additive & Synergistic activity
Bakthavatchalam et al, 2017 prospectively studied the in-vitro anti-microbial activity of

cefixime-ofloxacin combination, specifically for *S. typhi*, using 283 non-duplicate isolates collected from blood culture, between 2012-2014 from a tertiary hospital in south India. The study used a checkerboard assay to evaluate the antimicrobial properties of the cefixime-ofloxacin combination. The investigators suggested that cefixime-ofloxacin combination, demonstrates a strain specific, synergistic or additive activity against *S. typhi* bacterium. This observation was based on the results which showed that in all isolates which were non-susceptible to fluoroquinolones, cefixime-ofloxacin combination demonstrated either an 'additive' inhibitory activity (89% isolates) and 'synergistic' (11% isolates) against *S. typhi*. There were no isolates where the combination showed an 'antagonistic' activity.

The investigators also used a time-kill assay (TKA) to demonstrate the additive / synergistic properties and bactericidal effects of cefixime-ofloxacin combination as compared to the individual components, i.e. cefixime and ofloxacin. The TKA was performed for three types of isolates –

- i. cefixime-resistant and ofloxacin resistant isolates
- ii. cefixime susceptible and ofloxacin moderately susceptible isolates.

iii. cefixime susceptible and ofloxacin resistant isolates.

For the cefixime susceptible, ofloxacin moderately susceptible isolate, the cefixime-ofloxacin combination showed synergy in the time-kill assay and highest bactericidal activity at 24 hrs compared to cefixime or ofloxacin alone. In the cefixime-resistant, ofloxacin resistant as well as cefixime susceptible and ofloxacin resistant isolate, cefixime-ofloxacin combination showed additive activity in the time-kill assay, but however a bactericidal effect was not reported in 24hrs.

Sawant C et al, 2015 reported the results of an in-vitro study evaluating the antimicrobial properties of five antibiotic combinations, including cefixime-ofloxacin combination, against *S. typhi*. For *S. typhi*, the investigators reported a 90% drop in the MIC of cefixime in the combination (0.01 mcg), as compared to the standalone MIC values of cefixime (0.09 mcg). There was a negligible difference in MIC for Ofloxacin in the combination (0.01mcg) as compared to the standalone MIC results of ofloxacin (0.009mcg). For *S. typhi*, there was 93% reduction in Cefixime's MBC (0.014mcg) and 30% reduction in Ofloxacin's MBC (0.014mcg) in the combination as compared to the standalone MBC values (0.2mcg and 0.02mcg respectively).

III. Clinical study evidence

a. Prospective post marketing observational studies^{7,9,10}

1. Naik et al [Nov 2010] conducted a post marketing clinical study to evaluate the clinical efficacy and tolerability of the fixed dose combination of cefixime 200mg-ofloxacin 200mg in typhoid patients. The study was designed as an open label, prospective, non-comparative, multicentric, observational, post marketing study, conducted across hospitals and clinics in India. The study enrolled 1230 patients (age between 18 – 75 years) across 572 centres, who were administered a fixed dose combination of cefixime 200mg-ofloxacin 200mg, twice daily for 10-14 days. The patients were evaluated at baseline and days 2,3, 5,7,10 and 14 (if required). The study results analysing data

from 1170 patients revealed –

- i. A reduction in body temperature of 101.0F at baseline to 98.120F on day 3, ($p < 0.0001$) and to 96.180F on day 14.
 - ii. A total of 53.4% (n=625) patients were afebrile on day 3 itself and this number increased to 93.1%(n=1089) on day 5 and finally all patients were afebrile by day 14.
 - iii. The mean defervescence time reported in the study was 4.9 days.
 - iv. The hepatomegaly, splenomegaly and other symptom scores were also reduced significantly ($p < 0.05$) on days 3,5,7 and 14 as compared to the baseline. The mean hepatomegaly score reduced from 0.67 at baseline to 0.38 on day 3, 0.22 on day 5, and 0.04 on day 14. Similarly, the splenomegaly score was 0.54 at baseline which came down to 0.32 on day 3, 0.17 on day 5 and 0.04 on day 14. Lastly, the mean abdominal pain score reduced from 0.88 at baseline to 0.37 on day 3, 0.20 on day 5, and 0.02 on day 14.
 - v. Other symptoms:
 1. Coated Tongue: (~57%) patients had a coated tongue at baseline, which came down 476(~41%) patients on day 3 and finally 337 (~29%) patients on day 14.
 2. Constipation: 713 (~61%) patients had constipation at baseline, which came down 477(~41%) patients on day 10 and finally 382 (~33%) patients on day 14.
 3. Diarrhoea: 682 (~58%) patients had diarrhoea at baseline, which came down 507(~43%) patients on day 3, 475 (~41%) patients on day 5, 399 (~34%) patients on day 7 and finally 220 (~19%) patients on day 14.
 - vi. Global assessment by physician:
 1. Efficacy: ~97% physicians rated the efficacy of the combination as 'Good to Excellent'
 2. Tolerability: ~95% physicians rated the tolerability of the combination as 'Good to Excellent'
 - vii. Global assessment by patient:
 1. Efficacy: ~97% patients rated the efficacy of the combination as 'Good to Excellent'
 2. Tolerability: ~95% patient rated the tolerability of the combination as 'Good to Excellent'
- The following adverse events (all

mild to moderate in intensity) were reported in the study – nausea (~10%), Abdominal pain (4%), Diarrhoea (~2%), Vomiting (~2%), constipation (~2%) and headache (1%).

The investigators thus concluded that the fixed dose combination of cefixime 200mg – Ofloxacin 200mg is effective and safe in the management of uncomplicated typhoid fever.

2. Naik et al [Aug 2010] conducted a post marketing clinical study to evaluate the clinical efficacy and tolerability of the fixed dose combination of cefixime 200mg-ofloxacin 200mg in typhoid patients with respiratory abnormalities. The study was designed as an open label, prospective, non-comparative, multicentric, observational, post marketing study conducted across hospitals and clinics in India. The study enrolled 386 patients (age between 18 – 75 years) across 72 centres, who had a respiratory abnormality like bronchial asthma or infection. The patients were administered a fixed dose combination of cefixime 200mg-ofloxacin 200mg, twice daily for 10-14 days. The patients were evaluated at baseline and days 2,3, 5,7,10 and 14 (if required). The study results analysing data from 365 patients revealed –
 - i. A reduction in body temperature of 101.70F at baseline to 98.30F on day 3, ($p < 0.0001$) and completely normalized day 5 onwards.
 - ii. A total of 89.9% (n=328) patients were afebrile on day 3 itself and this number increased to 94.5%(n=345) on day 5 and finally all patients were afebrile by day 14.
 - iii. The mean defervescence time reported in the study was 3.2 days.
 - iv. The hepatomegaly, splenomegaly and other symptom scores were also reduced significantly ($p < 0.05$) on days 3,5,7 and 14 as compared to the baseline. The mean hepatomegaly score reduced from 1.54 at baseline to 0.6 on day 3, 0.23 on day 5, and 0.04 on day 14. Similarly, the splenomegaly score was 1.60 at baseline which came down to 0.33 on day 3, 0.1723 on day 5 and 0.04 on day 14. Lastly, the mean abdominal pain score reduced from 1.82 at baseline to 0.48 on day 3, 0.23 on day 5, and 0.02 on days 10 & 14.

V. Other symptoms:

1. Coated Tongue: 279 (~76%) patients had a coated tongue at baseline, which came down 166 (~46%) patients on day 3 and finally 70 (~19%) patients on day 7 and only 14 (3.8%) patients on day 14

2. Constipation: 235 (~64%) patients had constipation at baseline, which came down to 213 (~58%) patients on day 10 and finally 201 (~51%) patients on day 14.

3. Diarrhoea: 88 (~24%) patients had diarrhoea at baseline, which came down to 53 (~15%) patients on day 3, 24 (~7%) patients on day 5, 22 (~7%) patients on day 7 and finally 10 (~3%) patients on day 14.

The following adverse events (all mild to moderate in intensity) were reported in the study – nausea (~9%), Abdominal pain (~5%), Diarrhoea (~2%), Vomiting (~2%), constipation (~1%) and headache (1%).

The investigators thus concluded that the fixed dose combination of cefixime 200mg – Ofloxacin 200mg is effective and safe in the management of uncomplicated typhoid fever patients with respiratory abnormalities.

vi. Faruqui et al 2012, studied the efficacy and tolerability of the fixed dose combination of cefixime 200mg & ofloxacin 200mg in a post marketing surveillance study in Indian patients. The study was conducted as a nonrandomized, open label, non-comparative, multi centric trial (5 centres), enrolling thirty patients aged 18-72 years suffering from typhoid fever. The patients were administered the study drug every 12 hours, for 10 – 14 days. Patients were assessed at baseline, day 3, 7, and 14 after enrolling into the study.

For the primary outcomes evaluated included the results were as follows:

i. Reduction in body temperature on 3rd, 7th, and 14th day from baseline – All patients reported fever on the first day of treatment. Body temperature was significantly reduced from baseline (mean \pm SD) value 101.5 ± 0.84 °F to 98.34 ± 1.42 °F, 97.26 ± 2.03 °F and 97.06 ± 2.03 °F on the 3rd, 7th and 14th days of treatment respectively. This reduction in body temperature was statistically significant ($p <$

0.0001) from baseline to 3rd day and onwards.

ii. Time to defervescence (i.e. normalization of body temperature to ≤ 98.40 F) during the study period - The time taken to achieve the normal body temperature was 2.93 ± 0.23 days.

iii. Interference in sleep patterns of the patients – At baseline, there was frequent nocturnal awakening (3.06 ± 0.88). Nocturnal awakening came down on day 3 (2.27 ± 0.70) and further down on day 7 (1.41 ± 0.73). On 14th day there were no or few cases of nocturnal awakening and the mean value was 0.44 ± 0.57 . Thus, there was a significant reduction in the nocturnal awakening from the baseline on 3rd day of treatment and onward 7th and 14th day of treatment ($P < 0.001$).

For the secondary outcome measures the results were as follows:

i. Global assessment of efficacy by investigator – ~97% reported 'Good to Excellent' efficacy.

ii. Global assessment of tolerability by investigator – ~93% reported 'Good to Excellent' tolerability.

Overall, only mild to moderate adverse events that did not require discontinuation of study drug like nausea, headache and epigastric pain were reported in ~13% patients. The investigators concluded that the fixed dose combination of cefixime and ofloxacin therapy is effective and achieves rapid clinical cure in typhoid fever, with excellent tolerability & safety.

b. Prospective prescription event monitoring study¹¹

Kadhe et al, 2012 conducted a post marketing prescription event monitoring study to evaluate the efficacy and safety of the fixed dose combination of cefixime 200mg – ofloxacin 200mg in Indian patients with typhoid fever. A total of 225 doctors enrolled 1029 patients suffering from typhoid fever in this prospective, open label, multicentric, post marketing prescription event monitoring study. The treatment given was cefixime-ofloxacin (200mg/200mg), twice daily for 14 days. Results were based on the analysis of data from physician recorded patient

responses, on a pre-designed prescription event monitoring questionnaire.

For the study end points the following results were reported:

i. Time to defervescence was 4.36 ± 2.53 days in 86% patients (n=883). However, noteworthy was the finding that the cefixime-ofloxacin combination showed a significant reduction in the body temperature after the first dose itself.

ii. Time to provide symptomatic relief was 4.76 ± 3.62 days in 89% patients (n=917)

iii. Time to complete cure was 7.12 ± 3.38 days in 87% patients (n=891)

iv. Reduction in need for hospitalization was seen in 86% patients (n=929)

v. Global assessment of treatment efficacy compared to standard treatment was reported as 'Good' in ~16.58%, 'Very Good' in 42.71% and 'Excellent' in 40.71% cases.

Overall, 92.4% investigators affirmed that they would recommend this combination for the treatment of enteric fever.

Of the 942 patients who reported adverse effects, ~85% (n=802) patients indicated that the adverse effects were not distressing and or disturbing their daily routine, while ~15% (n=140) patients considered the side effects as distressing or disturbing their daily routine.

The investigators thus concluded that cefixime-ofloxacin combination is efficacious, safe, offers quick symptomatic relief and a lesser need for hospitalization in patients with typhoid fever.

c. Retrospective Observational Survey Study¹²

Patil et al 2015, studied the efficacy of cefixime-ofloxacin 400mg sustained release tablets in the treatment of enteric fever in community settings of India. The study was designed on a retrospective, questionnaire based survey methodology, involving 78 family physicians across the country. A total of 881 patient data forms were analysed, of which cefixime-ofloxacin 400mg SR tablet was prescribed in 580 patients. The duration of therapy ranged from 5 days to 14 days, depending on

the clinician's judgement. Fever clearance on the 7th day was reported in 97% cases (n=565) treated with cefixime-ofloxacin SR tablets. A further sub-analysis of high risk cases, i.e. relapse/recurrence, showed equally good response to the combination as cases without defervescence on day 7 were only 1.3%. The study results also included cases with co-morbid conditions like diabetes (n=97), hypertension (n=106), others (n=41). Thus overall, the investigators concluded that cefixime-ofloxacin 400mg SR tablets as an optimal choice in the management of typhoid fever, including cases with co-morbidities like diabetes and hypertension.

IV. Drug utilization pattern study¹³

Rajaram et al, 2016 analysed the drug utilization patterns in primary health centres from a semi-urban area in south India. General practitioner's prescription data from 500 patients was collected and analysed. The results showed that in general, the doctors mainly used combination therapy (92%) for the patients. Cefixime-ofloxacin was the most commonly recommended antibiotic combination, i.e., 30% patients and the 2nd most commonly recommended antibiotic, behind only cefixime monotherapy, which was recommended to 36% patients.

3. Regulatory Status in India: Cefixime-Ofloxacin combination is approved by the Indian Regulatory Authority. The Indian Regulatory Authority website shows approvals for six formulations of cefixime-ofloxacin combination as listed in Table 3.¹⁴

In the recent years, many FDCs were re-evaluated by the Indian regulatory authorities for their rationality and continuance of manufacturing and marketing in India.¹⁴ Cefixime-ofloxacin combinations also figure in the list FDCs permitted for continued manufacturing and marketing in respect of the applicants under 18 months' policy decision (as on 21.02.2017) published by Indian Regulatory Authority website (Table 3)

Apart from cefixime-ofloxacin combination, combinations of cefpodoxime and ofloxacin in various formulations / strengths

are approved by Indian Regulatory Authority. There do not seem to be any other antibiotic combinations in the list of approvals on the Indian Regulatory Authority website for typhoid fever.

4. Guideline Recommendation in the Indian context: It is becoming clearer that monotherapy is not effective for typhoid fever, the best is considered to be combination therapy.³ The 2015, Association of Physicians of India (API) recommendations for the management of typhoid fever highlight the fact that, a number of physicians currently use fixed-dose combinations in typhoid.⁴ In a recent (2016) knowledge, attitude, practices study with general practitioners in Indian for typhoid fever, the investigators reported that in 38% of typhoid cases combination therapy is used.⁵ This is in line with reports of Butler et al 2011, suggesting that the use of a combination of cephalosporin and fluoroquinolone is very common in the United states of America. WHO (also supports the use of combination therapy for the treatment of typhoid fever.⁶ The 2015 API recommendations for the management of typhoid fever, cite the lack of clear guidelines for the use of monotherapy and combination therapy in typhoid fever. However, API also recommends the use of a combination therapy (Cefixime + Fluoroquinolone like ciprofloxacin and ofloxacin), but still reserves its use to cases where response to monotherapy is inadequate or unresponsive. Of special relevance here is the specific recommendation by API for cefixime in the context of combination therapy with fluoroquinolones, further reinforcing the advocacy for cefixime-ofloxacin combination in the treatment of typhoid fever.⁴
5. Clinical Evidence in the Indian context: The in-silico studies, in-vitro studies, clinical studies (retrospective, post marketing observational / surveillance, prescription event monitoring, interventional studies) have all been done in the Indian setting, i.e., with Indian strains of typhoid

pathogens, patients and treatment facilities and have all been done between 2010 – 2017, and hence can be considered convincingly relevant to the Indian typhoid landscape. Also, the combination of cefixime-ofloxacin seems to be the only combination backed by multiple research initiatives and robust Indian data for typhoid fever. The available clinical evidence in this context has already been reviewed in detail in the earlier sections.

6. Physician usage and prescription trends in the Indian Context: As mentioned earlier, clinicians currently use combination therapy often in their practice. Mukherjee et al reported the usage data for various antibiotics, including cefixime-ofloxacin combination in the Indian context, as of September 2015. The data quite interestingly suggests that there are 142 branded generics of cefixime 200mg -ofloxacin 200mg combination and it is the 7th most prescribed antibiotic amongst all antibiotics in the Indian market, despite being available for use only since 2010. A closer look at the data reveals that, cefixime 200mg -ofloxacin 200mg combination is the number one prescribed antibiotic combination by the Indian healthcare practitioners.¹⁵

Antimicrobial resistance is a global problem and is definitely a cause of concern in India too, in the context of typhoid fever. It is becoming clearer that monotherapy is not effective for typhoid fever and the option to be considered is combination therapy. The Global Antibiotic Research & Development Partnership (GARDP), a joint initiative of DNDi and the WHO, aims to develop and deliver new treatments for bacterial infections where drug resistance is present or emerging, or for which inadequate treatment exists. GADRP R&D priorities include in-vitro evaluation of combination therapies as well as evaluation of salvage regimens for multi-drug resistant typhoid fever. In this context GADRP report highlights the following:¹⁶

- Development of combination regimens for typhoid fever and invasive salmonella infections.
- Data to suggest that in other

Table 2: List of formulations approved by Indian regulatory authority

Formulation Details	Indication	Approval date
Cefixime 100 mg + Ofloxacin 100 mg Tablets	For the treatment of patients with typhoid fever and urinary tract infection in adults.	26.04.10
Cefixime 200 mg + Ofloxacin 200 mg Tablets	For the treatment of patients with typhoid fever and urinary tract infection in adults.	26.04.10
Cefixime SR 200mg + Ofloxacin 200 mg Tablets	(Additional Strength) For the treatment of patients with typhoid fever and urinary tract infection in adults.	31.08.10
Cefixime SR 400 mg + Ofloxacin 400 mg Tablets	(Additional Strength) For the treatment of patients with typhoid fever and urinary tract infection in adults.	31.08.10
Cefixime Trihydrate IP Eq. to Anhydrous Cefixime 100 mg + Ofloxacin IP 100 mg/ Dispersible Tablet	(Additional dosage form) For the treatment of patients with typhoid fever and urinary tract infection in adults.	20.04.11
Cefixime Trihydrate IP Eq. to Anhydrous Cefixime 200 mg + Ofloxacin IP 200 mg Dispersible Tablet	(Additional dosage form) For the treatment of patients with typhoid fever and urinary tract infection in adults.	20.04.11

diseases combination therapy may reduce the emergence of antibiotic resistance.

- Evidence of synergy cephalosporins and quinolones in fluoroquinolone resistant strains
- Potential impact on duration of acute faecal shedding, development of chronic carriers and resultant disease transmission.
- Potential to shorten the required course of treatment and improve compliance.

In India, there are very few antibiotic combinations that are approved and backed by clinical evidence, for the treatment of typhoid fever. Cefixime-ofloxacin combination is approved by Indian Regulatory Authority and has a good body of clinical evidence in the current Indian context. The two drugs act on different sites of the pathogen, as well as have complementary actions i.e. cefixime acting on the extracellular pathogens, while ofloxacin acting on the intracellular pathogens. In-silico studies have demonstrated positive rationale of combining these two drugs, while in-vitro studies have substantiated the same by showing a strain specific synergistic and or additive activity between the two drugs against *S.typhi*. Clinical studies in Indian patients have shown multiple benefits of using this combination in typhoid fever such as a quick time to defervescence (~3 days), complete clinical cure in ~7 days, effective symptomatic relief, efficacy in relapse cases and a reduced need for hospitalization. The drug

combination also demonstrates a very good tolerability profile. Recommendations of the Association of physicians of India also back this combination in typhoid fever, where response to monotherapy is inadequate or unresponsive. Thus, in the current era of emerging antibiotic resistance, cefixime-ofloxacin is a safe, effective and reliable treatment option for clinicians to treat uncomplicated typhoid in the Indian community setting. Further studies evaluating the efficacy of this combination compared to monotherapy, in first time cases as well as relapse and non-responsive cases will help establish the role of the combination further in the treatment of uncomplicated typhoid fever.

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Table 3: Indian Regulatory Authority - FDCs permitted for continued manufacturing and marketing in respect of the applicants under 18 months policy decision (as on 21.02.2017)

Formulation details	Date of NOC
Cefixime (as Trihydrate) IP Eq. to anhydrous Cefixime 50mg + Ofloxacin IP 50mg per 5ml of reconstituted suspension	17.07.15
Cefixime Trihydrate IP eq. to (anhydrous) Cefixime 50mg/100mg/200mg+Ofloxacin IP 50mg/100mg/200mg uncoated tablets	17.07.15
Cefixime 200mg/100mg+Ofloxacin 100mg/200mg tablets	17.07.15
Cefixime Trihydrate IP Eq. to anhydrous Cefixime 200mg/400mg+Ofloxacin IP 200mg/400mg tablets	17.07.15
Cefixime trihydrate 200mg+Ofloxacin 200mg film coated tablets	17.07.15
Cefixime IP (as Trihydrate) Eq. to anhydrous Cefixime 200mg+Ofloxacin IP 200mg dispersible tablets	17.07.15
Cefixime Trihydrate IP eq. to Anhydrous Cefixime 100mg/200mg+Ofloxacin IP 100mg/200mg film coated tablets/dispersible tablets	03.02.16

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