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"In vivo resistance to ceftriaxone in enteric fever": In a tertiary care teaching hospital, Central India

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Original Report Study

Every year around 21 million new cases of enteric fever are diagnosed out of which 2,22000 succumb to the disease, with the highest mortality in young children in developing countries like India (1,2). It is a systemic infection characterized by fever and abdominal pain caused by gram-negative bacilli Salmonella enteric Serovar typhi (*S.Typhi*) or salmonella enteric serovar paratyphi (*S.Typhi*) which is again categorized into S.Paratyphi A, S.paratyphi B and S. Paratyphi C (2). Early antimicrobial therapy with ceftriaxone, cefixime, and azithromycin is essential as there is widespread resistance to most of the earlier antimicrobials like chloramphenicol, cotrimoxazole,amoxicillin,ampicillin,andfluoroquinolones like ciprofloxacin and ofloxacin has been seen in India (3 ,4). Recent phylogenetic studies suggest the multidrug resistant clade H58 originated in India and afterwards expanded through Asia and Africa, causing unrecognized outbreaks in the latter in areas previously considered free of the disease.

This study was done to assess the in vivo susceptibility among patients with *in vitro* susceptibility to ceftriaxone. This was a retrospective study in which after obtaining Institute Human Ethical Committee (IHEC) consent, we collected the list of patients with enteric fever whose blood culture was positive, from the records of Microbiology laboratory, All India Institute of Medical Sciences (AIIMS), Bhopal. During this study period from January 2015 to March 2017, a total of 45 cases were diagnosed as enteric fever after blood culture, out of which 11 were admitted to AIIMS Bhopal. Ten patients admitted and including a child (11 years). We accessed records of these 11 patients from Medical Records section & collected the following data: Blood culture and sensitivity reports, temperature charts, initial antimicrobial therapy and continuation anti-microbial therapy on availability of culture sensitivity reports, which were usually available within 48 hours. All of them showed *in vitro* sensitivity to ceftriaxone, azithromycin and levofloxacin, but resistance to cotrimoxazole, ampicillin, amoxicillin- clavulanic acid, and chloramphenicol. *In vivo* ceftriaxone sensitivity was considered when the patient become afebrile within 3±1.2 days after starting parenteral ceftriaxone 1 gm b.i.d. dose, persistence of even ≥ 1 typhoid related symptoms after at least 4 days of therapy was labeled as *in-vivo* ceftriaxone resistance (1,5 ,6,7,8).

All the eleven patients showed in vitro sensitivity to ceftriaxone; but only 4 of them showed i*n vivo* sensitivity

to ceftriaxone in that they became afebrile and other symptoms common in typhoid within 3±1.2 days after start of therapy, out of these 4 patients one was a child. All of these 4 patients continued to receive ceftriaxone. In the remaining 7 patients azithromycin 500mg o.d was added to the ongoing regimen in 3 patients and in the other 4, azithromycin 500 mg o.d plus levofloxacin 250 mg b.i.d were added. All the 11 patients recovered eventually with an uneventful course during their hospital stay.

Temperature charts were also accessed, none of the 11 patients showed classical step-ladder pattern of fever described for typhoid (9).The temperature charts showed random spikes and variations indistinguishable from any other common viral fever.

Emerging resistance to ceftriaxone, which is now a corner stone of therapy in enteric fever, is a major concern in India. Ceftriaxone is a parenteral antimicrobial which in a dose of 1 gm b.i.d. is recommended as the most effective drug in complicated enteric fever as per the professional guidelines for the treatment of enteric fever in south Asia which were issued by the Indian Association of Pediatrics (IAP),2006(10).Clinicians are in a fix with many a times ceftriaxone showing *in-vitro* sensitivity but *in vivo* resistance. The only viable alternatives are azithromycin and probably levofloxacin.

This study highlights the potential problems in treating enteric fever, where the cases are on the increase and antimicrobials are few; especially in resource poor countries like India.

Competing interests: There are no competing interests to declare.

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