In-vitro activity of Cefotaxime in the Era of Antimicrobial Resistance

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Abstract- In the past, Cefotaxime inhibited greater than 90% of enteric bacilli at a minimum inhibitory concentrations of less than or equal to 0.5 microgram/ml. But with the emergence of ESBL (Extended Spectrum Beta Lactamase) producing bacteria the activity of cefotaxime became questionable. So the objective of this study was to see the in-vitro efficacy of cefotaxime against common clinical isolates in this hospital. 207 culture positive samples from different sources (urine, sputum, pus and blood) were processed. Isolation and identification of microorganism was done by standard microbiological procedure and antibiotic susceptibility testing was done by Kirby Bauer disc diffusion method, MIC was calculated by E-test strip (HiComb MIC Test) and interpreted following CLSI guidelines. The sensitivity of different isolates was found to be as follows: *Staphylococcus aureus* 66-70%, Enterobacteriaceae (ESBL non producers) 50-75%, Moraxella 91% whereas *Streptoococcus pneumoniae* and *Haemophilus influenzae* were 100% sensitive against cefotaxime. *Acinetobacter spp* however was 33-75% sensitive against cefotaxime. The MIC_{90} of all the isolates were within the sensitive range.

Index Terms- Antimicrobial sensitivity, Cefotaxime, ESBL, MIC

I. INTRODUCTION

Cefotaxime, a third-generation cephalosporin, has broad spectrum activity against Gram positive and Gram negative bacteria. Most anaerobes are highly susceptible to cefotaxime. It inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs). This inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell wall, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

The potent antimicrobial activity of cefotaxime appears to be the result of a combination of characteristics which include: beta-lactamase stability (types I, III, IV and V), good ability to pass through the cell membrane, strong affinity for lethal penicillin-binding proteins 1a, 1b(s), and 3, minimal limitation by the inoculum effect, and bactericidal action at or close to the inhibitory concentration (1). It can achieve its adequate level in plasma within 30 minutes following a single injection(2).

Cefotaxime cannot act against extended spectrum beta lactamase (ESBL) producers. An ESBL is a β-lactamase that may confer resistance or reduced susceptibility to the oxyimino-cephalosporins (i.e., cefotaxime, ceftriaxone, ceftazidime) and monobactams (i.e., aztreonam) (3). However, ESBLs do not hydrolyze the cephamycins (e.g., cefoxitin and cefotetan), (4) and the carbapenems (imipenem, meropenem) and their hydrolytic activity can be inhibited by several β-lactamase inhibitors such as clavulanic acid and tazobactam (5). However, they can become resistant to cephamycins by loss of outer membrane porin (4) But it can act effectively against ESBL non-producers (6). So our objective was to see the in-vitro activity of cefotaxime against common clinical isolates in this hospital.

II. MATERIAL AND METHODS

The study was conducted in the Department of Microbiology, Medical College, Kolkata from April 2013 to July 2013. 207 culture positive samples from different sources (urine, sputum, pus and blood) were processed. Isolation and identification was done by standard microbiological procedure and antibiotic susceptibility was done by Kirby Bauer disc diffusion method, MIC was calculated by E-test strip (HiComb MIC Test) and interpreted following CLSI (Clinical and Laboratory Standard Institute) guidelines.

ESBL detection was done by disc potentiation test (using cefotaxime/ cefotaxime clavulinic acid) and in-vitro effectiveness of cefotaxime was evaluated among ESBL non-producers.

III. RESULT

Among 69 urine isolates, 17 were E.coli, 13 Enterobacter spp., 12 Klebsiella spp, 10 Citrobacter spp., 10 S.aureus, 4 Proteus spp. and 3 Acinetobacter spp. Their sensitivity against cefotaxime were studied. 25% were ESBL producers.

Table1: Activity of cefotaxime against urinary isolates

Urinary isolates	ESBL producer	ESBL non producer	ESBL non-producer resistant	Susceptible	%sensitivity (among ESBL non-producer)
S.aureus (10)	-	-	-	7	70%
E.coli (17)	4	13	6	7	53.84%
Klebsiella spp. (12)	4	8	3	5	62.5%
Enterobacter (13)	4	9	3	6	66.67%
Citrobacter spp.(10)	2	8	4	4	50%
Proteus spp.(4)	0	4	2	2	50%
Acinetobacter (3)	-	-	-	1	33.33%

Among 72 sputum isolates, 26 were Klebsiella spp, 13 S.aureus, 12 Moraxella spp., 9 Enterobacter spp., 6 Pneumococcus spp., 4 Acinetobacter spp., and 2 H.influenzae . Their sensitivity against cefotaxime were studied. 20% were ESBL producers.

Table 2: Activity of cefotaxime against sputum isolates

Sputum isolates	ESBL producer	ESBL non producer	ESBL non producer resistant	Susceptible	%sensitivity (among ESBL non-producer)
S.aureus (13)	-	-	-	9	69.24%
Klebsiella spp. (26)	6	20	9	11	55%
Enterobacter (9)	1	8	2	6	75%
Moraxella (12)	-	-	-	11	91.66%
Pneumococcus (6)	-	-	-	6	100%
H.influenzae (2)	-	-	-	2	100%
Acinetobacter (4)	-	-	-	3	75%

Among 36 pus isolates, 11 Klebsiella spp, 9 S.aureus, 8 E.coli, 5 Proteus spp. and 3 Acinetobacter spp. were studied to see their sensitivity against cefotaxime. 29.16% were ESBL producers.

Table 3: Activity of cefotaxime against pus isolates

Pus isolates	ESBL producer	ESBL non producer	ESBL non-producer resistant	Susceptible	%sensitivity (among ESBL non-producer)
S.aureus (9)	-	-	-	6	66.66%
E.coli (8)	5	3	1	2	66.67%
Klebsiella spp. (11)	2	9	4	5	55.56%
Proteus spp. (5)	0	5	2	3	60%
Acinetobacter (3)	-	-	-	1	33.33%

Among 30 blood isolates, 10 E.coli, 10 S.aureus, 8 Klebsiella spp., and 2 Acinetobacter spp. were examined to see their sensitivity against cefotaxime. 38.89% were ESBL producers.

Table 4: Activity of cefotaxime againstus blood isolates

Blood isolates	ESBL producer	ESBL non producer	ESBL non-producer	Susceptible	%sensitivity (among ESBL non-producer)
S.aure (10)	-	-	-	7	70%
E.coli (10)	5	5	3	2	40%
Klebsiella spp. (8)	2	6	3	3	50%
Acinetobacter (2)	-	-	-	1	50%

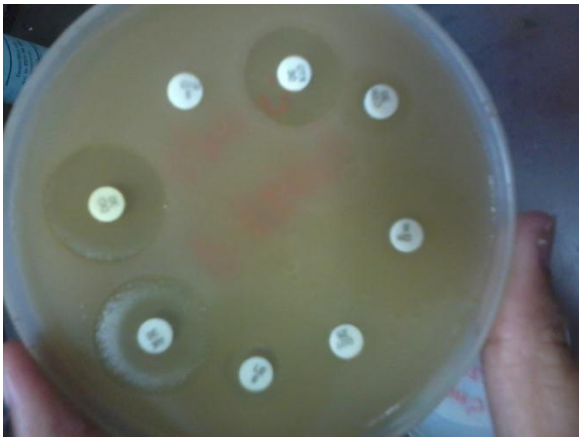

Figure 1: Showing the sensitivity of cefotaxime (arrow head) against clinical isolates

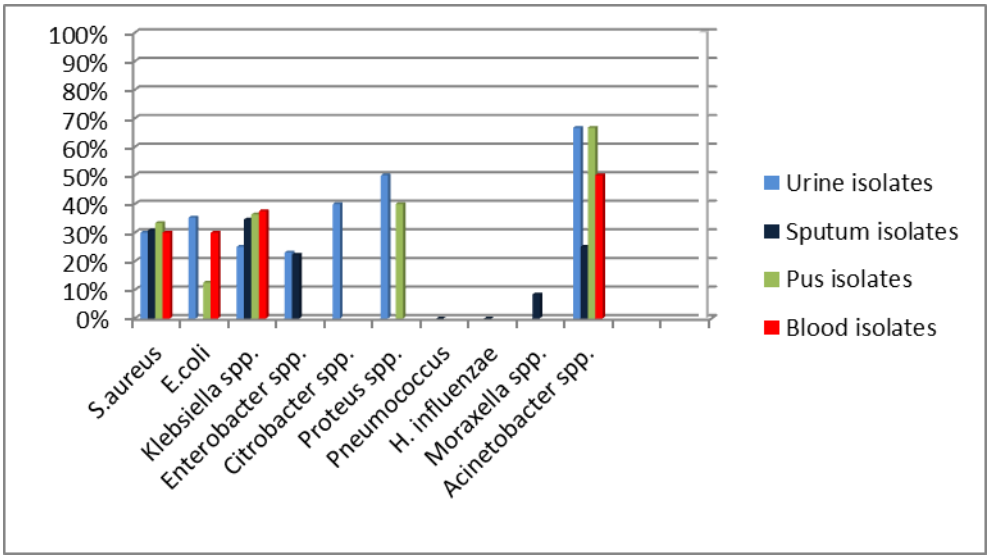

Figure 2: Overall resistance pattern of different isolates (ESBL non-producer) against cefotaxime

Table 5: MIC profile of common clinical isolates (ESBL non-producer) against cefotaxime

Clinical isolates	**MIC_{90}**
S.aureus	.512
E.coli	.512
Klebsiella spp.	1.024
Enterobacter spp.	.256
Citrobacter spp.	1.024
Proteus spp.	2
Pneumococcus	.032
H. influenzae	.064
Moraxella spp.	.128
Acinetobacter spp.	2.048

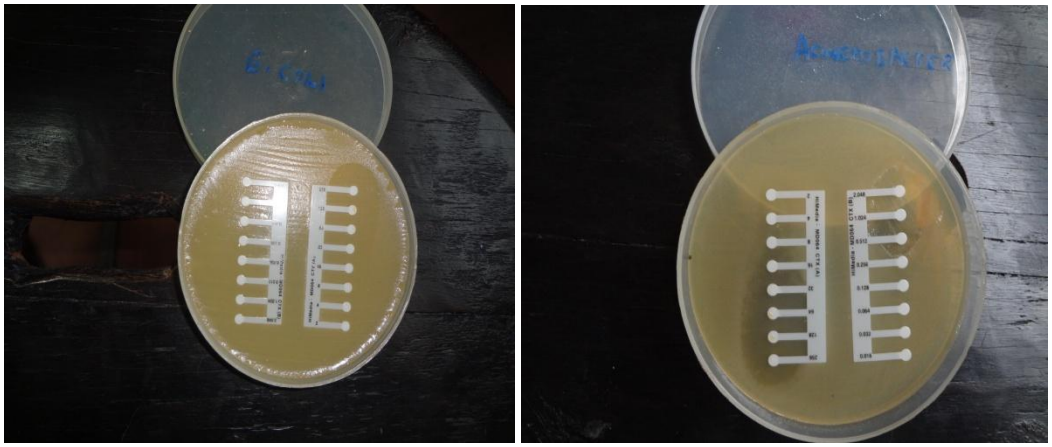

Figure 3: MIC of E.coli and Acinetobacter spp. against Cefotaxime

IV. DISCUSSION

Extensive use of antibiotics has led to increase in antibiotic resistance. (7) In the past, Cefotaxime inhibited greater than 90% of enteric bacilli at a minimum inhibitory concentrations of less than or equal to 0.5 microgram/ml; For staphylococci and nonenterococcal streptococci, the mean values for the minimal inhibitory concentration50 (MIC50) of cefotaxime (i.e., the lowest concentration inhibiting growth of 50% of tested strains) were 1.1-1.9 microgram/ml and 0.01-0.05 microgram/ml, respectively. (8) But in present scenario the emergence of ESBLs has changed the picture. Cefotaxime cannot act against ESBL producers. But it is still showing a very good sensitivity against ESBL non-producers. In this study the sensitivity of *Staphylococcus aureus* was 66-70%, Enterobacteriaceae (ESBL non producers) was 50-88%, *Moraxella spp* was 91% whereas *Streptococcus pneumoniae* and *Haemophilus influenzae* were 100% sensitive against cefotaxime. *Acinetobacter spp* however was 33-75% sensitive against cefotaxime. Similar result was seen in one study (8) where cefotaxime was shown to be moderately active against *Acinetobacter calcoaceticus subspecies anitratus.*

The presence of isolates that are less susceptible to cefotaxime could potentially result from the use of cefotaxime once or twice daily as opposed to adequate dosage of three times a day. (9)(10)(11) A study showed that even in E.coli causing UTI in children the cefotaxime susceptibility was 49% (12) which indicates that cefotaxime is fairly susceptible in non ESBL producers. Another study by Ortega et al showed that only 12% of Klebsiella spp. isolated from blood were resistant to cefotaxime. (13)

According to MIC interpretative criteria, in this study, the MIC_{90} of all the isolates were within the sensitive range. Cefotaxime is active against *Streptococcus pneumoniae*, *H.influenzae*, *Moraxella spp*. and have MIC ≤ 0.5 in 99% culture for all three organisms. (14) The same is shown in our study and hence cefotaxime is a good drug for respiratory pathogens.

Cefotaxime was found to be inactive against *Streptococcus faecalis* and most other serogroup D streptococci. In one study by G. Peters et al the in- vitro activity of cefotaxime (HR 756) was tested in comparison with cefuroxime, cefamandole, cefoxitin, cefazolin, ampicillin, mezlocillin, gentamicin and amikacin and MIC values were investigated on 168 freshly isolated gram-positive and gram-negative bacteria from clinical sources. They found Enterococci and *Pseudomonas aeruginosa* behaved cefotaxime-resistant and all the other species examined showed a very good sensitivity range against cefotaxime. (15) Because the activity of cefotaxime against Enterobacteriaceae and nonfermentative gram-negative bacilli varied, the in vitro susceptibility testing must be used as a guide to therapy.

V. CONCLUSION

According to sensitivity pattern of different clinical isolates by MIC profile as well as by disk diffusion antimicrobial susceptibility testing, the in-vitro activity of Cefotaxime was found to be very good against Streptococcus pneumoniae, H.influenzae, Moraxella spp., Stapylococcus aureus and Enterobacteriaceae (ESBL non-producer). However, it was moderately active against Acinetobacter spp.

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