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An observational retrospective cohort Study of pattern of fever & duration of time taken by ceftriaxone for clinical cure in enteric fever, in a tertiary care teaching hospital, central India

Rupesh Gupta*, Santenna chenchula ¹, Akash vishwe¹ ¹ Department of Pharmacology, AIIMS, Bhopal

*Corresponding Author:

Rupesh Gupta, Senior Resident, Department of Internal Medicine AIIMS, Bhopal.

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ABSTRACT OBJECTIVE:

To study the time duration taken by ceftriaxone for clinical cure in typhoid patients and to study patterns of fever in enteric fever, in a tertiary care teaching hospital, India.

METHOD: The present retrospective observational study was conducted on 45 blood-culture proven *salmonella typhi* & *para typhi* inpatients. Data was collected from patient record files from 2015 January to 2017 March Medical Records Department (MRD), AIIMS, Bhopal.

RESULTS: Among them only 12 patients were admitted to internal medicine in patient department (IPD). Among these 12 in patients 4 patients showed clinical improvement within 4 days. And remaining did not show any improvement. All of their temperature chart showed intermittent pattern variety with everyday temperature declining to the normal set point rather than the classical step ladder pattern

Conclusion: The fever patterns are not likely to be helpful diagnostically in enteric fever. For the clinical cure of enteric fever with injectable ceftriaxone 1gm bd it takes minimum 4 days.

Keywords: Typhoid fever, ceftriaxone, fever pattern, clinical cure.

INTRODUCTION

Even after 134 years from the isolation of the salmonella bacterium by the German Scientist Gaffky, and with major developments in modern medicine, enteric fever is still responsible for substantial morbidity and mortality. Every year there are around 21 million new cases of enteric fever are out of which 161,000 are succumb to the disease, with the highest mortality in young children from economically lowest areas (1). Among these over 80% cases of enteric fever belong to Asia and Africa. Enteric fever is a major public health problem in developing countries like India (2).

Enteric fever is a systemic infection characterized by fever and abdominal pain caused by Salmonella enteric Serovar typhi (S.Typhi) or Salmonella enteric

(S.Paratyphi Paratyphi Α serovar A). S.schottmuelleri (S. paratyphi B), and S. hirschfeldii (S. Paratyphi C). They usually spread through contaminated food and water. The ratio of disease caused by S. Typhi to S. Paratyphi is about 10:1(2). Initiating treatment with specific antimicrobials is an essential part in the treatment of enteric fever. Chloramphenicol was the drug of first choice in the management of enteric fever since 1948, but very soon resistances came and lead to change this wonderful drug from the list as a first choice drug for enteric fever (3).Afterward, cotrimoxazole and ampicillin began to be used as a 1st choice drugs but bacteria got resistant to these too, later these bacteria strains called as Multi Drug Resistant (MDR) strains. So, in 1980, these MDR strains changed treatment

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options to ciprofloxacin, ofloxacin, broad-spectrum 3rd and 4th generation cephalosporin's azithromycin and levofloxacin which were proved to be effective against these resistant strains (4). Resistance to Ciprofloxacin and Ofloxacin lead to use of broadspectrum 3rd and 4th generation cephalosporin like ceftriaxone, cefotaxime, cefepime, azithromycin, levofloxacin, tigecycline and penems as first line choice of antimicrobials for enteric fever (5-6). Patients in the United Kingdom (UK) and the United States (US) who traveled to the developing world especially Southeast Asia detected with strains resistant to all three first-line drugs ciprofloxacin, ofloxacin and ceftriaxone (7-8). Even in some resource poor countries like Bangladesh, Pakistan and Philippines also reported Resistance to ceftriaxone (9). Most of the previous studies they concluded that it took minimum 3 ± 1.2 days to become afebrile with ceftriaxone 1 gram bd dose (10-12). Pattern of fever is an important indicator for diagnosis of type of infection responsible for the fever in the patient.

OBJECTIVE:

The present retrospective observational study was conducted to study the time duration taken by ceftriaxone for clinical cure and to study patterns of fever in enteric fever, in a tertiary care teaching hospital, India.

METHODS AND MATERIALS:

It is a 3 years retrospective study. Data was collected from patient record files from Medical Records Department (MRD), AIIMS, Bhopal. We were included cases from 2015 January to 2017 March. In this course of time, we got around 45 *Salmonella typhi* and *Para typhi* positive cases that were positive in blood culture studies. First, we observed all these culture-positive patients *in vitro* antimicrobial culture

Fever charts:

Temperature charts; Figure 1-12

sensitivity study by microbiology department, from the patient case sheets. The test was done on Muller-Hinton agar using standard Kirby-Bauer disc diffusion test. Antibiotic discs used were ciprofloxacin, amoxicillin-clavulanic acid, ampicillin, ceftriaxone, azithromycin, and levofloxacin as well. We collected and observed the data in the patient medical records.

We studied temperature charts as well of these patients for the finding of fever pattern. Fever defined as an A.M temperature of $> 37.2 \,^{\circ}C \,(>98.9^{\circ}C)$ or temperature of $>37.7^{\circ}C \,(>99.9^{\circ}C)$ at any time during the day (11-12). It is an important clinical indicator of infectious diseases for medical consultations. Fever has been described as sustained/continuous, intermittent and remittent fever. In Persistent fever temperature does not fluctuate by more than 1°C during 24 hours; in remittent fever temperature oscillates by 2°C during a day but does not touch normal, and an intermittent fever is present for only several hours at a time and returns to normal (13-14).

RESULTS:

Out of 45 salmonella culture-positive patients, only 12 patients were admitted to IPD. All of them showed in vitro sensitivity to ceftriaxone. In these 12 positives patients, in 4 patients improved symptomatically by becoming afebrile within 4 days. And the remaining 8 patients did not become afebrile with ceftriaxone with 1 gram bd dose. They were all alternative anti-microbial agents given like azithromycin 500mg 0D for clinical improvement.

We studied the entire 12 patient's temperature charts for the finding of variety pattern of fever as well. All of them showed intermittent pattern variety with everyday temperature declining to the normal set point rather than the classical step ladder pattern.









Figure 3

Figure 4















Figure 9







DISCUSSION:

In the year 1948 chloramphenicol was the first choice treatment of enteric fever, and it was the greatest milestone in modern medicine. It was the treatment of choice for typhoid fever for nearly 4 decades, particularly in low economic countries like India. But due to plasmid-mediated resistance and bone marrow depression its usage has been declined (3). After this cotrimoxazole and ampicillin were used but they also got resistance and MDR strains came into existence. In 1980 fluoroquinolones were used in the place of cotrimoxazole and ampicillin for the treatment of



enteric fever. Wide spread use of fluoroquinolones for may enteric fever have led to point mutations in the gyr A gene and occasionally the par C gene of S.typhi and Para typhi A isolates with needed increase in Minimum Inhibitory Concentrations (MIC) for both commonly using fluoroquinolones ciprofloxacin and ofloxacin across Asia and in parts of Africa (15-16). In India MDR enteric fever was first described in 1988 in Mumbai and has since spread throughout the region in the last two decades (17). Studies show that salmonella isolates in Indian subcontinent areas are fully resistant fluoroquinolones (18). In the year 2000, a study done

Volume 1, Issue 4; November-December 2018; Page No. 185-190 © 2018 IJMSCR. All Rights Reserved by *Das et al.*in Orissa found 2.5% of S. Typhi strains were resistant to ciprofloxacin, in a surveillance study from Kolkata conducted during 2009 to 2013, 18% of *S. Typhi* and no *S. Para typhi* isolates were multidrug resistance (MDR) (19-20).

Since resistance to fluoroquinolones ceftriaxone is a first line injectable antimicrobial for complicated typhoid fever and cefixime for uncomplicated typhoid fever. The most recent professional guidelines for the treatment of enteric fever in south Asia was issued by the Indian Association of Pediatrics (IAP) in October 2006. Even though these guidelines were published for the pediatric population, the authors felt that they were also applicable to adult cases. For empirical treatment of uncomplicated enteric fever, the IAP recommends cefixime and, as a second-line agent, azithromycin. For complicated typhoid fever, they recommended ceftriaxone.Aztreonam and imipenem are also second-line agents for complicated cases (21). The recommended dose of ceftriaxone for enteric fever in adults is 2 g bd or in children and infants 50-75 mg/kg body weight/day IV for 10-14 days.

In the year 2016 The Ministry of Health and Family Welfare. India released National Treatment Guidelines for Antimicrobial Use in Infectious Diseases. These guidelines recommend ceftriaxone as the first line antimicrobial agent for complicated Salmonella typhi positive enteric fever in patients. Once the ceftriaxone treated patient become afebrile, he/she can be switched over to oral cefixime to finish total duration of 14days (22). Several isolated reports of in vitro ceftriaxone-resistant S.Typhi strains were reported in Pakistan and patients in UK and US travelers who visited Southeast Asia (7). Among 45 enteric fever positive blood culture patients, 12 of them were admitted to IPD of both Pediatric and Medicine wards. Most of the patients were treated outside our tertiary care teaching hospital, although they have got blood culture positive for typhoid. Only who did not get any clinical improvement, came to our tertiary care teaching hospital. All the 12 REFERENCES

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salmonella positive patients presented with insidious onset of fever and their antibiotic sensitivity reports were showed susceptibility to ceftriaxone. In these 12 positives in patients, 4 of them improved symptomatically by becoming afebrile within 4 days. 8 out of 12 patients, did not responded to ceftriaxone even after 4 days and they did not become afebrile alone with ceftriaxone. All of the 7 patients treated with other alternative antimicrobial azithromycin 500mg OD for remaining 7days along with ceftriaxone.

We studied fever patterns as well in these patients. Usually, slow stepwise temperature rise over the course of each day that drops by the subsequent morning are classical features of enteric fever with peaks and troughs progressively over time (23-25). But in our study, most of them showed intermittent pattern variety fever. And this might be because most of the patients with fever self-medicate with antibiotics and antipyretics before consulting a healthcare professional (12).In 1979 a study published in JAMA Internal Medicine concluded that there is no clinical significance for fever patterns in diagnosis of enteric fever (26).

By this, we conclude that the findings we have reported in this present study suggest that the firstchoice injectable salmonella antimicrobial i.e. ceftriaxone takes minimum 4 days for the clearance of fever, and clinical cure in enteric fever. Our findings further helps to find out whether ceftriaxone is showing clinical efficacy or got clinical resistance by salmonella bacterium. Our study strongly supports the previous studies conclusion that the fever patterns are not likely to be helpful diagnostically in enteric fever.

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