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CORRELATION OF DURATION OF IV CEFTRIAXONE TO MEAN FEVER CLEARANCE TIME IN CHILDREN WITH ENTERIC FEVER.

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ARTICLE INFO **ABSTRACT** **ORIGINAL RESEARCH ARTICLE**

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Context: Enteric fever is one of the most common and serious infections in a developing country like India. IV ceftriaxone remains the mainstay of therapy in its management. But in a resource-limited setting, the long duration of therapy requiring inpatient admission is not a viable option. The minimum duration of IV ceftriaxone to be given before switching to an oral alternative like cefixime is poorly understood. Fever clearance is one indicator that can be used as a guide for shifting to oral antibiotics. **Aims and Objective:** To study the minimum duration of IV ceftriaxone before switching to oral cefixime in cases with enteric fever in a resource-limited setting. **Materials and Methods:** We performed a cross-sectional study on pediatric patients who were admitted with enteric fever. 170 children admitted to the pediatric ward as enteric fever cases or subsequently diagnosed post fever workup were included in the study. **Statistical analysis used:** Statistical testing was conducted with the statistical package for the social science system version SPSS 23.0. **Results:** Our study showed that only 2.4% of patients had fever beyond one week of ceftriaxone therapy. The mean fever clearance time after initiating IV ceftriaxone was 3.58 days (SD-1.49). No mortality was reported as a complication of enteric fever. **Conclusion:** Seven days of IV ceftriaxone followed by seven days of oral cefixime is a reasonable alternative for the treatment of enteric fever in pediatric population in resource-limited settings.

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INTRODUCTION

Enteric fever is one of the serious prevalent infections in many developing countries, especially in the Indian sub-continent. In India, the estimated prevalence of typhoid (lab confirmed) across hospital studies was 9.7% and paratyphoid was 0.9% among a population with fever [1]. The causative agent is Salmonella enterica serovars Typhi and Paratyphi A, B, and C. The clinical profile of

typhoid fever ranges from a mild illness with low-grade fever, lethargy, and dry cough, to a severe clinical picture with multiple complications. Case fatality rates are higher in the younger age group with severe complications like toxicity, shock, and disseminated intravascular coagulation. Blood culture forms the mainstay of the diagnosis of enteric fever, even though cultures from other anatomical sites may also be used. Appropriate use of antimicrobial agents and timely initiation of treatment can considerably reduce the morbidity and mortality in typhoid fever. Ceftriaxone is the drug of choice for the treatment of enteric fever when given for 10-14 days. The long duration of IV ceftriaxone makes it difficult to complete this course in several cases. Oral cefixime has also been advocated in uncomplicated enteric fever. There is a practice of switching from IV ceftriaxone to oral cefixime which is guided by improvement in symptoms, particularly fever resolution. The duration of this afebrile period to switch to oral cefixime is not specified. The present study is thus aimed to evaluate the fever clearance time following initiation of IV ceftriaxone therapy so that a minimum duration of IV therapy can be recommended before a switch to oral antibiotic is done.

METHODS

This was a hospital-based cross-sectional analytical study performed between November 2017 to April 2019 at a tertiary care Pediatric center of the Indian Armed Forces. The study protocol was approved by the institutional ethical committee.

Children in the age group of 6 months to 12 years admitted as confirmed cases of enteric fever and receiving IV ceftriaxone for the same were included in the study, after taking parental consent. Enteric fever was confirmed by either a positive blood culture report by the BACTEC method or a positive Typhoidot IgM test. Children with mixed infections and those on long-term immunosuppressants were excluded from the study. Two groups of patients were included, those who were diagnosed with enteric fever based on investigations done on an OPD basis and admitted subsequently for treatment, and the second group who were admitted on clinical suspicion, investigated, and subsequently found to have enteric fever based on the study criteria. Both were treated with intravenous ceftriaxone at 100 mg/ Kg/day. Antibiotics were continued for a total of 14 days, with either Ceftriaxone alone, or switching to oral cefixime at 20 mg/Kg/ day. The parents of the cases were interviewed by using a structured questionnaire. Daily charting for progression of signs and symptoms, including temperature charting was done. Patients were followed up for fever clearance following ceftriaxone therapy.

Sample size calculation was done based on references from previous similar studies where the mean fever clearance time after starting ceftriaxone therapy was 4 to 5 days. Taking a precision of 0.15 at a 5% level of significance, a study group of 170 patients was found to be sufficient for our study.

Statistical analysis: Statistical testing was done with the statistical package for the social science system version SPSS 23.0. Continuous variables were presented as mean +/- SD or median (IQR) for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. To determine the correlation of age with fever clearance time, statistical significance was tested by using Pearson correlation coefficient and ANOVA among different age groups. For all statistical tests, a ‘p’ value of less than 0.05 was taken to indicate a significant difference.

RESULTS

A total of 170 children between the age group of 6 months to 12 years were admitted over 18 months and were enrolled in the study. The mean age was

7.6 (SD 3.04) years. The maximum number of cases were in the age group of 8- 12 years (52.3%), followed by 4- 8 years (35.3%),

and the least in the 6 months – 4 years' group (12.4%). The male to female ratio of the study population was 1.6:1. A maximum number of patients presented with a fever duration of 6-10 days (n=108, 63.5%). The mean duration of fever was 7.82 days (SD 5.66). Five cases presented with fever more than 15 days (3.1%), and one case with a history of 2 months of fever [Fig 1].

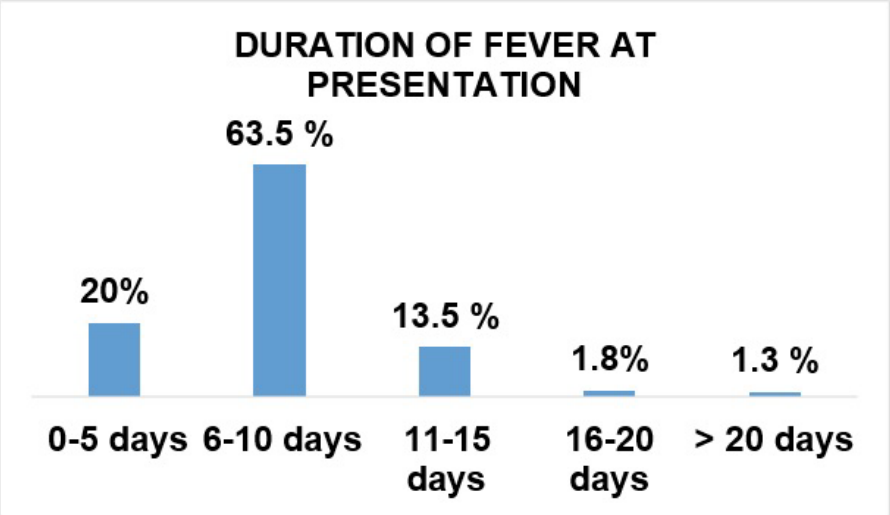

Fig 1. Graph showing percentage of cases having fever at presentation in various age groups.

Out of the total 170 subjects, 167 had a valid blood culture report, and the balance had grown commensals. Out of the valid 167 cultures, Salmonella species was grown in 134 cases (80.2%) and was negative for any organism in 33 cases (19.8%). In the culture-positive cases, 92.6% (n=126) were Salmonella typhi, and 7.4% (n=8) were Salmonella paratyphi positive. The mean duration of IV ceftriaxone therapy in our study was 10.32 days (SD= 3.29). The minimum duration was 3 days. In all cases, therapy was completed with oral cefixime if ceftriaxone was not given, for a total antibiotic duration of 14 days.

Mean fever clearance time after starting IV ceftriaxone was 3.5days (SD 1.49). While 53.5% of cases had fever clearance by day 3, 81.8% achieved fever clearance by day 4. 2.4% of cases had fever beyond one week of treatment initiation. The maximum time taken was 10 days in one patient [Table 1 & 2].

Table 1. Day of fever clearance after starting iv ceftriaxone therapy & mean fever clearance time.

Day of Fever Clearance	Frequency	Percent
1.0	9	5.3
2.0	22	12.9
3.0	60	35.3
4.0	48	28.2
5.0	18	10.6
6.0	6	3.5
7.0	3	1.8

9.0	3	1.8
10.0	1	0.6
Total	170	100.0

Table 2. Mean fever clearance in the study population.

Derivatives	**Duration of fever after IV Ceftriaxone**
Mean	3.582
Median	3.000
Mode	3.0
Std. Deviation	1.4982
Minimum	1.0
Maximum	10.0

No significant correlation was noticed between the duration of fever before ceftriaxone and the duration of fever after ceftriaxone [Fig 2].

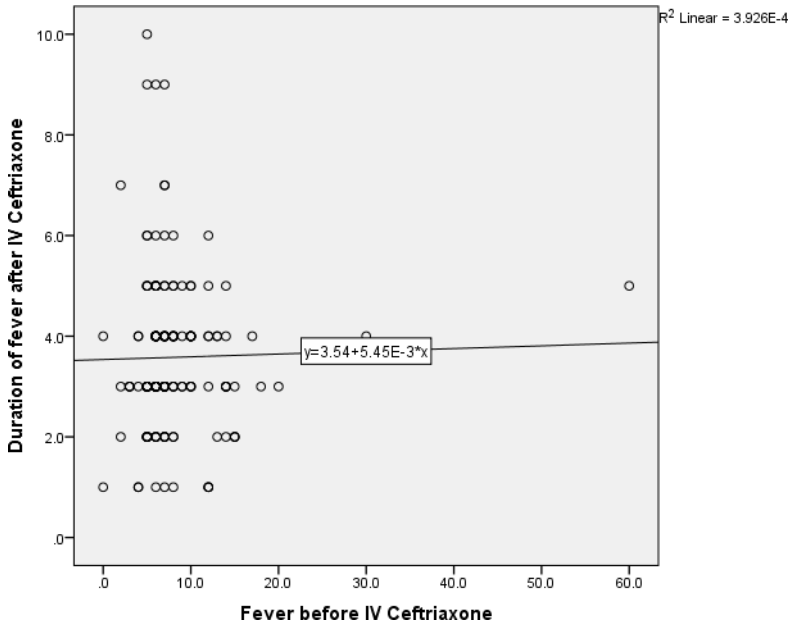

Fig 2. Scatter plot showing a correlation between duration of fever before and after IV ceftriaxone.

DISCUSSION

In the present study 21 cases (12.4%) were in the age group 6 months- 4 years, 60 cases (35.3%) in the age group 4-8 years, and 89 cases in the age group of 8- 12 years. A similar study by Sinha et al [2] had 10.9% cases below 5 years of age. Kumar et al [3] observed that 25.8% of their study population was under 5 years of age, and Sattar et al from Bangladesh [4] observed that 20.3% cases are under 5 years of age. The male to female ratio in our study was 1.6:1. Similar observations were made in the study by Kumar et al and Essa et al [5]. The mean duration of fever in our study was 7.8

days (Range 1- 60 days). Most cases had a fever for 6-10 days (63.5%) at presentation. Five cases presented with a fever of more than 15 days (3.1%). One case presented with a history of fever for nearly 2 months.

Out of the total 170 subjects, 167 had a valid blood culture report, and the balance had grown commensals. Out of the valid 167 cultures, Salmonella species was grown in 134 cases (80.2%) and was negative for any organism in 33 cases (19.8%). High positivity of cultures has been reported by other authors as well: RK Arora et al (83%), K Garg et al. (75%) [6,7]. Blood cultures are not only 100% specific, but also provide information regarding the antimicrobial sensitivity of the isolate, which is vital in today's scenario of multidrug-resistant organisms. Of the culture-positive cases, 92.6% (n=126) were Salmonella typhi, and 7.4% (n=8) were Salmonella paratyphi positive. A similar prevalence of S typhi (89.5%) and paratyphi (10.5%) was reported by Jeeyani et al [8]. Other studies however showed a variation of prevalence of S typhi (72- 76%) and paratyphi (26-28%) respectively [9]. The mean fever clearance time after starting IV ceftriaxone was 3.58 (SD- 1.49) days in our study. 81.8% of subjects achieved fever clearance by day 4. Mean defervescence time while using ceftriaxone as a single therapy was 4.2 days in a study by Jog et al and 6 days in the group assessed by Chowta et al [10,11]. A study comparing four RCTs conducted in Nepal had a mean fever clearance time of 3.06 days [12]. All these outcomes were comparable with our findings.

CONCLUSION

Our study reveals that only 2.4% of patients had fever beyond one week of ceftriaxone therapy. Ensuring at least 7 days of IV ceftriaxone followed by oral cefixime is thus a good alternative when compared to giving 14 days of IV ceftriaxone. This regime can reduce the length of hospitalization and lower associated costs.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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