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# EFFICACY OF AZITHROMYCIN AND CEFTRIAXONE FOR THE TREATMENT OF ENTERIC FEVER IN TWO TERTIARY CARE HOSPITALS OF KATHMANDU NEPAL

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## ABSTRACT

Enteric fever is a potentially fatal acute systemic illness caused primarily by *Salmonella enterica* serovar Typhi and *Salmonella enterica* serovar Paratyphi A, B, and C. The term "enteric fever" is a collective term that refers to both typhoid and paratyphoid fever, and "typhoid" and "enteric fever" are often used interchangeably. The differential diagnosis of typhoid fever is challenging due to the similar symptoms with other febrile illness. Although there are many antimicrobials being used in enteric fever in Nepal and globally, resistance to commonly used drugs including fluoroquinolones is a serious problem. Currently ceftriaxone and Azithromycin are being used successfully in the treatment of enteric fever. The objective of the study was to evaluate the efficacy of Azithromycin and Ceftriaxone used in the treatment of enteric fever methods: A questionnaire was administered to 250 patients suspected of enteric fever presenting to the emergency, outpatient and inpatient departments of Patan Hospital (n=140) and Civil Services Hospital (n=110) of Nepal. Patients were enrolled into two treatment groups, Group l receiving Ceftriaxone (n=125) and Group ll receiving Azithromycin (n= 125). Response to therapy in terms of the subjective disappearance of fever and other symptoms, and adverse events were recorded. Fever clearance time and clinical cure was analysed for each treatment groups for culture positive enteric fever. Out of 250 cases137 (54.8%) were males and 113 (45.2%) were females, similarly, average age of patients was 31.47 (+/- 16.13). Fever was present in all patients. Fever clearance time was 2.8 days and 4.1 days for ceftriaxone and azithromycin respectively. The clinical cure was observed in 100% patients in ceftriaxone group and 94.4% patients in azithromycin group. There was no mortality during study period. Minor allergic reaction was observed in two patients which resolved with treatment. Ceftriaxone was more effective in the treatment of enteric fever with shorter fever clearance time and high clinical cure rates compared to azithromycin.

## INTRODUCTION

Enteric fever (EF) is a bacterial infection that is fecal-oral transmissible disease caused by the bacterium *Salmonella enterica*, serotype *S typhi*. A similar clinical syndrome is caused by *Salmonella enterica*, serotype *S paratyphi*, *Salmonella enterica* serovars *Paratyphi* A and *Paratyphi* B (and uncommonly *Paratyphi* C) cause a disease (paratyphoid fever) that is clinically indistinguishable from typhoid fever, particularly in parts of Asia. Typhoid fever and paratyphoid fever are collectively termed *enteric fever*. [1, 2]. World Health Organization (WHO) mention the following key facts about Enteric fever (EF) [2]. EF is caused by the bacterium *Salmonella Typhi.* And is a life-threatening infection. An estimated 11–21 million people get sick from enteric fever and between 128 000 and 161 000 people die from it every year. Prolonged fever, fatigue, headache, nausea, abdominal pain, and constipation or diarrhoea are the main symptoms. Antibiotics are the main group of medicine to treat enteric fever. But the resistance creating the threat and is making treatment more complicated. Vaccines especially typhoid conjugate vaccine with longer lasting immunity was prequalified by WHO in December 2017. Many Antibiotics are prescribed for empirical as well as definitive treatment of Enteric fever. But cephalosporins and azithromycin are used in the affected regions rather than others due to the emerging resistance to antibiotics. The disease burden is acute in South and South-East Asia and sub-Saharan Africa [3, 4, 5, 6]. *SalmonellaTyphi* mainly spread through contaminated food or water. In digestive tract, where they are taken in by cells called mononuclear phagocytes. In the case of *S. typhi*, however, the bacteria are able to resist and survive ingestion by the phagocytes, and multiply within these cells. The incubation period is 10 to 14 days. When huge numbers of bacteria fill an individual phagocyte, they spill out of the cell and into the bloodstream, where their presence begins to cause typhoid fever symptoms. [7,8,9] In Nepal 41 % patient suffered from *S typhi* and 28 % from *S paratyphi.* Antibiotics such as nalidixic acid, Ampicillin, Co-trimoxazole, Chloramphenicol and quinolones have whispered resistance but and the MICs (minimum effective concentrations) against azithromycin declined, confirming the utility of these alternative drugs for enteric fever treatment. The high incidence of diseases starts with monsoon in Nepal where typhoid and diarrhoea are the most common. The six year's data on Enteric fever found in the annual reports published by the Department of Health Service (DoHS) in 2016/17 emphasized the required attention towards the Enteric fever. [10, 11.12].

Clinical diagnosis of Enteric fever is often difficult due to non-specific presentation of this fever and moreover, it may be confused with a wide range of other common febrile illnesses in endemic area. So, clinical diagnosis leads to inaccurate surveillance data and a considerable misrepresentation of the incidence of enteric fever, and can also result in inappropriate treatment. The diagnosis relies on isolation of *S. Typhi* by blood culture but the sensitivity is only 60 % of a single blood culture. The available serological tests currently are compromised by a variable antibody response to the pathogen which may persist for variable periods, and cross-reactivity of *S. Typhi* (and *S. Paratyphi A*) with other enteric bacteria. All patients with typhoid and paratyphoid fevers excrete the organisms at some stage during their illness. About 10% of patients with typhoid fever excrete S. typhi for at least three months following the acute illness, and 2-5% becomes long-term carriers (more than one year). Ceftriaxone is a beta lactam antibiotic irreversible inhibitor of bacterial cell wall synthesis by binding to

transpeptidases. Ceftriaxone is an antibiotic useful for the treatment of a number of bacterial infections. Ceftriaxone was completely absorbed following IM administration with mean maximum plasma concentrations occurring between 2 and 3 hours post-dose. Multiple IV or IM doses ranging from 0.5 to 2 gm at once or twice a day intervals resulted in 15% to 36% accumulation of ceftriaxone above single dose values. Pharmacodynamics Cephalosporins exhibit time-dependent killing (T > MIC). Pharmacokinetics: Dose of 1g Cmax: 123-151mcg/L Half-life: 8 hours and Volume of distribution: 10.7L. [13,14]. In Nepal, Ministry of health and Population recommend the treatment according to the level of health institution (that is different for health posts / sub-health posts/ district hospitals one regimen and zonal level and above and referral hospitals another scheme as following: [15].

**Table -1: Recommended Treatment by Government of Nepal[15]**

| Health Posts/ Sub-health posts and district hospital | Zonal hospitals and above referral centre |
|---|---|
| Cotrimoxazole 160/800 mg 12 hourly for 14 days or<br>Ciprofloxacin 500 mg 12 hourly for 14 days or<br>Ofloxacin 400 mg 12 hourly for 14 days | Cotrimoxazole 160/800 mg 12 hourly for 14 days or<br>Chloramphenicol 500 mg 6 hourly for 14 days<br>Ciprofloxacin 500 mg 12 hourly for 14 days or<br>Ofloxacin 400 mg 12 hourly for 14 days<br>Inj Ceftriaxone 1 g 12 hourly for 7 days |

**Table -2: Antimicrobial therapy for treatment of Typhoid fever [16]**

| Optimal Therapy | | | | Alternative Effective Drugs | | |
|---|---|---|---|---|---|---|
| Susceptibility | Antibiotic | Daily dose Mg/kg | Days | Antibiotic | Daily dose Mg/kg | Days |
| Mild Disease | | | | | | |
| Fully sensitive | Ciprofloxacin or Ofloxacin | 15 | 5-7 | Chloramphenicol<br>Amoxycilin<br>Cotrimoxazole | 50 -75<br>75 – 100<br>8 - 40 | 14 – 21 14<br>14 |
| Multi drug resistant | As above or Cefixime | 15<br>15-20 | 7<br>7-14 | Azythromycin<br>Cefixime | 8 – 10<br>15 - 20 | 7<br>7-14 |
| Quinolone resistance | Azithromycin<br>Rocephin | 8-10<br>75 | 7<br>10-14 | Cefixime | 20 | 7-14 |
| Severe illness | | | | | | |
| Fully sensitive | Ciprofloxacin or Ofloxacin | 15 | 10 -14 | Chloramphenicol<br>Amoxycilin<br>Cotrimoxazole | 100<br>100<br>8 – 40 | 14 – 21<br>14<br>14 |
| Multi drug resistant | As above or Cefixime | 15<br>15-20 | 10 -14<br>10 -14 | Rocephine<br>Cefotaxime | 75<br>80 | 10– 14<br>10– 14 |
| Quinolone resistance | Rocephin<br>Cefotaxime<br>Azithromycin | 75<br>80<br>8-10 | 10 -14<br>10 -14<br>10 -14 | Fluoroquinolones | 20 | 7-14 |
| Definition of multidrug-resistant typhoid fever: Multidrug-resistant typhoid fever (MDRTF) is defined as typhoid fever caused by *S. Typhi* strains which are resistant to all the three first-line recommended drugs for treatment, i.e., chloramphenicol, ampicillin, and co-trimoxazole. | | | | | | |

**Table l: Fever Clearance of time**

| Fever Clearance of time (FCT) in enteric fever (days) | | Std. deviation | | Remarks |
|---|---|---|---|---|
| Azithromycin | Ceftriaxone | Azithromycin | ceftriaxone | Ceftriaxone shows the more efficacious than Azithromycin |
| 4.1 | 2.8 | 1.01 | 0.83 | |

**Table II: Blood culture**

| Group | No. of sample sent | No of sample positive for *salmonella Typhi* | After treatment *salmonella Typhi* ***(sterile)*** |
|---|---|---|---|
| Azithromycin | 125 | 53 | -ve |
| Ceftriaxone | 125 | 73 | -ve |

**Table III: Clinical Response**

| Response | Group and Number of patients | | |
|---|---|---|---|
| **Group** | **Azithromycin** | **Ceftriaxone** | **Remarks** |
| Clinical cure | 118 (94.4%) | 125 (100%) | Ceftriaxone shows the better performances |
| Not responded to therapy | 7/125 | 0/125 | 7 patients not showing clinical response to azithromycin were successfully treated with ceftriaxone. |
| ADRs ( Type B) | 1 | 1 | Hypersensitivity reaction ( rash) |
| Death | 0 | 0 | |

## MATERIALS AND METHODS

The data collection form was developed to record symptomatic care like fever, Anorexia, Nausea and Vomiting, headache, constipation or diarrhea. Blood culture pre-and post-medication was sent to the Pathology department. The therapeutic response in relation to fever and other symptoms were recorded. The ethical approval was taken from Nepal health research Council and data collection both site hospital directors.

Regarding blood sample, the volume of blood was 3 mL from those aged <14 years; 8 mL from those aged ≥14 years.

**Inclusive criteria**: Fever of≥38.0 °C and for at least 4 days, Older than 4 years to 65 years of age, patients who can take tablet orally, follow-up visits, access of telephone/mobile phone 24 h a day for communication, patients or their guardians who are ready to give their consent (in addition to parental consent) were included in study.

**Exclusion criteria:** Patients having Fever for more than 10 days, Diabetes mellitus, Pregnancy, severe infection, clinical/visible jaundice, active gastrointestinal bleeding, Shock, hypersensitivity to drugs, Patient requiring intravenously administered were excluded.The obtained data were analyzed using SPSS version 16.

## RESULT AND DISCUSSION

**Fever clearance time (FCT):** The lesser FCT the better efficacy of the Drugs will be better. In this regards Ceftriaxone

showed the better performances than that of Azithromycin (2.8 days Vs 4.1days) In our study the Fever clearance time (FCT) for ceftriaxone was 2.8 and Azithromycin 4.1 days.Other researchers reported that Ceftriaxone in short courses has emerged as an effective alternative to chloramphenicol for the treatment of typhoid fever [17,18]. The mean time taken for clearance of bacteraemia was longer in the azithromycin group than in the ceftriaxone [19].Combined therapy of third-generation cephalosporin and azithromycin for enteric fever may surpass monotherapy in terms of FCT and time to elimination of bacteremia [20].

We found in our research that in initial blood sample of all patients (125 for ceftriaxone and 125 for Azithromycin) were sent for culture to pathology department. Out of which 53 samples were positive (53/125 =42.40 % in azithromycin group) and 73 (73/125 = 58.40 %) samples were of positive in Ceftriaxone. After treatment with particular drugs, Blood culture was negative (sterile). The blood culture was repeated after completion of therapy and found all cases were sterile as well. The patients with blood culture negative were also on antibiotic as per the clinical judgment and based on symptoms (screened as per inclusive criteria). Patients having culture positive were also fine and found without fever after treatment of antibiotics

**Clinical cure:** Our finding showed that in ceftriaxone group the percentage of clinical cure was 100% whereas Azithromycin was 118/125 (94.4%). But the other researcher reported that A total of 31 (91%) of the 34 patients treated with azithromycin and 29 (97%) of the 30 patients treated with ceftriaxone were cured ($P > .05$) [21]. Another researcher reported that the advantages of Ceftriaxone use include rapid clinical response, short course of treatment, and lack of serious adverse drug reactions [22]

## CONCLUSION

The widespread emergence and spread of resistance to commonly used first line antimicrobials and fluoroquinolone group of drug against enteric fever challenges the treatment of enteric fever. Our results suggest that although both Azithromycin and Ceftriaxone are effective against enteric fever, ceftriaxone has lower fever clearance time and better clinicalefficacy compared to Azithromycin. Early diagnosis and treatment of enteric fever with effective antimicrobial drug is critical for optimal patient cure. In addition, preventive measures against the disease including clean water supply, sanitary faces disposal and effective vaccination are crucial for disease control.

**Limitation of the study:** This study is limited to two tertiary care hospitals of Kathmandu Valley and cannot be generalized for whole country

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