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ASSOCIATION OF CEFTRIAXONE RESISTANCE WITH CLINICAL OUTCOMES AMONG CRITICALLY ILL PATIENTS ADMITTED WITH BACTERIAL INFECTIONS

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ABSTRACT: Background: The rise in antibiotic resistance has rendered many antibiotics less effective, making it increasingly challenging to treat infections. **Objectives:** The objectives of this study were to determine the association between ceftriaxone resistance and in-hospital mortality and length of hospital stay among critically ill patients with bacterial infections and to analyze ceftriaxone resistance patterns among patients with bacterial infections. **Methods:** A written informed consent was taken from participants who fulfilled inclusion criteria and were willing to participate. Demographic profile and clinical characteristics of participants were documented. **Results:** The duration of hospital stay in ceftriaxone sensitive group and ceftriaxone resistant groups was represented as mean \pm SD (in days), in ceftriaxone sensitive group it was 9.73 ± 3.66 days and in ceftriaxone resistant group it was 16.00 ± 11.06 days. The patients in the ceftriaxone resistant group had a longer hospital stay. On comparing the clinical outcome between the two groups the survival rate was better in ceftriaxone sensitive group. **Conclusion:** The clinical outcome and duration of hospital stay between the ceftriaxone sensitive group and ceftriaxone resistant group was statistically significant and this indicated that the patients in the ceftriaxone sensitive group had a shorter hospital stay and better clinical outcome than ceftriaxone resistant group.

INTRODUCTION: Antimicrobial resistance (AMR) poses a significant global public health challenge in this century. The swift rise of resistant bacteria around the world has rendered previously effective antibiotics ineffective¹. Due to drug resistance, antibiotics and other antimicrobial treatments lose their effectiveness, making infections harder or even impossible to treat. This situation heightens the risk of disease transmission, severe health complications, disability, and death, ultimately requiring higher doses of antimicrobial drugs and extended hospital stays².

This places a substantial financial and clinical burden on patients, their families and world health care system thus an organized efforts are needed to implement new policies, and steps to manage this crisis³. Antibiotic resistance crisis is mainly linked to misuse and overuse of antibiotics and pharmaceutical industry's failure to develop new antibiotics due to stringent regulatory requirements and diminished economic incentives⁴.

Infections caused by gram-negative and gram-positive bacteria can be treated using cephalosporins. Meningitis, pneumonia, soft tissue infections, skin infections, and various diseases have all been successfully treated by the five generations of cephalosporins⁵. Third-generation cephalosporins, such as cefotaxime, ceftazidime, cefdinir, ceftriaxone, cefpodoxime, cefoperazone, and cefixime, are effective against both gram-positive and extended gram-negative bacteria⁶.

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Mainly ceftriaxone and cefotaxime when administered intravenously can cross blood brain barrier (BBB) and target the bacteria in the CSF⁷. Bactericidal activity of ceftriaxone results from inhibiting the bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs) and it has a very long half-life compared to other cephalosporins⁹. Ceftriaxone has a relative safe adverse effect profile and good effectiveness against multi-drug resistant Enterobacteriaceae. Usually, beta-lactamase hydrolysis, changed PBPs, or decreased bacterial cell permeability result in resistance to ceftriaxone⁸. Bacteria producing extended-spectrum beta-lactamase (ESBL)¹⁰ has beta-lactamase enzyme, allowing them to resist a wide range of penicillin and cephalosporin antibiotics¹⁰. Bacteria that are resistant to ceftriaxone has been highlighted by WHO as pathogens of major importance, particularly in areas where ceftriaxone is widely used empirically for treatment of severe infections¹¹. In India ceftriaxone is the antibiotic of choice as empirical treatment in patients admitted to a tertiary care hospital. Thus, this study focused on analyzing ceftriaxone resistance with clinical outcomes and its effect on patients in a tertiary care center.

Objectives:

Primary Objective: To determine the association between resistance to ceftriaxone and in hospital mortality as well as length of hospital stay among critically ill patients with bacterial infections

Secondary Objective: To analyze ceftriaxone resistance patterns among patients with bacterial infections.

METHODOLOGY:

Study Design: Prospective Cohort study

Study Period: May 2023 - December 2024

Study Setting: M S Ramaiah Medical College and Hospitals

Study Population: Critically ill patients with bacterial infections who showed positivity on performing a culture sensitivity test and who were on ceftriaxone admitted to the ICU

Ethics Committee Approval: This study was approved by the Ethics Committee, M S Ramaiah

Medical College, Bangalore, Karnataka (MSRMC/EC/PG-02/04-2023).

Inclusion Criteria:

1. Male and Female patients of age 18 years and above admitted to the ICU with bacterial infections and culture sensitivity report at M S Ramaiah Medical College and Hospital
2. Patients who gave written informed consent

Exclusion Criteria:

1. Patients with skin and local mucosal infections
2. Patients with commensal growth.

Method of Data Collection: Eligible patients were identified and informed consent was obtained. If the patients were not able to give an informed consent due to their illness, informed consent was taken from their attenders. The study objectives and processes were explained to the patient's/patient's attenders in their own language to obtain informed consent.

All relevant data including the demographic profile, pre-existing diseases, drugs received by the patient, their dosage, duration of disease and culture sensitivity report was collected and analyzed. Patients were divided into two groups based on their sensitivity or resistance to ceftriaxone. The groups were evaluated for their clinical outcomes (survival/mortality) and length of hospital stay. Patients were evaluated at the start of the admission until their discharge from the hospital.

Sample Size Estimation: From a prospective cohort study conducted by Rebecca et al. it was observed that the mortality among resistant and sensitive group to ceftriaxone was 45% and 36% respectively¹³.

In the present study expecting to get similar results with 80% power, 95% confidence level and minimum detectable difference between the 2 groups as 18%, the study required a minimum of 45 subjects in each group.

Statistical Methods: IBM SPSS version 29.0 was used for data analysis, the study employed

descriptive methods to analyze qualitative variables, such as age, gender, organisms isolated, culture sensitivity, mortality and morbidity in terms of frequencies and percentages. Quantitative variables like length of hospital stay in terms of days were summarized in terms of mean days \pm

standard deviation. Chi square test was used to compare proportion of mortality & morbidity between the two groups. Independent t-test was used to compare the length of hospital stay between the two groups.

RESULTS:

TABLE 1: AGE DISTRIBUTION

Age group (years)	Ceftriaxone sensitive group (n-45)	Ceftriaxone resistant group (n-45)	P-value
19-28	7	2	0.8239
29-38	4	1	
39-48	9	6	
49-58	5	14	
59-68	9	16	
69-78	11	3	
79-88	0	3	
Age (Mean \pm SD)	54.46 \pm 16.64	55.24 \pm 14.46	

The age distribution between the groups were comparable.

TABLE 2: GENDER DISTRIBUTION

Gender	Ceftriaxone sensitive group (n-45)		Ceftriaxone resistant group (n-45)		P-value
	Number	Percentage	Number	Percentage	
Male	29	64.44	30	66.66	0.8244
Female	16	35.56	15	33.34	

The gender distribution between the groups were comparable.

TABLE 3: DISTRIBUTION OF ORGANISMS ISOLATED FROM CULTURE SENSITIVITY

Organisms	Ceftriaxone Sensitive Group	Ceftriaxone Resistant Group	Total	Percentage
<i>Escherichia coli</i>	8	14	22	24.4
<i>Klebsiella pneumonia</i>	9	12	21	23.3
<i>Acinetobacter baumannii</i>	4	8	12	13.3
<i>Proteus species</i>	4	5	9	10
<i>Pseudomonas aeruginosa</i>	7	2	9	10
<i>Enterobacter cloacae</i> Complex	6	1	7	7.8
Coagulase Negative Staphylococci	1	1	2	2.2
<i>Enterococcus faecium</i>	1	1	2	2.2
<i>Streptococcus</i>	1	0	1	1.1
<i>Serratia marcescens</i>	1	0	1	1.1
Non Fermenting Gram Negative Bacilli	1	0	1	1.1
Methicillin susceptible <i>S. aureus</i>	0	1	1	1.1
<i>Salmonella species</i>	1	0	1	1.1
<i>Providencia stuart</i>	1	0	1	1.1
Total Organisms	45	45	90	100

TABLE 4: DISTRIBUTION OF OVERALL BACTERIAL SENSITIVITY/RESISTANCE TO CEFTRIAZONE

Organisms	Total Isolated	Sensitive	Sensitive Percentage	Resistance	Resistance Percentage
<i>Escherichia coli</i>	22	8	36.36	14	63.64
<i>Klebsiella pneumonia</i>	21	9	42.85	12	57.15
<i>Acinetobacter baumannii</i>	12	4	33.33	8	66.67
<i>Proteus species</i>	9	5	55.6	4	44.4
<i>Pseudomonas aeruginosa</i>	9	7	77.8	2	22.2
<i>Enterobacter cloacae</i> complex	7	6	85.7	1	14.3
<i>Enterococcus faecium</i>	2	1	50	1	50
Coagulase negative Staphylococci	2	2	100	0	0

<i>Streptococcus</i>	1	1	100	0	0
<i>Salmonella</i> species	1	0	0	1	100
Non fermenting gram negative bacilli	1	1	100	0	0
<i>Serratia marcescens</i>	1	1	100	0	0
methicillin susceptible <i>S. aureus</i>	1	0	0	1	100
<i>Providencia stuart</i>	1	0	0	1	100

TABLE 5: COMPARISON OF CLINICAL OUTCOME (SURVIVED / DIED)

Culture Report	Ceftriaxone Sensitive Group (N=45)	Ceftriaxone Resistance Group (N=45)	P- value
Survived	42	30	0.001565
Died	3	15	

Note - The two tailed p-value is 0.001565 and this difference is statistically significant. Patients in the ceftriaxone sensitive group had a statistically significant survival rate than those in the ceftriaxone resistant group.

TABLE 6: COMPARISON OF DURATION OF HOSPITAL STAY (IN DAYS) AMONG THE TWO GROUPS

Group	Ceftriaxone Sensitive Group (N=45)	Ceftriaxone Resistance Group (N=45)	P- value
Mean \pm SD	9.73 \pm 3.66	16.00 \pm 11.06	0.0005
SEM	0.55	1.65	

Note - The two tailed p-value is 0.0005 and this difference is statistically significant. Patients in the ceftriaxone sensitive group had a shorter duration of stay compared to the ceftriaxone resistant group which was statistically significant.

DISCUSSION: A total of 90 patients were screened and included in the study after obtaining written informed consent with 45 patients in ceftriaxone sensitive group and 45 patients in ceftriaxone resistant group. The majority of the participants were older adults, particularly those between the ages of 61 and 80 years **Table 1**.

In a study done by Litegebew *et al.* Ceftriaxone resistance among patients at GAMBY teaching general hospital, the highest prevalence of microbial isolates (52.9%) was observed in the age groups of 15–44 years which was different to the age group distribution as seen in our study. In a study done by Litegebew *et al.* female participants were more in number as compared to male participants but in our study male subjects were more in number compared to female subjects. The main focus of our present study was to evaluate the duration of hospital stay in ceftriaxone sensitive group and ceftriaxone resistant group. The mean \pm SD duration of hospital stay (in days) in ceftriaxone sensitive group was 9.73 \pm 3.66 and in ceftriaxone resistant groups was 16.00 \pm 11.06 and the p value was 0.0005 between the two groups which was statistically significant. On comparing the clinical outcomes between the two groups, in the ceftriaxone sensitive group out of 45 patients, 42 survived and in ceftriaxone resistant group out of 45 patients, 30 survived. The p-value between the two groups was 0.001565 which was statistically significant. This result was similar to the findings as seen in the study done by Rebecca *et al.*¹³ which

showed that patients that were resistant to third-generation cephalosporins had increased risk of death and longer hospital stays than patients that were sensitive to third generation cephalosporins **Table 5 & 6**.

Of the collected clinical samples in the present study, the most common samples collected were blood 21 (23.3%), tissue 17 (18.9%) and sputum 11 (12.2%) and other samples that were included in the present study were wound, urine, pus, stool, ascitic fluid, ET secretions, CSF and pleural fluid. Totally from 90 clinical samples 14 types of bacteria were identified. Of this *E. coli* 22 (24.4%), *K. pneumonia* 21 (23.3%), *A. baumannii* 12 (13.3%), and *Proteus* species 9 (10%) were the predominant bacteria isolated respectively **Table 3**. These isolates of organisms were somewhat similar to the study findings as done by Litegebew *et al.*¹² which showed *E. coli* isolates at 114 (28.4%) but the study findings of *E. coli* isolates in Southern Ethiopia was higher and indicated *E. coli* isolates at (42.9%). The observed mortality in our study in the ceftriaxone resistance group was in line with other studies conducted elsewhere in the world. Early recognition of bacterial infections and rapid isolation of organism with its resistance / sensitivity pattern and optimized antibiotic usage strategies along with steps to control antimicrobial resistance will be required to improve outcomes for patients with bacterial infections in a tertiary care center.

CONCLUSION: Ceftriaxone resistance has emerged as a significant global health concern, particularly due to its impact on the treatment of bacterial infections. The rise in resistance is largely driven by the overuse and misuse of antibiotics, inadequate infection control measures, and the horizontal transfer of resistance genes among bacterial populations. Continued research into novel antimicrobial agents, combination therapies, and rapid diagnostic techniques are essential to combat this growing threat of antimicrobial resistance.

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CONFLICT OF INTEREST: None

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