Int.j.pathol.2017;15(2):78-80

Case Report

Multi-drug resistant Salmonella Typhi resistant to Ceftriaxone isolated in a Tertiary care Hospital

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Abstract: Enteric fever is a systemic infection caused by *Salmonella typhi* and *Salmonella para-typhi A and B*. It is a major cause of morbidity and mortality worldwide. Multi-drug resistant (MDR)*S. typhi*has been reported since 1997 rendering the primary anti-typhoidal drugs and the fluoroquinolones as no longer a choice for typhoid treatment, thus leaving Ceftriaxone as the mainstay for enteric fever treatment. There are reports of emerging resistance to Ceftriaxone from many Asian countries. We report the first case of Ceftriaxone Resistant*S. typhi* from Children hospital, PIMS.A four-and-a-half-year-old girl presented with fever, abdominal pain and loss of appetite for last one month. Systemic examination revealed abdominal tenderness and mild hepatomegaly. The Typhidot test was positive for IgM. Blood culture was initially done in BACTEC 9050,(Automated blood culture system by B.D.) and was positive after 24 hours' incubation at 35^{o}C. This sample was later sub culturedon Blood and MacConkey'sagarand showed *S. typhi* colonies which were further confirmed by api, (analytical profile index,byBiomeurex, Italy). Sensitivity was applied according to Kirby Bauer's Disc diffusion method using CLSI 2016 guidelines,and the organism was found sensitive to only three drugs: Augmentin, Chloramphenicol and Imipenem. The patient was treated with Imipenem intravenously and recovered.MDR*S. typhi* is on the rise worldwide and effective surveillance methods need to be brought into action to curtail these resistance trends.

Keywords: Multi-drug resistant *Salmonella Typhi*, Enteric fever, Kirby Bauer's Disc diffusion method

Introduction

"Enteric fever" includes both typhoid and para-typhoid fevers. It occurs as a result of systemic infection caused by *Salmonella typhi* and *Salmonella para-typhi A, B&C*. It is transmitted via feco-oral route and is a major cause of morbidity and mortality worldwide. In the year 2014,it was estimated that over 21.6 million (incidence of 3.6 per 1,000 population) of typhoid occurrences worldwide, resulting in 216,000-600,000 deaths and that more than 90% of this morbidity and mortality occurred in Asia.[1]

Resistance of *S. typhi* to has become a major public health concern.Drug resistant *S. typhi* has been reported as early as 1972 in Mexico and been observed in other countries like Bangladesh, Thailand, Vietnam, Korea, Peru and India.[2] Until the mid-1980's the first line drugs ampicillin, chloramphenicol and co-trimoxazole were used as standard treatment for enteric fever. There were reports of isolates resistant to all three first-line anti-salmonella drugs in 1990's resulting in a decline in their usage and fluoroquinolones and extended spectrum cephalosporin became the drug of choice for enteric fever treatment. Simultaneous resistance to three or more different groups of drugs is defined as Multi-DrugResistant(MDR) *S. typhi*. Reduced susceptibility to fluoroquinolones has become a major problem in Asia.Outbreaks with such strains affected eight thousand people in Tajikistan in 1997 resulting in 150 deaths.[3] In a recent study conducted by Dr. Haniya Rashid in the year 2016 (unpublished), at PIMS hospital, showed fluoroquinolone resistance to be as high as 90% but no ceftriaxone resistance was reported. Ceftriaxone has been the mainstay for enteric fever treatment in children and adults likewise. There are reports of emerging resistance to ceftriaxone in studies conducted in Bangladesh, Philippines and Pakistan[2].Currently, emerging resistance to two of the major second line drugs like ciprofloxacin and ceftriaxone poses a major health threat in a developing country like Pakistan. Here, we report the first case of ceftriaxone resistant *S. typhi* infection in Children hospital, PIMS.

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Case Report

A four-and-a-half-year-old girl named Maryam presented to children hospital OPD on 30th May, 2017 with a history of fever, abdominal pain and loss of appetite for last one month. On physical examination she appeared irritable and dehydrated. Her nutrition status was poor, her vitals were as follows, Heart rate:110/min, Respiratory rate: 35/min and Temperature: 102°F. Systemic examination was unremarkable with the exception of abdominal tenderness and a mild hepatomegaly. She tested positive for IgM in Typhidot test conducted two weeks prior to admission. She was previously given Levofloxacin, Ciprofloxacin and Ceftriaxone with no effect. She was admitted to Children hospital and following tests were conducted, Blood CP, LFT's, RFT's, Serum electrolytes, Urine RE &C/S and Blood C/S. Her urine culture was negative and blood CP showed T.L.C.:5.7 10^9/L, Red cell count: 3.7 million/ul, Hb: 9.2 g/dl, HCT: 28.7, MCV: 77.6 fl, MCH: 24.9 pg, MCHC:32.1 g/dl and Platelet count of 130,000/ul. DLC showed 45.5% Neutrophils, 52.3 % Lymphocytes and 2.2% mixed cells.

Her blood culture was received in MCH lab on 30th May, 2017. Blood culture was initially incubated in BACTEC and was positive after 24 hours' incubation. This sample was later sub cultured onBlood and MacConkey's agar. After incubation for 18 hours at 35°C, on Blood agar: grey-white, small, 2-3 mm diameter non-hemolytic colonies were seen which were oxidase negative and catalase positive. On MacConkey's agar non-lactose fermenting small, pale and non-mucoid thin flimsy colonies were seen. Biochemical identification was done via API (analytical profile index), which further confirmed the organism isolated as *S. typhi*.

Sensitivity was applied according to Kirby Bauer's Disc diffusion method using CLSI 2016 guidelines. The initial panel of drugs included Ampicillin, Chloramphenicol, Co-trimoxazole, Nalidixic acid, Ciprofloxacin, Ceftriaxone and Imipenem. On second day, the drug panel was extended to rule out ESBL production(extended spectrum beta-lactamase production) and antibiotic discs for Augmentin, Ceftriaxone, Ceftazidime and Cefixime were tested. The isolate was found to be non-ESBLand resistant to ceftriaxone but sensitive to Augmentin. The isolate was termed asMDR *S. typhi*. It was the first ceftriaxone resistant strain to have been isolated from blood samples received at Children hospital. The patient was diagnosed as a case of Typhoid fever caused by *S. typhi* resistant to Ceftriaxone, which is the drug of choice for typhoid treatment in our setting. The patient was further treated with Imipenem intravenously for two weeks with complete resolution of signs and symptoms. She was rendered afebrile on day 7 of treatment and her abdominal pain settled and appetite improved by 10th day. She was discharged on 10th of June, 2017.

Discussion

Enteric fever due to *S. typhi* is generally treated with Ceftriaxone in our setting. As Ciprofloxacin resistance has emerged over a period of time, Ceftriaxone became a preferred drug of choice for enteric fever for the clinicians. This is the first reported case of Ceftriaxone resistance at Children hospital, Islamabad. A previous study conducted in Fatima Memorial hospital, Lahore in the year 2006 showed of 7% (n=6/86) isolates were resistant to Ceftriaxone(2). Similar reports of resistance were made in a study conducted in Philippines in 2008.[4] A study conducted in Bangladesh in 2015 showed a remarkably higher resistance of 68.57% which is contradictory to other reports of resistance.[5] Linkages between qnr plasmids, genes encoding extended spectrum beta lactamases and AmpC type beta lactamases may reflect association between resistance to quinolones and extended spectrum cephalosporin which was concluded in a study published in Journal of Global infectious Diseases. No other details are available on ceftriaxone resistance mechanisms as yet.[6] This emerging Ceftriaxone resistance leaves us with fewer options to treat Enteric fever e.g. Imipenem which is the alternative to treat MDRST. The sensitivity to chloramphenicol can be attributed to its rollback sensitivity as the usage of all first line drugs had been stopped by the year 1990 due to their widespread resistance. This still cannot be adopted as a drug of choice since the mechanisms of resistance developed earlier can affect their efficacy in the long term again. Azithromycin is another drug which showed resistance as high as73.4 %,as reported earlier in a study conducted at PIMS in the year 2016 (unpublished), other latest studies conducted in Bangladesh and India showed Azithromycin resistance rates of 79.49% and 21.9% respectively.[7,8] We stress that before starting any antibiotic the blood culture should be done and the therapy may be given according to the sensitivity results available.

Conclusion

Multi-Drug Resistant *Salmonella Typhi* is on the rise worldwide and is an alarming global health concern. This necessitates further studies into genetic mechanisms underlying Ceftriaxone resistance and to monitor local antimicrobial resistance patterns in hospitals. Effective surveillance methods need to be brought into action to curtail these resistance trends.

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HISTORY	
Date Received:	09.05.2017
Date Sent for Reviewer:	18.05.2017
Date Received Reviewers' Comments:	05.07.2017
Date Received Revised Manuscript:	15.08.2017
Date Accepted:	07.09.2017

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