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STUDY TO EVALUATE THE MINIMUM INHIBITORY CONCENTRATION TRENDS OF CEFTRIAXONE AND CIPROFLOXACIN IN BLOOD CULTURE OF PEDIATRIC PATIENTS SUFFERING FROM TYPHOID FEVER IN MAX SUPER SPECIALTY HOSPITAL, PATPARGANJ, NEW DELHI - A RETROSPECTIVE STUDY

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Abstract:
Enteric fever caused by Salmonella enterica continues to be a major public health problem worldwide. In the last decade, ceftriaxone and ciprofloxacin have become the drugs of choice for treating enteric fever caused bySalmonella enteric serovar typhi. A retrospective study to understand the prevalence and evolving the minimum inhibitory concentration trends of ceftriaxone and ciprofloxacin . A total of 100 blood samples were collected from patients attending inpatient and outpatient departments of of pediatric patients suffering from typhoid fever at MSSH, Delhi from May 2012 to December 2013.Since enteric fever is endemic in India, accurate drug susceptibility surveillance is crucial to ensure empiric management of enteric fever is appropriate. This retrospective study aimed to evaluate the minimum inhibitory concentration trends of ceftriaxone and ciprofloxacin in blood culture of pediatric patients suffering from Typhid fever in Max Super Specialty Hospital, New Delhi, India

Keywords-*Typhoid fever, ciprofloxacin, pediatric patients, retrospective study.*

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1. INTRODUCTION:

Typhoid fever is a commonly encountered systemic disease caused by the gram-negative bacteria Salmonella enteric serovar typhi[1]. For the developing countries of the tropics and subtropics it continues to be big public health problems as the sanitation and public health standards are poor[2]. It is an endemic in the south East Asian countries[3,4]. It is an infectious feverish disease caused by the bacterium Salmonella typhi (*Salmonella enterica* Serovar Typhi) and less commonly by *Salmonella paratyphi*. Acute generalized infection of the reticuloendothelial system, intestinal lymphoid tissue, and the gall bladder[5, 6]. The infection always comes from another human, either an ill person or a healthy carrier of the bacterium. The bacterium is passed on with water and foods and can withstand both drying and refrigeration[7]. Typhoid and paratyphoid fever continue to be important causes of illness and death, particularly among children and adolescents in south-central and Southeast Asia, where enteric fever is associated with poor sanitation and unsafe food and water[8]. High-quality incidence data from Asia are underpinning efforts to expand access to typhoid vaccines. Efforts are underway to develop vaccines that are immunogenic in infants after a single dose and that can be produced locally in countries of endemicity[9, 10]. The growing importance of *Salmonella enterica* serotype Paratyphi A in Asia is concerning. Antimicrobial resistance has sequentially emerged to traditional first-line drugs, fluoroquinolones, and third-generation cephalosporins, posing patient treatment challenges[11]. Typhoid fever, a common worldwide bacterial disease, which is spread through contaminated food and water that causes liver inflammation. Typhoid fever is an infection that causes clinical symptoms of fever, abdominal pain, body rashes, terry stool, weakness, poor appetite, headaches, generalized aches and pains and lethargy etc. It is caused by Salmonellae typhi, under Enterobacteriaceae family, is a Gram negative motile bacteria[12, 13]. *S.* Typhi or *S.* Paratyphi A infect human and cause typhoid and paratyphoid fever, respectively. The incubation period of the disease is usually 10-14 days and varies considerably from 8-15 days, but may be as short as 5 days and as long as 30 or 35 days depending upon the inoculums size and the state of host defenses. Occurrence of the disease has to be confirmed by the presence of the pathogen either *S.* Typhi or *S.* Paratyphi in patient, which requires isolation of the bacteria from blood, stool or bone marrow. The sensitivity of the test decreases with increased duration of fever[14]. In 2000, it was estimated that over 2.16 million episodes of typhoid fever occurred worldwide, resulting in 216000 deaths and that more than 90% of this morbidity and mortality occurred in Asia. The prevalence of severe typhoid fever caused by multi-drug-resistant strains of Salmonella typhi has recently increased in Calcutta[15].

2.Investigation plan:

2.1 Study Title

Study to evaluate the minimum inhibitory concentration trends of ceftriaxone and ciprofloxacin in blood culture of pediatric patients suffering from typhoid fever in Max Super Specialty Hospital, Patparganj, New Delhi - a Retrospective Study

2.2 Study Site

This study was carried out in Max Super Specialty Hospital, Patparganj, and New Delhi.Max Healthcare model visualizes setting up of a world-class healthcare model offering the best medical assistance delivered seamlessly through state-of-the-art medical facilities.

2.3 Objectives

To evaluate the MICs trends of ceftriaxone and ciprofloxacin in blood culture of pediatric patients suffering from typhoid fever at Max Super Specialty Hospital, Patparganj.

2.4 Study Design

This is Retrospective observational study on pediatric patients suffering from typhoid fever and who were treated in Max Super Specialty hospital, Patparganj between years May 2012 to December 2013.

2.5 Study Method

A retrospective analysis of the case records of the patients admitted to ICUs and wards during a time period were noted and taken for analysis. An analysis of this data was done so as to evaluate the minimum inhibitory concentration trends of ceftriaxone and ciprofloxacin in blood culture of pediatric patients suffering from typhoid fever.

All patients who satisfied the inclusion criteria were included in the study. In total 100 patients being treated with antibiotics were included in the study.

2.5.1 Study criteria

Inclusion criteria: -

Patients eligible for the study include:

- Patients of typhoid fever
- Patients not above 15 years
- Patients who were culture positive for Salmonella typhi

Exclusion criteria:-

- Patients who cannot be included in the study:
- Patients above 15 years of age

2.5.2 Duration of study- from May 2012 to December 2013

2.5.3 Sample size- 100 patients

2.5.4 Sources of data

- Physician's Prescribing Records

- Patient's Medical Records
- Patient's Discharge Summary
- Lab Reports of patients
- Hospital Information System's Software

2.6 Data Elements

The following details were entered:

- The age and sex distribution of the patients were noted.
- The diagnosis recorded in discharge summary was noted.
- MIC of Ceftriaxone and Ciprofloxacin were noted.
- Culture and Sensitivity reports were studied.
- Continuous follow-up of patients was done up to discharge.

2.7 Culture and sensitivity testing:

When a patient is having an infection of any kind or is suspected to have an infection, its critical to know which antibiotic is effective against the particular pathogen (i.e. disease causing agent) causing the problem? This means that **(1)** the species of bacteria must be identified and **(2)** the drug most effective at inhibiting their growth must be determined. The only reliable way this can be done is a culture and sensitivity test.

3. Methodology:

Culture and sensitivity tests are carried out at microbiology lab in Max Hospital by lab technician (Microbiologists) by using fully automated microbiology system by BD Phoenix.

The culture and sensitivity testing include following steps:

1. Inoculation and streaking of culture on blood agar plates and Mc- Conkey agar plates.
2. Incubation of agar plates at 37ºC for 18-24 hrs.
3. Identification of gram positive and gram negative bacterial colonies by gram staining method.
4. Identification (ID) and Antibiotic sensitivity testing (AST) are done for isolated colonies using BD Phoenix Automated Microbiology System.
5. Results for identification of bacteria, antibiotic sensitivity test and minimum inhibitory concentration are generated automatically.

3.1 BD Phoenix Automated Microbiology System:

The BD Phoenix Automated Microbiology System is designed to perform identification and susceptibility testing of clinically relevant bacteria. The instrument is intended for the *in vitro* rapid identification (ID) and quantitative determination of antimicrobial susceptibility by minimum inhibitory concentration (MIC)The system incorporates state of the art optical measuring technology, Multi-parameter Determination identification technology, and the AST Advantage System to produce consistently rapid, accurate and reproducible results. Work flow of this system includes following steps:

3.2 Prepare ID Broth:

- Add microorganism to ID Broth.
- Vortex the tube for 5 second.
- Make 0.50-0.60 McFarland (standard inoculums) or 0.20-0.30 McFarland (Low inoculums). BD Phoenix Spec Nephelometer is used to confirm density.

3.3 Prepare AST Broth:

- Add one free falling drop of AST indicator into AST broth.
- Add 25µL prepared ID Broth (Standard inoculums) or 50 µL prepared ID Broth (Low Inoculums).

3.4Selection and inoculation of Panel:

Isolates must be tested with a gram stain test to assure the appropriate selection of Phoenix panel type. Once the Gram stain reaction is confirmed, select the appropriate Phoenix panel for inoculation (e.g. PMIC/ID panel for use with Gram Positive organism and NMIC/ID panel for use with Gram Negative organism)

A panel is a sealed and self-inoculating molded polystyrene tray, with 136 micro-wells containing dried reagent.

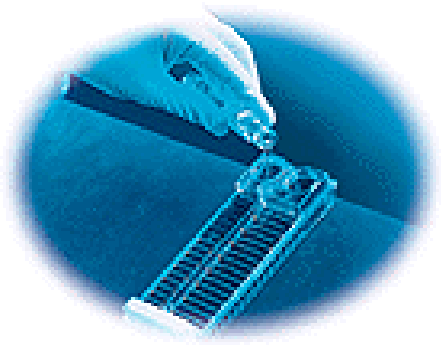

Figure 3.4 Phoenix panel

- The combination panel includes an ID side with dried substrate for bacterial identification, an AST side with varying concentration of antimicrobial agents, and growth and fluorescent controls at appropriate well locations.
- Pour the ID tube inoculums into the fill port on the ID side of the panel (51-well side) and AST tube

inoculums into the fill port in the AST side of the panel (85-well side).

- Inoculate panel with prepared ID Broth within (≤) 60 Minutes.
- Inoculate panel with prepared AST Broth within (≤) 30 Minutes.

3.5 After panel inoculation, place closure securely on the panel to seal: Before placing closure, check for residual droplets of inoculums on the edges of the fill port. If a droplet is present, remove the droplet with absorbent material.

3.6 Load panel into BD Phoenix instrument: Panel must be loaded into the instrument within 30 minutes of inoculation.

4. **Results:** Organism identification will appear on Phoenix Report Form with a probability percentage from the Phoenix database based on the substrate reaction profile. The MIC result and Interpretive Categorical Result will be shown for the appropriate organism/antimicrobial agent combination.

We report here the result of the study titled "to evaluate the minimum inhibitory concentration (MICs) trends of ceftriaxone and ciprofloxacin in blood culture of pediatric patient suffering from typhoid fever in Max Super Specialty Hospital, Patparganj, and New Delhi – A Retrospective Study."This was a retrospective study carried out in the ICU and wards of Max Super Specialty Hospital, patparganj, New Delhi. The data for a period of six months was collected and analyzed for obtaining these results and deriving conclusion from it.

Typhoid fever is a common worldwide bacterial disease, which is spread through contaminated food and water. Typhoid fever is an infection that causes clinical symptoms of fever, abdominal pain, body rashes, tarry stool, weakness, poor appetite, headaches, generalizes aches and pains and lethargy etc. It is caused by salmonella typhi and paratyphi; Enterobacteria under Enterobacteriaceae family, Gram negative motile bacteria. A total of 100 blood culture positive Salmonella enterica isolates were recovered over the span of one year and seven months. Of these, 91 isolates were identified as Salmonella typhi, and 9 were Salmonella paratyphi 'A'. In case of Salmonella typhi the majority of the positive samples were from males (56/91) [Table-4.1(a)] and in case of Salmonella paratyphi 'A' the majority of the positive samples were from male (6/9)) [Table-4.1(b)] and most of the positive cases belonged to age group of 1-5 years for Salmonella typhi[Table-4.2(a)] and for Salmonella paratyphi 'A' positive cases belonged to age group of 10-15 years [Table-4.2(b)].

The antibiotic susceptibility pattern of Salmonella typhi and Salmonella paratyphi 'A' against various antibiotics is shown in Table- 4.3[b,c,d,e]. Salmonella typhi was found to be most sensitive to ceftriaxone (100.0%), followed by ciprofloxacin (87.50%). Salmonella paratyphi 'A' also was found to be most sensitive to ceftriaxone (100.0%), followed by ciprofloxacin (100.0%). Salmonella typhi was found to be 35.30% resistant to ciprofloxacin from Jan 2013 to April 2013 followed by 24.00% for ciprofloxacin from May 2013 to August 2013. No resistant to ceftriaxone for Salmonella typhi from May 2012 to December 2013. And Salmonella paratyphi A was found to be resistant to ceftriaxone (100.0%) from May 2013 to August 2013, and there is no resistant to ciprofloxacin from May 2012 to December 2013 and intermediate resistant to ciprofloxacin (33.33%) for Salmonella paratyphi 'A' from Jan 2013 to April 2013.

4.1Demographic details:

(a) The following table 4.1 gives the sex wise distribution of the patients in case of Salmonella typhi from May 2012 to December 2013 included in the study:-

Sex wise distribution of the patients in case of salmonella typhi, (n= 91)

Sex	No. of patients	percentage
Male	56	61.53%
Female	32	35.16%

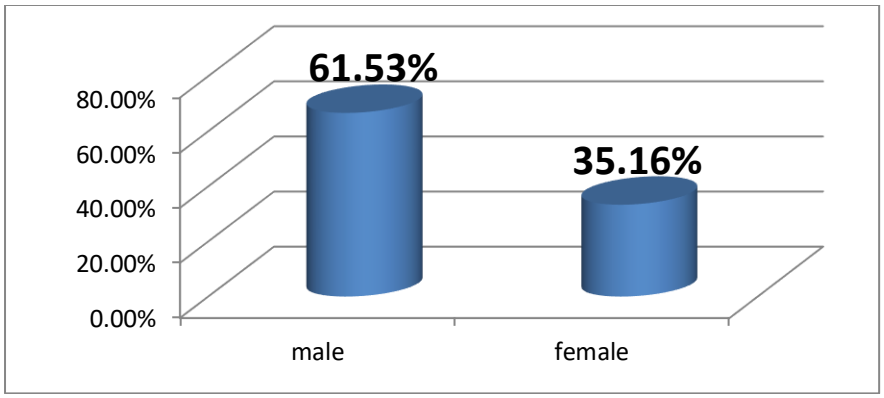

Figure 4.1 (a) Sex wise distribution of patients for S. typhi

The study includes more male patients as compared to female patient. A total of 61.53 % patients were male while 35.16 patients were female in case of salmonella typhi from May 2012 to December 2013.

(b) The following table 4.1 gives the sex wise distribution of the patients in case of Salmonella paratyphi A from May 2012 to December 2013 included in the study:-

Sex wise distribution of the patients in case of salmonella paratyphiA , (n=9)		
Sex	**No. of patients**	**percentage**
Male	6	66.66%
Female	3	33.33%

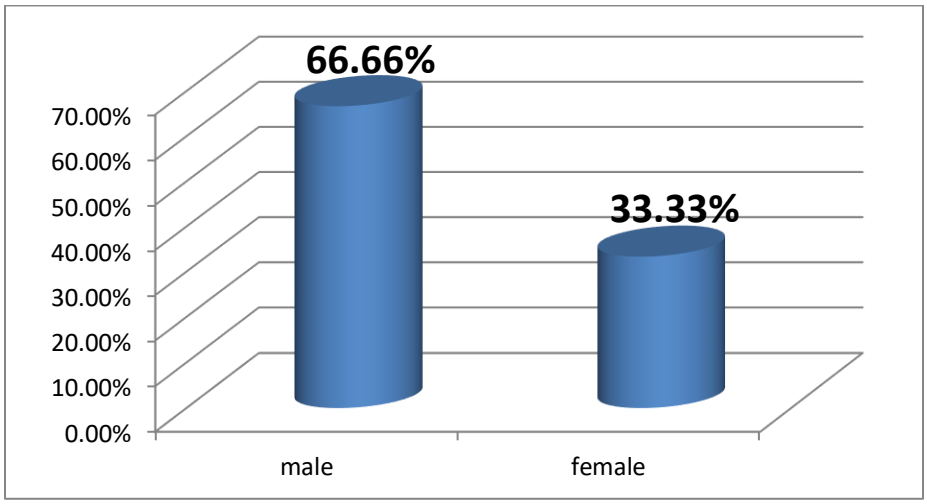

Figure 4.1 (b)Sex wise distributions of patients for S. paratyphi A

The study includes more male patients as compared to female patient. A total of 66.66 % patients were male while 33.33 patients were female in case of salmonella paratyphi A from May 2012 to December 2013.

4.2:-Demographic details:

The following **table 4.2** gives the age wise distribution of the patients in case of salmonella typhi from May 2012 to December 2013 included in the study:

Age wise distribution of the patients in case of salmonella typhi, (n= 91)		
Age group (in yrs)	**No. of patients**	**percentage**
1-5	39	42.85%
5-10	27	29.67%
10-15	25	27.47%

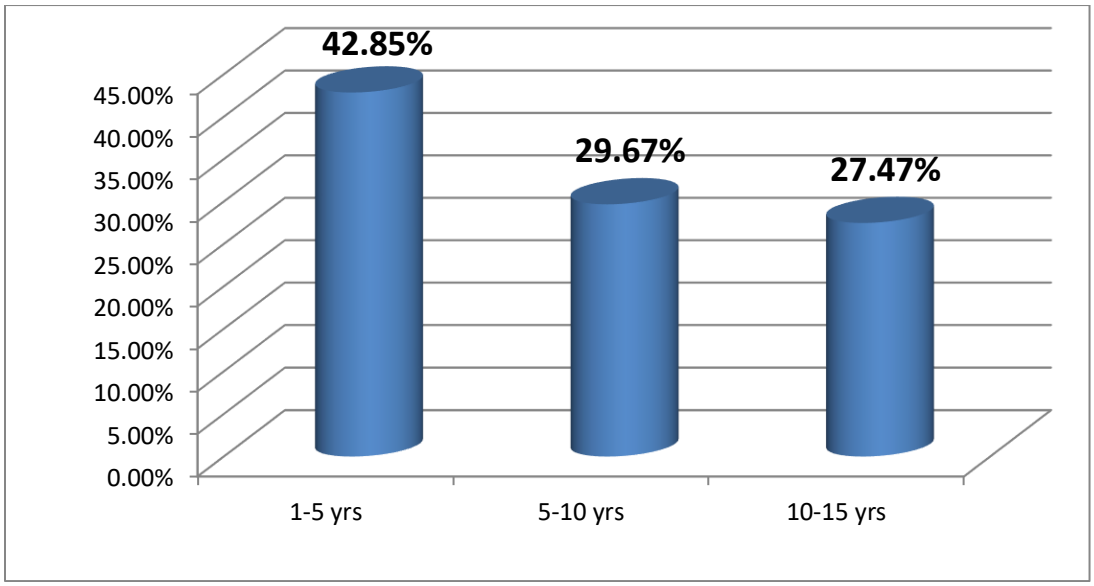

Figure 4.2 (a) Age wise distributions of patients for S. typhi

For the salmonella typhi the maximum numbers of patients belongs to the age group of 1 to 5 years which is 42.85% of total population followed by age group of 5 to 10 years which is 29.67% of total population.

(a) The following **table 4.2** gives the age wise distribution of the patients in case of salmonella paratyphi A from May 2012 to December 2013 included in the study:

Age wise distribution of the patients in case of S. paratyphi A, (n= 9)		
Age group (in yrs)	**No. of patients**	**percentage**
1-5	2	22.22%
5-10	3	33.33%
10-15	4	44.44%

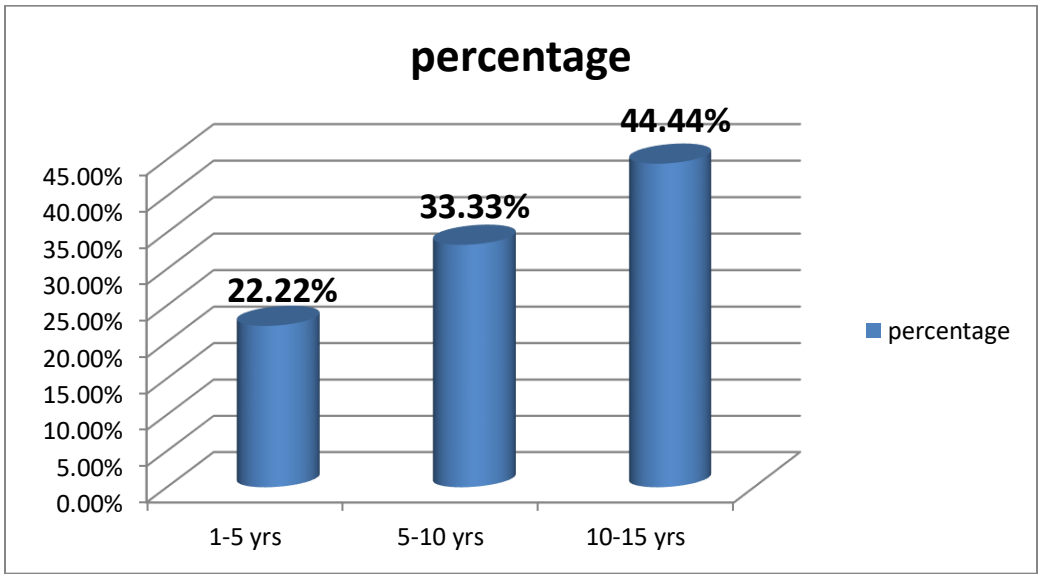

Figure 4.2 (b) Age wise distributions of patients for S. paratyphi A

For the salmonella paratyphi A, the maximum numbers of patients belongs to the age group of 10 to 15 years which is 44.44 % of total population followed by age group of 5 to 10 years which is 33.33% of total population.

4.3:-Microbiological reports:-

(a) The following table shows organism wise distribution of the patients for typhoid fever from May 2012 to December 2013 included in the study:

Distribution of isolated organism for typhoid fever, (n=100)		
Organism	**No. of samples**	**percentage**
Salmonella typhi	91	91%
Salmonella peratyphi A	9	9%

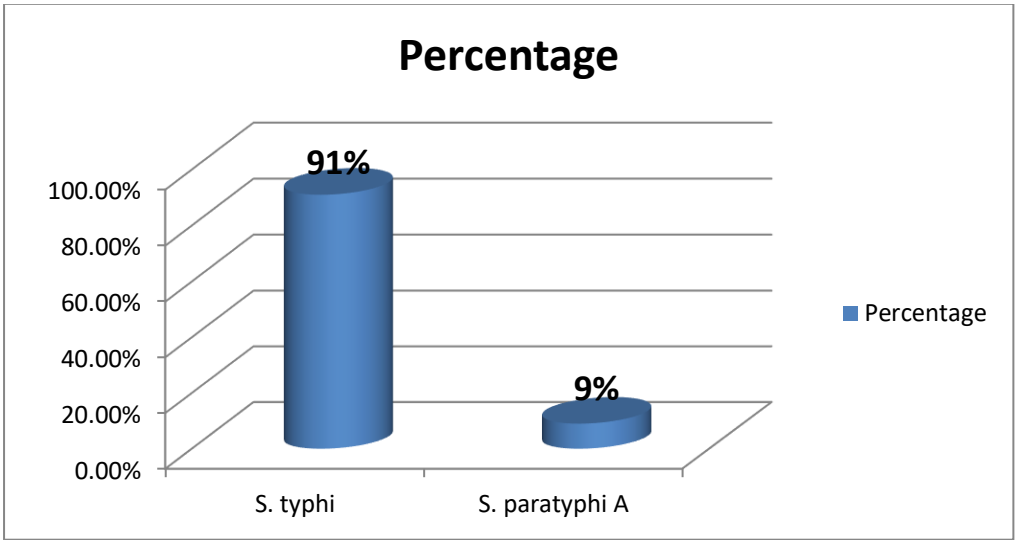

Figure 4.3 (a) Distribution of isolated organism for typhoid fever

A total of 100 isolates of Salmonella causing typhoid fever were included in the study. Most commonly isolated culture showed the presence of Salmonella typhi (91.00%) and S. paratyphi A (9.00%). The study includes maximum cases of S. typhi as compared to S. paratyphi A in typhoid fever from May 2012 to December 2013.

4.3 (b): The following table showsmonth wise antimicrobial susceptibility pattern of Ceftriaxone for the Salmonella typhi from May 2012 to December 2013

No. of **S. typhi isolates**	**Month**	**ceftriaxone**		**ceftriaxone**		**ceftriaxone**	
		S	%	I	%	R	**%**
n=16	May-Aug 2012	16	100%	0	0	0	0
n=11	Sep-Dec 2012	11	100%	0	0	0	0
n=17	Jan-April 2013	17	100%	0	0	0	0
n=21	may-Aug 2013	21	100%	0	0	0	0
n=26	Sep-Dec 2013	26	100%	0	0	0	0

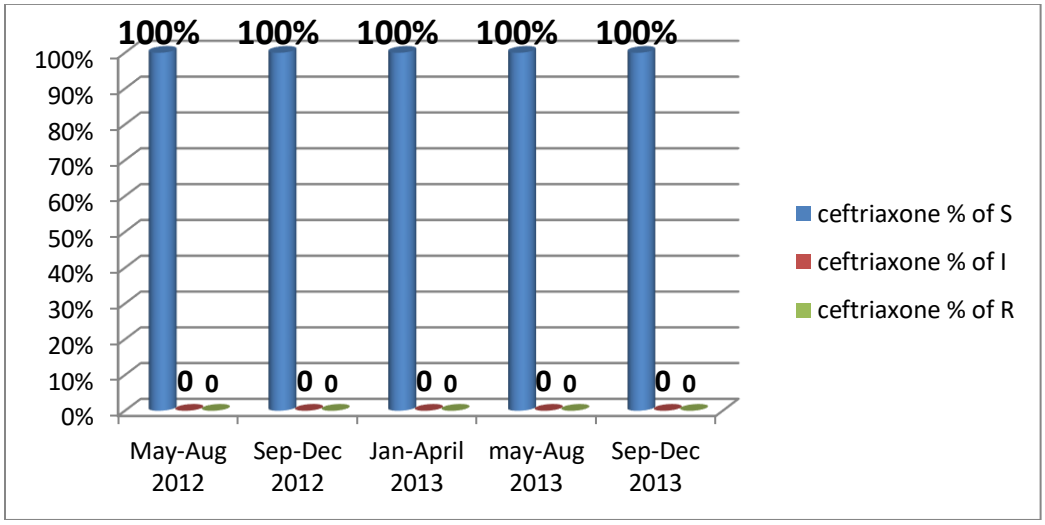

Figure 4.3 (b) Month wise susceptibility pattern of ceftriaxone for S. typhi

The antibiotic susceptibility for S. typhi isolates for the study period are shown in above table 4.3(b). All the 91 isolates were sensitive to ceftriaxone. Third generation cephalosporin were 100% susceptible in all months that is over the period from May 2012 to December 2013. And resistance to third generation cephalosporins was seen in 0 % of strains of S.typhi from May2012 to December 2013.

4.3 (c): The following table showsmonth wise susceptibility pattern of Ciprofloxacin for the Salmonella typhi from May 2012 to December 2013:

No. of **S. typhi isolates**	**Month**	**ceftriaxone**		**ceftriaxone**		**ceftriaxone**	
		S	%	I	%	R	**%**
n=16	May-Aug 2012	16	100%	0	0	0	0
n=11	Sep-Dec 2012	11	100%	0	0	0	0
n=17	Jan-April 2013	17	100%	0	0	0	0
n=21	may-Aug 2013	21	100%	0	0	0	0
n=26	Sep-Dec 2013	26	100%	0	0	0	0

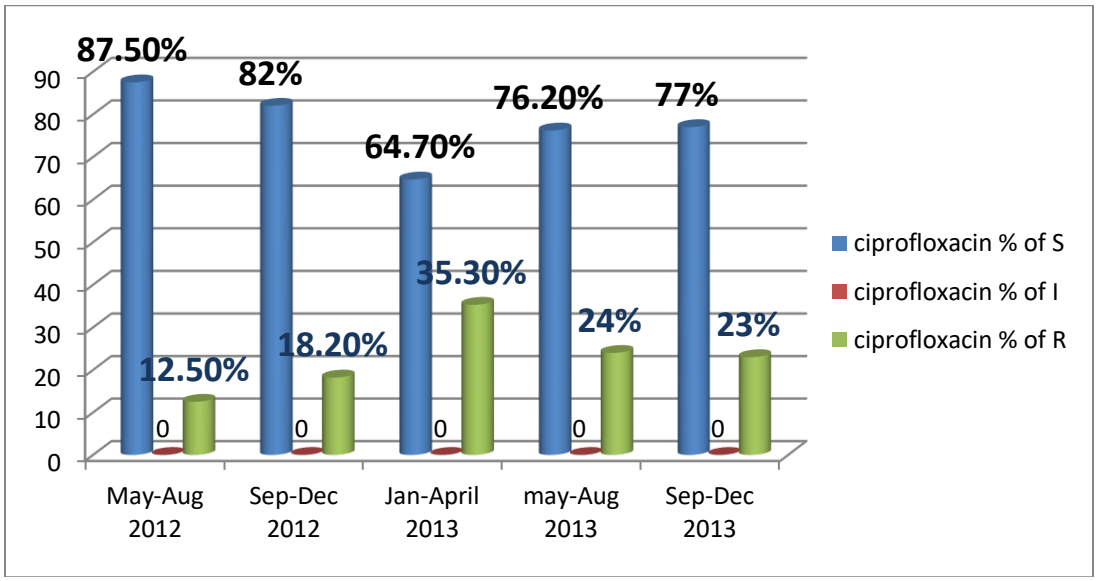

Figure 4.3 (c) Month wise susceptibility pattern of ciprofloxacin for S. typhi

In case of S. typhi, the reports of antibiotic sensitivity are variable from time to time, 87.50% sensitive to ciprofloxacin was seen in May2012 to August 2012 and showed a decreasing trend till Jan 2013 to April 2013.
After that there was a sudden increase in sensitive to 76.20% in May 2013 to August 2013 followed by a increase in sensitive to 77% in Sep 2013 to Dec 2013.
Ciprofloxacin resistance was low in 12.50% in May to Aug 2012 and Sep 2012 to December 2012 which increased from Jan2013 to April 2013 onwards.

4.3 (d): The following table showsmonth wise antimicrobial susceptibility pattern of Ceftriaxone for the S. paratyphi A from May 2012 to December 2013:

No. of S. Paratyphi A isolate	Month	ceftriaxone		ceftriaxone		ceftriaxone	
		S	%	I	%	R	%
n=3	May-Aug 2012	3	100	0	0	0	0
n=0	Sep-Dec 2012	0	0	0	0	0	0
n=3	Jan-April 2013	3	100	0	0	0	0
n=1	may-Aug 2013	0	0	0	0	1	100
n=2	Sep-Dec 2013	2	100	0	0	0	0

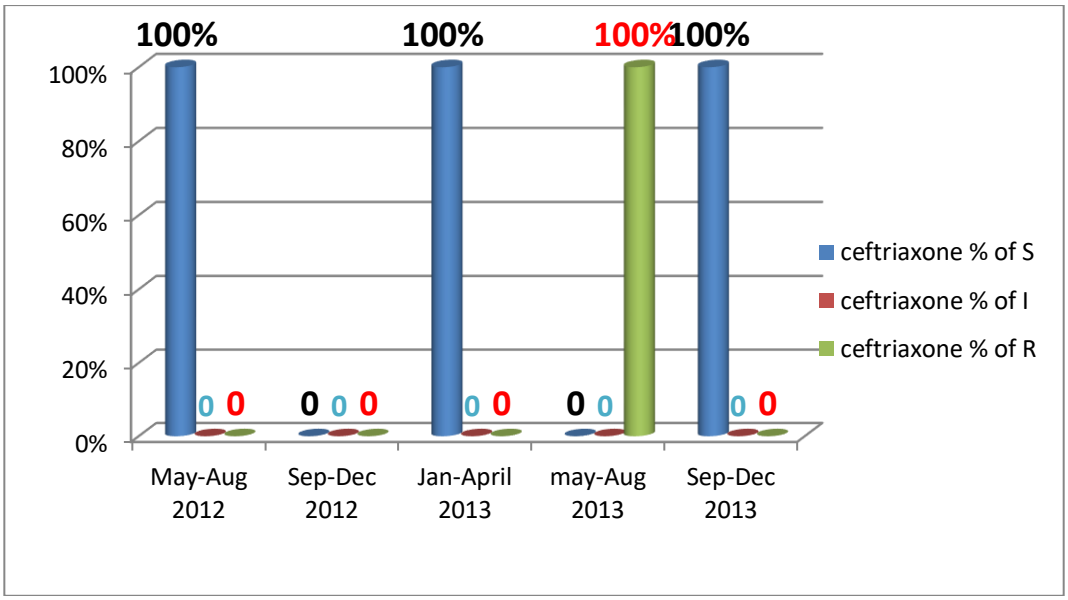

Figure 4.3 (d) Month wise susceptibility pattern of ceftriaxone for S. paratyphi A

In case of S. typhi 100% sensitive to ceftriaxone was seen in may to august 2012, Jan to April 2013 and Sep to December 2013. Apart from this in case of S. paratyphi A 100% resistance to ceftriaxone was seen in May to August 2013.

4.3 (e): The following table showsmonth wise antimicrobial susceptibility pattern of Ceftriaxone for the S. paratyphi A from May 2012 to December 2013:

No. of **S. Paratyphi A isolate**	**Month**	**Ciprofloxacin**		**Ciprofloxacin**		**Ciprofloxacin**	
		S	**%**	**I**	**%**	**R**	**%**
n=3	May-Aug 2012	3	100	0	0	0	0
n=0	Sep-Dec 2012	0	0	0	0	0	0
n=3	Jan-April 2013	2	66.7	1	33.4	0	0
n=1	may-Aug 2013	1	100	0	0	0	0
n=2	Sep-Dec 2013	2	100	0	0	0	0

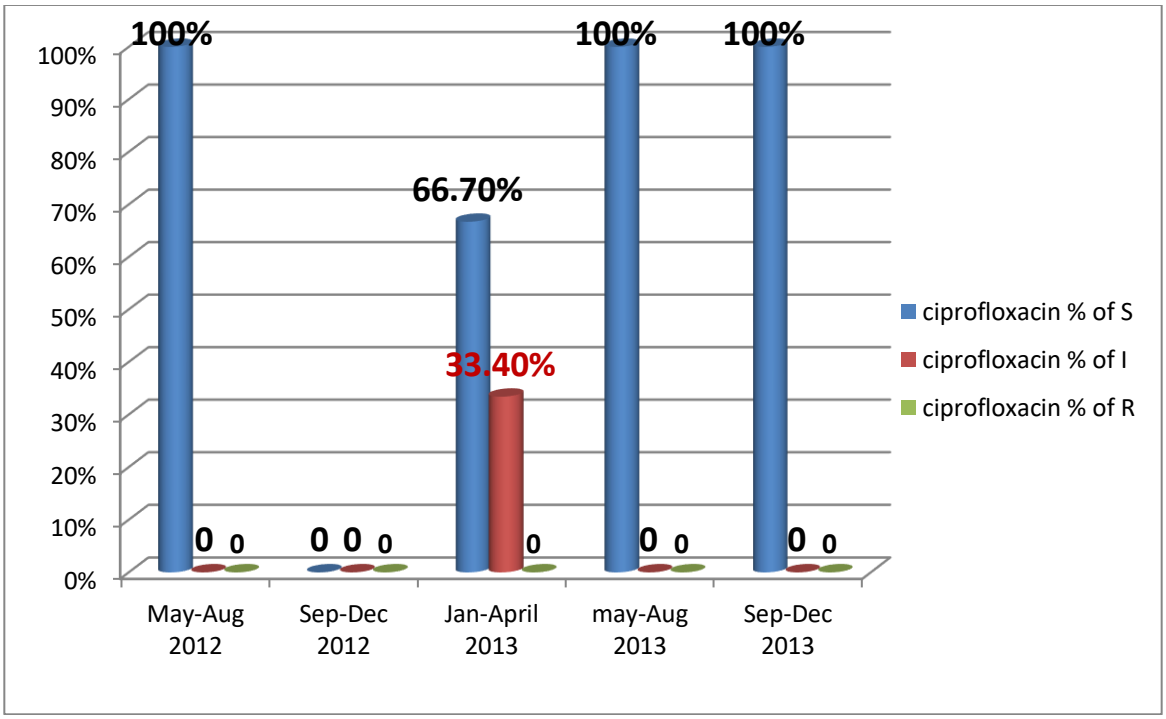

Figure 4.3 (e) Month wise susceptibility pattern of ciprofloxacin for S. paratyphiA.

All the 100% isolates were resistance to ciprofloxacin as shown in above. In case of S.paratyphi A 100% sensitive to ciprofloxacin was seen in May to Aug,2012 and showed a decreasing trend till Sep to Dec,2012. After that there was a sudden increase in sensitive to 66.70% in Jan to April, 2013 followed by a increase in sensitive to 100% in May 2013 to Dec 2013. And also 33.40% intermediate sensitive to ciprofloxacin was seen in Jan to April 2013.

4.4 (f): The following table shows Minimum Inhibitory Concentration trends of Salmonella typhi isolates from blood in pediatric patients against two antimicrobials from May 2012 to December 2013 (n=91):

Drug concentration for S. typhi	**Ceftriaxone**		**Ciprofloxacin**	
(µg/ml)	**No. of sample**	**%**	**No. of sample**	**%**
<=0.5	0	0	48	52.70%
<=1	1	1.09%	0	0
1	1	1.09%	21	23.07%
<=2	82	90.10%	0	0
>2	0	0	22	24.17%
<=4	7	7.69%	0	0

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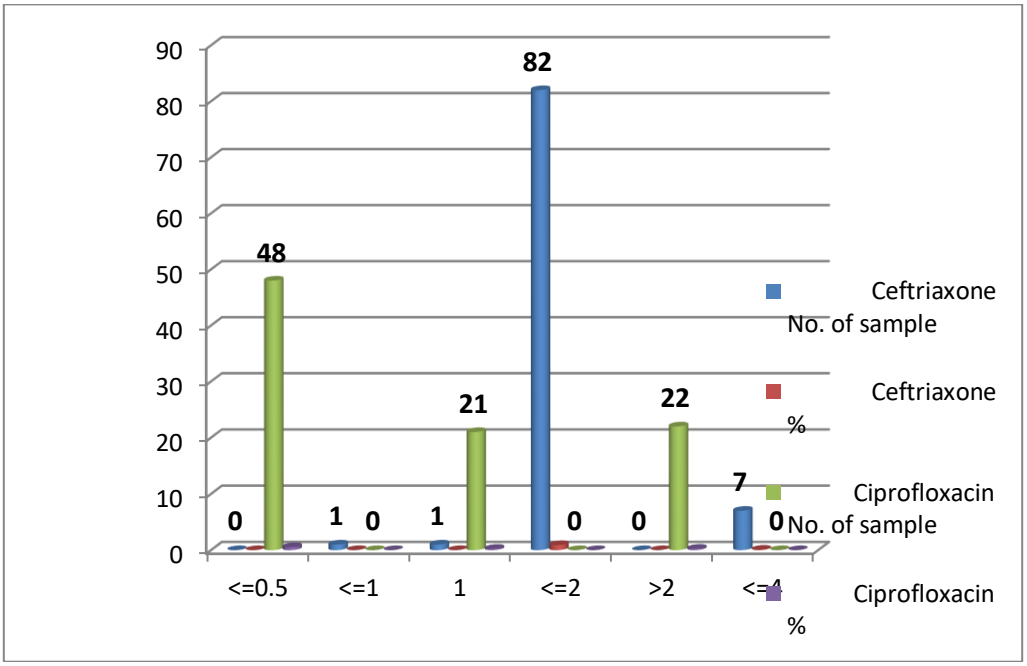

Figure 4.3 (f) Summary of MIC data for S.typhi

Summary of MIC data for S.typhi

In case of Salmonella typhi the highest recorded sensitivity for **Ceftriaxone** was 82 (90.10%) for <=2 and lowest was 0 for <=0.5 followed by 0 for >2, and the highest recorded sensitivity for **Ciprofloxacin** was 48 (52.70%) for <=0.5 and lowest recorded sensitivity 0 for <=1, <=2, <=4.

4.3 (g): The following table shows Minimum Inhibitory Concentration trends of Salmonella Paratyphi 'A' isolates from blood in pediatric patients against two antimicrobials from May 2012 to December 2013 (n=9):

Drug concentration for S. paratyphi 'A'	**Ceftriaxone**		**Ciprofloxacin**	
(µg/ml)	**No. of sample**	**%**	**No. of sample**	**%**
<=0.5	1	11.11%	0	0
1	0	0	8	88.88%
<=2	6	66.66%	0	0
2	0	0	1	11.11%
<=4	1	11.11%	0	0
>16	1	11.11%	0	0

In case of Salmonella paratyphi 'A' the highest recorded sensitivity for **Ceftriaxone** was 6 (66.66%) for <=2 and lowest was 0 for 1 and followed by 0 for 2, and the highest recorded sensitivity for **Ciprofloxacin** was 8 (88.88%) for 1 and lowest recorded sensitivity 0 for <=0.5, <=2, <=4and >16.

5. SUMMARY AND CONCLUSION:

The present work is a retrospective study to evaluate the minimum inhibitory concentration trends of Ceftriaxone and ciprofloxacin in blood culture of pediatric patient suffering from typhoid fever at MSSH, Patparganj, New Delhi.

The observational made are as follow:-

- In the study, male population was more than female population for Salmonella typhi and Salmonella paratyphi 'A'.
- Sample size included 100 patients.
- Majority of patients belong to age group 1-5 years for Salmonella typhi and age group 10-15 years in case of S. paratyphi 'A'.
- Out of 100 patients, 91 patients were positive blood culture for S. typhi and 9 patients were positive culture for S. paratyphi 'A'.
- Most commonly diagnosed condition was typhoid fever.
- Most commonly isolated cultures were S. typhi (91.00%) and S. paratyphi 'A' (9.00%). S. typhi is more sensitive to Ceftriaxone (100%) than ciprofloxacin while S. paratyphi 'A' was sensitive to ceftrixone and ciprofloxacin as well.
- In case of Salmonella typhi the highest recorded sensitivity for **Ceftriaxone** was 82 (90.10%) for <=2 and lowest was 0 for <=0.5 followed by 0 for >2, and the highest recorded sensitivity for **Ciprofloxacin** was 48 (52.70%) for <=0.5 and lowest recorded sensitivity 0 for <=1, <=2, <=4.
- In case of Salmonella paratyphi 'A' the highest recorded sensitivity for **Ceftriaxone** was 6 (66.66%) for <=2 and lowest was 0 for 1 and followed by 0 for 2, and the highest recorded sensitivity for **Ciprofloxacin** was 8 (88.88%) for 1 and lowest recorded sensitivity 0 for <=0.5, <=2, <=4and >16.
- This study helps us to identify the MIC trends of ceftriaxone and ciprofloxacin antibiotic consumption in various indications.
- An overview of totality of evidence suggests that use of ceftriaxone are found to be more effective and appropriate than ciprofloxacin.

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