Original Research Article

Comparison of in- vitro activity of Cefixime to Doxycycline and Minocycline against Gram-negative bacteria isolated from Patients Suffering from Respiratory Tract Infections at a Tertiary Care Centre in Northern India

Abstract

Background: Respiratory tract infections (RTI) form a major part of common ailments encountered by a general physicians hailing from a developing country. Antibiotics are used for treating any infection but inappropriate use of antibiotics lead to development of multidrug resistance (MDR). This study was performed to analyze the comparative in-vitro activity of Cefixime and Tetracyclines by antibiotic susceptibility testing (AST) against the pathogens isolated from respiratory samples.

Material and methods: We performed a prospective study in the Bacteriology section of the Department of Microbiology at a teaching hospital in Northern India from Jan 2022 to June 2022. Cefixime, Doxycycline, and Minocycline were tested for susceptibility against 100 Gram-negative bacteria from respiratory samples. The antibiotic susceptibility testing for each of the isolates was performed by the Kirby Bauer Disc Diffusion method, according to the CLSI 2019 guidelines.

Results: Our study cohort included 100 Gram negative isolates with a majority of them obtained from Endotracheal aspirate samples (43, 43%) followed by Sputum (37, 37%) samples. The most common microorganism tested for susceptibility to this drug was Klebsiella pneumoniae (39, 39%) followed by Escherichia coli (33, 33%). *Escherichia coli* was identified as the most

isolated to all the antibiotics and was 12.12% (4/33, 12.12%) susceptible to all three drugs. On overall analysis activity of Doxycycline was better than Cefixime among inducible *Enterobacteriaceae* and non-fermenter isolate.

Conclusion: Doxycycline is a proficient antimicrobial agent for treating an array of Gram-negative bacteria-associated infections showing better in-vitro activity in comparison to Minocycline and other bactericidal agents like Cefixime.

Keywords: Respiratory tract infection (RTI), Cefixime, Tetracycline, Gram-negative bacteria, MALDI-TOF-MS.

Introduction

Respiratory tract infection, which could be an upper respiratory tract infection (URTI) or a lower respiratory tract infection (LRTI) forms a major part of common ailments encountered by a general physician in routine practice, hailing from a developing country [1]. Although the use of antibiotics is the mainstay of treating any infection, overuse or inappropriate use of antibiotics can lead to adverse drug reactions as well as the development of multidrug resistance (MDR) [2]. Not only can antibiotic resistance occurs naturally but also due to easy availability of most antibiotics over the counter, along with a rampant prescription of a drug that should be saved for last resort has led to emerging drug resistance to most first-line drugs used for the treatment of respiratory infections along with an increase in the total cost of treatment [3, 4].

Cefixime is an oral third-generation cephalosporin, commonly used in the treatment of upper respiratory tract infections [5]. It is a beta-lactam antibiotic that is capable of attaching to the penicillin-binding proteins (PBP) of the pathogen and prevents the synthesis of peptidoglycans resulting in a degraded bacterial cell wall. Its bactericidal activity has led it to be

utilized as a broad-spectrum antibiotic against gram-positive, gram-negative, and also atypical bacteria like Chlamydia and Mycoplasma [6].

Tetracyclines are antibiotics that inhibit the protein synthesis of microorganisms by preventing the attachment of aminoacyl-tRNA to the ribosomal acceptor (A) site. They are bacteriostatic, broad-spectrum antibiotics exhibiting activity against gram-positive, gram-negative, and activity against atypical bacteria like rickettsia, mycoplasma, Chlamydia, and other protozoan parasites [7]. Patients suffering from chronic airway obstruction not improving on antibiotics are administered Tetracyclines when a presentation of acute infection is suspected [8].

The predominant presence of MDR organisms in respiratory infections in patients admitted to inpatient wards has been demonstrated by recent studies [9, 10]. We performed this prospective study at a 1600-bedded teaching hospital in Northern India to analyze the comparative in-vitro activity of Cefixime and Tetracyclines (long-acting tetracycline) which include Doxycycline and Minocycline through antibiotic susceptibility testing (AST)against the pathogens isolated from respiratory samples included in our study cohort.

Material and methods

Study design

A prospective observational study was conducted in the Bacteriology section of the Department of Microbiology at a university hospital in Northern India from Jan 2022 to June 2022. We intended to demonstrate the in-vitro activity of Cefixime against the Gram-negative bacteria isolated from the respiratory samples included in this study over six months and to compare its activity to two tetracycline antibiotics which include Doxycycline, and Minocycline that was regularly used in the wards and critical care units of our hospital. We did not test its activity

against all non-lactose fermenting bacteria except *Pseudomonas aeruginosa* as there are no cut-off guidelines. The study was approved by the institute ethics committee (2021-48-EMP-EXP Dated 29/11/2021).

The identification of each isolate was done using conventional biochemical tests and/or Matrix Assisted Laser Desorption/Ionization – time of flight- Mass spectrometry (MALDI-TOF-MS) assay. The type of respiratory sample from which the isolate was obtained was recorded in our study. We did not make any endeavor to identify the pathogenic or colonizing nature of the microorganism, nor was the ability of the infection to influencing the outcome of the patients.

Selection of the isolates

We included non-repeat samples in the study so that no similar Gram-negative isolate was included in the study twice. Samples that were inappropriate or delayed in transport were excluded. All Gram-positive isolates along with bacterial isolates belonging to *Neisseria*, *Haemophilus*, and *Moraxella* species were discarded. Bacterial isolates against which Cefixime was tested mainly include Gram-negative bacteria isolates from respiratory samples which include sputum, tracheal aspirates, and endotracheal aspirates. Samples from only patients admitted to our hospital were included in the study and samples from the outpatient department (OPD) were excluded.

Antimicrobial susceptibility testing

The antibiotic susceptibility for each of the bacterial isolates was conducted by using the Kirby Bauer Disc Diffusion method, according to the CLSI 2019 guidelines [11]. Antibiotic discs containing Cefixime (5 mcg), Doxycycline (30 mcg), and Minocycline (30 mcg) were obtained from HiMedia diagnostics (Mumbai, India). Standard inoculums for each bacterial isolate were prepared and set to 0.5 McFarland and a lawn culture was applied on Cation-adjusted Muller-

Hinton agar plates. The above-mentioned antibiotic discs were manually placed on the lawn cultured plates and incubated overnight at 37º C. The measurement of zones of inhibition for each antibiotic against each isolate was measured and classified as sensitive, intermediate, and resistant according to the tables and guidelines by CLSI 2019 [11]. The sensitivity of Doxycycline, Minocycline, and Cefixime was assessed by recording the zone diameters of each antibiotic according to the CLSI 2019 [11], as shown in Table 1. Escherichia coli American Type Culture Collection (ATCC; Rockville, MD, USA) 25922 and Pseudomonas aeruginosa ATCC27853 were used for daily quality control testing recommended by the CLSI.

Result

A total of 100 non-repeat Gram-negative isolates were obtained from respiratory samples obtained from adult patients admitted to the inpatient department of our hospital. Figure 1 shows the distribution of samples from which the isolated microorganisms were tested for susceptibility to Cefixime, Doxycycline, and Minocycline. The majority of isolates were obtained from Endotracheal aspirate samples (43, 43%) followed by Sputum (37, 37%) and Tracheal aspirate samples (20, 20%).

The most common microorganism tested for susceptibility to this drug was Klebsiella pneumoniae (39, 39%) followed by Escherichia coli (33, 33%), Acinetobacter baumanii (13, 13%), and Pseudomonas aeruginosa (13, 13%), as seen in Table 2. The efficacy of the three said antibiotics were predominantly tested for their susceptibility against the non-inducible *Enterobacteriaceae* group (which includes *Escherichia coli* and *Klebsiella pneumoniae*) in comparison to the inducible *Enterobacteriaceae* group (which includes *Enterobacter aerogenes*), which is 72% (n=72) versus 2% (n=2) respectively. We also tested the susceptibility of the antibiotics against non-fermenters groups in 26.0% (n=26) isolates identified in our study. Being

a single-center study, no comparison in the prevalence of the isolates being tested could be made among other centers and this limits our study from representing the susceptibility to Cefixime, Doxycycline, and Minocycline among the isolates identified from other centers located in Northern India.

Table 3 represents the susceptibility of the isolates included in the study to Cefixime, Doxycycline, and Minocycline. *Escherichia coli* was identified as the most isolated to all the antibiotics and was 12.12% (4/33, 12.12%) susceptible to all three drugs. *Pseudomonas aeruginosa* (12/13, 92.31%) and *Klebsiella pneumoniae* (31/39, ~79.48%) were identified as the isolates most resistant to all three antibiotics. *Pseudomonas aeruginosa* (12/13, 92.31%) was found to be equally resistant to all three antibiotics. *Klebsiella pneumoniae* was most resistant to Minocycline (39/39, 100%) followed by Cefixime (35/39, 89.74%), and was marginally more susceptible to Doxycycline (31/39, 79.48%). Overall susceptibility to all the antibiotics in descending order was: Doxycycline (35/100, 35.0%), Cefixime (17/100, 17.0%), and Minocycline (5/100, 5.0%). Among the commonly isolated isolates, *Acinetobacter baumannii* was identified as the most susceptible pathogen to Doxycycline and Cefixime. *Escherichia coli* was identified as 54.54% (18/33, 54.54%) susceptible to Doxycycline, 27.27% (9/33, 27.27%) susceptible to Cefixime. Among the 100 isolates tested for susceptibility to Minocycline, *Escherichia coli* (4/33, 12.12%) was the most susceptible to it.

Among the non-inducible *Enterobacteriaceae*, *Escherichia coli* was least susceptible to Minocycline (4/33, 12.12%) and most susceptible to Doxycycline (18/33, 54.54%). *Klebsiella pneumoniae* followed the same pattern of susceptibility as *Escherichia coli* and was least susceptible to Minocycline (0/39, 0.0%) and most susceptible to Doxycycline (8/39, 20.51%). Among the inducible *Enterobacteriaceae*, only two isolates of *Enterobacter aerogenes* were

tested for susceptibility to the antibiotics. Only one isolate of *Enterobacter aerogenes* was found susceptible to Doxycycline, whereas none of the isolates were susceptible to Minocycline or Cefixime.

On overall analysis, the activity of Doxycycline was comparatively better than Cefixime among the inducible *Enterobacteriaceae* and non-fermenter isolates included in our study. Similarly, the activity of Doxycycline was almost 50% better in comparison to the activity of Cefixime in the case of non-inducible *Enterobacteriaceae* which includes *Escherichia coli* and *Klebsiella pneumoniae*. Further comparative activity of Cefixime and Doxycycline against the microorganisms isolated from the samples included in our study has been discussed in Table 4.

The four most common microorganisms isolated from respiratory samples included in our study cohort were *Klebsiella pneumoniae* (n=39), *Escherichia coli* (n=33), *Acinetobacter baumanii* (n=13), and *Pseudomonas aeruginosa* (n=13). The isolates were sensitive to both Doxycycline and Cefixime in 21.21% (7/33)*Escherichia coli*,15.38% (2/13)*Acinetobacter baumannii*, and 5.13% (2/39)*Klebsiella pneumoniae*. The isolates were resistant to both Doxycycline and Cefixime in 84.62% (11/13) *Pseudomonas aeruginosa*, 74.36% (29/39) in *Klebsiella pneumoniae*, 50.0% (1/2) in *Enterobacter aerogenes*, 30.77% (4/13) in *Acinetobacter baumannii*, and 30.30% (10/33) in *Escherichia coli*. The isolates were sensitive to Doxycycline and resistant to Cefixime in 33.33% (11/33) *Escherichia coli*, 23.07% (3/13) *Acinetobacter baumannii*, 10.26% (4/39) *Klebsiella pneumoniae*, and 7.69% (1/13) *Pseudomonas aeruginosa*. Only one isolate of *Escherichia coli* was found to be resistant to Doxycycline but sensitive to Cefixime.

Intermediate sensitivity of a bacterial isolate to an antibiotic is recognized when the bacteria is inhibited in vitro by a concentration of this drug but its therapeutic effect at that

concentration is uncertain. The isolates were intermediate sensitive to Cefixime and sensitive to Doxycycline in50.0% (1/2) *Enterobacter aerogenes*, 15.38% (2/13) in *Acinetobacter baumannii*, and 5.13% (2/39) in *Klebsiella pneumoniae*. The isolates were intermediate sensitive to Doxycycline and sensitive to Cefixime in7.69% (1/13) *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, 5.13% (2/39) in *Klebsiella pneumoniae*, and 3.03% (1/33) in *Escherichia coli*.

Among the 100 isolates, 92% (92/100) isolates were found to be multidrug-resistant organisms (MDROs). Among these isolates, *Klebsiella pneumoniae* (39/39) and *Pseudomonas aeruginosa* (13/13) were found to be 100% and *Escherichia coli* was found to be 60.60% (20/33) resistant to one drug in three or more categories of antimicrobials. While isolates were found most resistant to fluoroquinolones (~ 90%), followed by third-generation cephalosporins (~80%), *Klebsiella pneumoniae* was found to be 100% (39/39), *Escherichia coli* was found to be 100% (18/18), *Pseudomonas aeruginosa* was found to be 92.31% (12/13) and Enterobacter aerogenes was 50.0% (1/2) sensitive to the drug of last resort, Colistin. While we report 1 isolate each of *Enterobacter aerogenes* and *Pseudomonas aeruginosa* to be extremely drug resistant.

Doxycycline had better activity in comparison to Minocycline among Tetracyclines against the Gram-negative isolates from the respiratory samples included in our study cohort. We recorded an intermediate susceptibility of the isolates to Cefixime in comparison to Doxycycline. Thus, in a predominance of multidrug-resistant Gram–negative bacteria isolated from respiratory samples; Doxycycline can be used as the drug of last resort.

Discussion

A significant amount of mortality, morbidity, and loss of monetary resources can be attributed to respiratory tract infections, worldwide. Lower respiratory tract infections (LRTIs) are common bacterial infections that tend to be multidrug-resistant (MDR) and needs increased use of antibiotics along with huge expenditure on antibiotic and hospitalization, accounting for 3 to 5% of deaths in patients above 60 years of age [12]. Cefixime, Doxycycline, and Minocycline have been used for the treatment of MDR lower respiratory infections due to resistance to first- and second-line drugs [13]. Newer antibiotic agents and antibiotic combinations are the need of the hour to combat the alarming increase in multidrug resistance among infection-causing Gram-negative bacteria. The results from this study show clearly that Doxycycline was significantly more effective in comparison to Cefixime and Minocycline by in-vitro antibiotic susceptibility testing on Gram-negative bacteria isolated from respiratory samples of patients admitted to the inpatient department of a tertiary care institute.

Cefixime is an oral third-generation cephalosporin, commonly used in the treatment of important lower respiratory tract infections [5]. In some non-comparative studies, the efficacy of Cefixime was found to be similar to Cefaclor, Cefalexin, Amoxicillin – clavulanic acid, and Cefuroxime axetil in patients suffering from LRTIs [14]. Comparative studies have suggested Cefixime be equally efficacious as intravenous Ceftriaxone, oral Cefalexin, Amoxicillin-clavulanic acid, and Clarithromycin. Statistical data evaluated by a study conducted by Ramdhani *et al* [1] suggested that comparisons of resistant and non-resistant conditions

from Cefixime and Tetracycline antibiotics defined a significant difference in the level of resistance in the use of the two antibiotics for the treatment of RTIs. Studies conducted by Ige *et al* [15] and Ullah *et al* [16]suggested that Cefixime is more effective in the treatment of respiratory infections in comparison to Moxifloxacin, Ofloxacin, and Ciprofloxacin.

Tetracycline are agents known to be widely effective against gram-positive, gram-negative, and atypical microorganisms and have a considerably favorable safety profile [17 - 21]. Tetracyclines evaluated in this study include Doxycycline and Minocycline that known to contain similar antibiotic properties. According to the recently updated American Thoracic Society (ATS)/Infectious Disease Society of America (IDSA), Doxycycline has been approved for monotherapy in patients without any comorbidity against MDR pathogens [22]. Although, a combination of Doxycycline and Beta-lactam antibiotics has been suggested for the treatment of ARTIs in patients suffering from comorbidities or those admitted to the hospital with contraindications to Fluoroquinolones and Macrolides [23]. Combination therapies with Ceftriaxone and Cefixime have also been found effective in treating *Chlamydia trachomatis* and *Neisseria gonorrhoeae* co-infections [24].

All isolates included in the study were grouped into inducible or non-inducible *Enterobacteriaceae* and non-fermenters, as observed in Table 2, and tested for susceptibility to each of the three antibiotics. Cefixime has been deemed less effective towards non-fermenters and members of inducible *Enterobacteriaceae* in a study by Markham *et al* [14] and is similarly observed in our study as only scarce susceptibility of the pathogens to Cefixime was observed in Table 3.

As observed in Table 3, among the 100 MDR microorganisms tested for susceptibility to the antibiotics, the overall susceptibility to Doxycycline was 35% (35/100, 35%), which was significantly higher in comparison to the overall susceptibility of Cefixime (17/100, 17%) which is in contrast to a study conducted by Ramdhani *et al* [1] where the test isolates were found to demonstrate better susceptibility to Tetracyclines. Tetracycline is a bacteriostatic agent that was

found to be more effective in treating the infections caused by the bacterial isolates in our study cohort due to extensive Beta-lactam resistance that has been observed in isolates identified from other infections in studies conducted at our center [25].

The outcome of patients in terms of mortality was 65% (65/100, 65%)of which 60(60/65, 92.31%) patients were on mechanical ventilation who could not be extubated and died during treatment with Colistin or Minocycline which were considered the go-to drugs of last resort. In-vitro activity of Doxycycline and Cefixime was found much better than that of Minocycline. Out of five patients who were on ambient air, one (1/5, 20%) was suffering from B-cell Acute Lymphoblastic Leukemia (BALL)and succumbed to it in the course of treatment. Four (4/65, 6.15%) other patients who died were not treated with Doxycycline but in-vitro susceptibility to Doxycycline was observed in them on AST of the pathogens. Thus, the use of Tetracyclines like Doxycycline holds a chance to improve the outcome of the patients admitted to the ward or intensive care unit.

Conclusion

Treatment with Doxycycline and Cefixime can show better results in the treatment of ARTIs in comparison to Minocycline in patients admitted to the ward and intensive care units. This study also identified the pathogenic bacteria infecting the patients in our study cohort along with their antibiotic susceptibility pattern which was more often found to be MDR.

Consent for publication

All individuals have given consent to participate in the study.

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Table 1. Categories of cefixime, Doxycycline, and Minocycline inhibition zone diameter inaccordance with the CLSI

Categories	Cefixime (in mm)	Doxycycline (in mm)	Minocycline (in mm)
Resistant	≤17	≤11	≤14
Intermediate	18 – 20	12-13	15-17
Sensitive	≥21	≥14	≥18

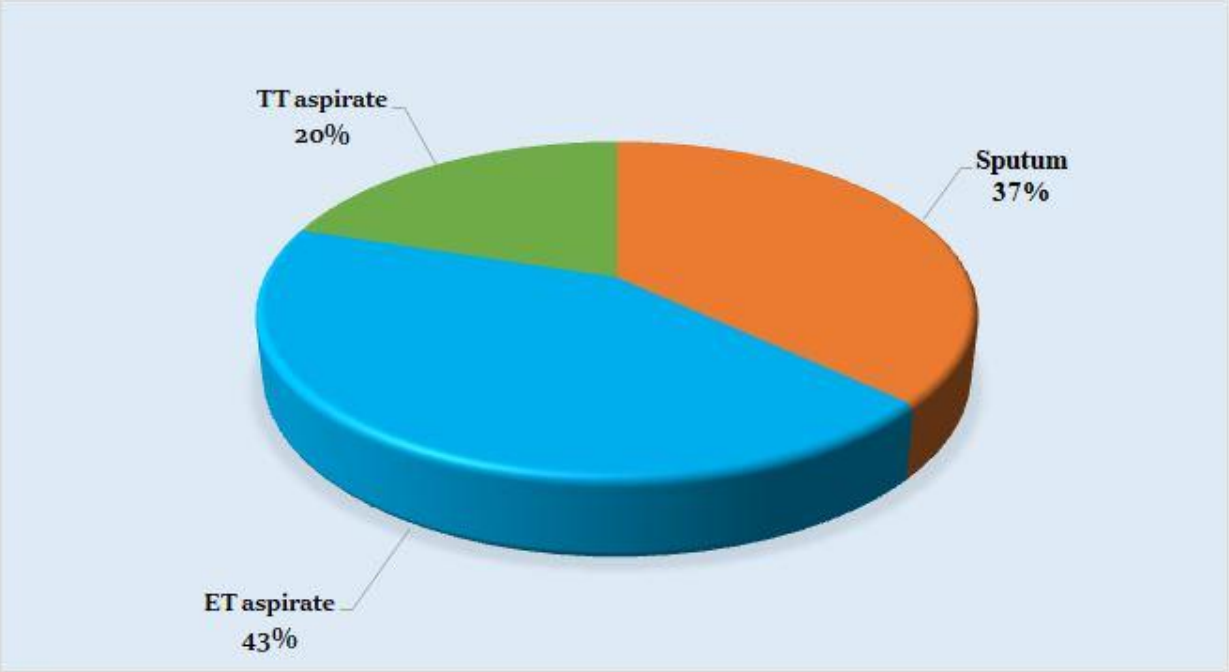

Figure 1. Distribution of respiratory samples that were included in our study (N=100)

Table 2. The microorganisms isolated from the samples included in our study (N=100)

Microorganism	Number of isolates (%)
Non-inducible Enterobacteriaceae (n=72)	
Escherichia coli	33 (33.00%)
Klebsiella pneumoniae	39 (39.00%)
Inducible Enterobacteriaceae (n=2)	
Enterobacter aerogenes	2 (2.00%)
Non – fermenters (n=26)	
Acinetobacter baumanii	13 (13.00%)
Pseudomonas aeruginosa	13 (13.00%)

Table 3. Antimicrobial susceptibilities of the evaluated species (N=100)

Antibiotics	*Acinetobacter baumannii* (n=13)	*Enterobacter aerogenes* (n=2)	*Escherichia coli* (n=33)	*Klebsiella pneumoniae* (n=39)	*Pseudomonas aeruginosa* (n=13)	All isolates (N=100)
Doxycyline	7 (53.85%)	1 (50.0%)	18 (54.54%)	8 (20.51%)	1 (7.69%)	35 (35.0%)
Minocycline	0 (0.0%)	0 (0.0%)	4 (12.12%)	0 (0.0%)	1 (7.69%)	5 (5.0%)
Cefixime	3 (23.08%)	0 (0.0%)	9 (27.27%)	4 (10.26%)	1 (7.69%)	17 (17.0%)

Table 4. Comparative activity of Cefixime and Doxycycline against the microorganisms isolated from the samples included in our study (N = 100)

Microorganisms	Susceptible to both Doxycycline and Cefixime	Resistant to bothDoxycycline and Cefixime	Resistant to Cefixime and Sensitive to Doxycycline	Intermediate sensitive to Cefixime and Sensitive to Doxycycline	Intermediate sensitive to Doxycycline and Sensitive to Cefixime
***Klebsiella pneumoniae* (n=39)**	2(5.13%)	29 (74.36%)	4 (10.26%)	2 (5.13%)	2 (5.13%)
***Escherichia coli* (n=33)**	7 (21.21%)	10 (30.30%)	11 (33.33%)	0 (0.0%)	1 (3.03%)
***Pseudomonas aeruginosa* (n=13)**	0 (0.0%)	11 (84.62%)	1 (7.69%)	0 (0.0%)	1 (7.69%)
***Acinetobacter baumannii* (n=13)**	2 (15.38%)	4 (30.77%)	3 (23.07%)	2 (15.38%)	1 (7.69%)
***Enterobacter aerogenes* (n=2)**	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)