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Paediatrics

EMERGING AZITHROMYCIN RESISTANCE IN ORGANISMS CAUSING ENTERIC FEVER IN UTTARAKHAND

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ABSTRACT Enteric fever is associated with significant morbidity worldwide. More than 26 million culture positive cases of enteric fever are seen throughout the world. This disease is endemic in India. Emergence of fluoroquinolone resistant and multidrug resistant strains has changed the global landscape of typhoid. There has been gradual shift in minimum inhibitory concentration effective antibiotics. Emergence of resistance to third generation cephalosporins and macrolides in India and neighboring countries poses a new challenge. Multi-drug resistant typhoid has been reposted from various parts of India. But studies involving pediatric age group are rare from Uttarakhand. This study was planned to study the resistance pattern of enteric fever from this region. Out of 67 cases included in the study, 20 were culture positive. 1 isolate each was resistant to ceftriaxone and cefixime while 3 isolates were resistant to azithromycin.

KEYWORDS : Enteric Fever, Typhoid, Resistance, Pediatric, Azithromycin.

INTRODUCTION:

Enteric fever, is an acute febrile illness caused by gram-negative microbe Salmonella enterica serovar Typhi (S. Typhi), Salmonella Paratyphi A, Salmonella Paratyphi B (Schotmulleri) and Salmonella Paratyphi C (Hirschfeldii). In 2010, 13.5 million cases of typhoid fever were reported, and both typhoid and paratyphoid fevers together accounted for >12 million disability- adjusted life-years(1). The same year, deaths due to typhoid fever were 7.2 per 100,000 population in sub-Saharan Africa. Antibiotics are the mainstay of treatment. Earlier chloramphenicol used to be the drug of choice for the treatment of typhoid fever. But the emergence of resistance, combined with side effects of the drug saw it being replaced by newer antibiotics. Drug resistance in Salmonella has continued to evolve and in the past 20 years, multidrug resistant and extremely drug resistant strains of S. Typhi have emerged(1). And now azithromycin resistance is being increasingly reported from India and abroad (31% and 33.65% respectively)(2). In Uttarakhand, studies pertaining to typhoid are few and there is a lack of literature regarding epidemiology, clinical characteristics and antibiotic sensitivity pattern of enteric fever. High prevalence of clinically similar seasonal febrile illness (malaria, scrub typhus, etc.) in the state makes it pertinent to have adequate studies about typhoid, its prevalence and antibiotic sensitivity pattern in the state.

REVIEW OF LITERATURE:

Global incidence of typhoid fever is 26,948,739 episodes annually(3, 4). Incidence of typhoid in India, is estimated to be 497.2 (95% CI, 291.9– 754.8)/100000/year(5). These estimates are derived from data of in-hospital patients. As most of the caseload is taken by OPD and only a fraction of patients attending OPD are admitted, true estimate of disease prevalence is hard to determine(6). Risk factors for community transmission of typhoid include food consumption from street vendors, socio-economic status, general hygiene, water storage and handling. More than 20% of homes in 6 of the 13 districts in Uttarakhand do not have a safe drinking water supply close to their homes. Percentage of households not covered by sanitation vary between 10-20% across districts of Uttarakhand(7).

Common manifestation of typhoid includes fever, coated tongue, anorexia, vomiting, loose stools, abdominal pain, and toxicity(1). Traditionally diagnosis of typhoid fever is confirmed by Widal test, rapid card tests based on serology, blood culture and at times culture from bone marrow or splenic aspirate. Blood cultures are positive in approximately 40– 60% of the patients. General principles of treatment in typhoid fever include adequate hydration, rest, correction of fluid and electrolyte imbalance if any, and proper use of antipyretics for symptomatic relief. Antibiotic therapy is started empirically based on prevalent antibiotic sensitivity pattern in the region and is later modified based on culture results if needed(1). Current recommendations are to use chloramphenicol or amoxicillin in uncomplicated enteric fever caused by fully sensitive strains, while fluoroquinolones or cefixime should be used for MDR strains and azithromycin and ceftriaxone should be used in case of quinolone resistant strains. In case of severe enteric fever, fluoroquinolones are recommended for fully sensitive as well as MDR strains, while ceftriaxone or cefotaxime is recommended for fluoroquinolones resistant strains(1).

Rising antimicrobial resistance in Salmonella typhi and S. paratyphi is a disconcerting development. Studies have shown widespread increase in antibiotic resistance among Salmonella typhi(2, 8, 9).

MATERIALS AND METHODS:

AIM: To study clinico-microbiological profile of enteric fever in children (6 months to 18 years).

OBJECTIVES:

Primary objective- Estimation of current resistance and sensitivity pattern of organisms causing enteric fever for commonly used antibiotics.

Secondary objectives-

1. Estimating the number of cases yielding a positive result on culture.
2. Antibiotic sensitivity of commonly used antibiotics in culture-positive cases.

Study population: AIIMS Rishikesh caters chiefly to patients from western Uttar Pradesh and Uttarakhand. As such, we get the population from the Himalayan and sub-Himalayan regions as well as from the great northern plains of India. Within this population, our study included those patients whose ages lay between 6months to 18 years. Patients presenting to AIIMS, Rishikesh, with history and clinical features suggestive of enteric fever were evaluated and enrolled in the study after confirmation of diagnosis by serology or culture.

Duration of study: 18 months (April 2018 to September 2019).
Place of study: AIIMS Rishikesh.
Study design: Cross-sectional observational study.
Sample size: Calculated by $4pq/l^2$

p= expected resistance to antibiotics (antibiotic resistance to

azithromycin and ceftriaxone is 21% and 23% respectively)
q= 1-p

l=precision(for this study, precision is taken as 10%) Hence sample size= 67.

Inclusion Criteria:
1. Willingness to participate (giving written informed consent).
2. Acute onset fever, without known focus, or with classical signs and symptoms of typhoid fever like fever, abdominal pain, headache, rash, malaise, diarrhea/constipation.
3. Age group- 6 months to 18 years.
4. Widal titre > 1:80. (O antigen) or Typhidot- IgM positive cases or Urine, blood or stool culture-positive for Salmonella typhi or Salmonella paratyphi.

Exclusion criteria:
1. Fever with a known focus other than typhoid (UTI, Upper respiratory tract infections, LRTI, etc.)
2. Unwilling to participate in the study.

Study Plan: All patients presenting to AIIMS Rishikesh OPD/IPD with complaints suggestive of typhoid fever were evaluated by history and examination. Other common febrile illnesses were ruled out by doing PS for MP, ICT for MP, Scrub typhus IgM, Dengue serology. Routine investigations, serological tests for enteric fever (Widal test or rapid card test for enteric fever) and blood culture were done. Cases testing positive by serology or culture were included for final analysis in the study.

Laboratory Methods: All microbiological tests were performed as per the latest Clinical and Laboratory Standards Institute (CLSI) guidelines. 2- 10 ml venous blood sample was obtained for blood culture under all aseptic precautions and transferred to BacT/ALERT pediatric bottles using the same syringe. These bottles were incubated for 72 hours and if any alert for growth was found, it was cultured on appropriate media as per guidelines. Cultures for Salmonella were incubated on Deoxycholate citrate agar and MacConkey agar for 1 week before declaring them as positive or negative. Rapid card test for detection of IgM and IgG antibodies against Salmonella typhi was done using Enteroscreen-WB kit, manufactured by Zephyr Biomedicals (a division of Tulip diagnostics private limited). Test was performed by putting a drop of serum (obtained after centrifuging blood sample in plain vial at 30,000 rpm for 2 minutes) in each of dual membrane kits. Widal test was done in 21 patients, who gave consent for the test. This test had to be dome extramurally as it was not being performed at laboratory of AIIMS Rishikesh during the period of this study.

Antibiotic sensitivity was checked for Chloramphenicol, Co-trimoxazole, Fluoroquinolones, Cefixime, Ceftriaxone, Azithromycin.

Antibiotic resistance was determined by using both conventional and automated methods based on MIC.

Data Collection:
Details of the patients were recorded in a pre-designed and pretested format. This included their presenting signs and symptoms, their laboratory parameters and outcomes.

OUTCOME PARAMETERS:
The outcome parameters were analyzed and recorded, in terms of objectives of the study.

RESULTS:

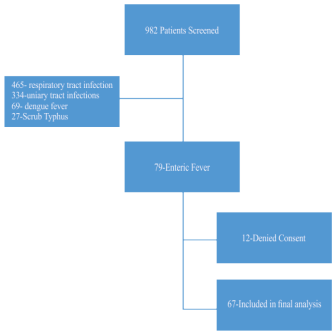

Figure 1: Diagram Showing Inclusion Of Patients In Study.

All patients testing positive by serology (rapid card test for antibodies and widal test) and blood culture were included in final analysis. Rapid card test for enteric fever, was positive in 54 of the 67 cases (80.6%). Widal test was done in 21 patients only (consent given by 21 patients only), as it was not done intramurally. It was positive for 17 of the 21 cases (81%). Table 1 shows demographics of patients included in study.

Table 1: Demographics of patients include d in study.

Demo graphic parameters	Values
State: ·Uttarakhand. ·UttarPradesh. ·Others.	 49 17 1
Agegroup: ·0-5years. ·6-10years. ·>10years.	 16 23 28
Sex: ·Males ·Females	 36 31
Management: ·OPD ·IPD	 42 25

Blood culture was sent for 64 of the 67 cases included in study, of which 20 were positive (31%). 1 culture was positive for Salmonella paratyphi A while 19 were positive for Salmonella typhi. The patient who tested positive for Salmonella paratyphi A was a resident of Rishikesh. The paratyphi A isolated, had intermediate sensitivity to ciprofloxacin, ceftriaxone and cefixime & was resistant to chloramphenicol. Lowest sensitivity was recorded for ciprofloxacin (11 of the 20 culture positive cases), while highest was recorded for ceftriaxone and cefixime (18 of 20 culture positive cases). Highest resistance was recorded for ciprofloxacin (8 of 20 cases) closely followed by chloramphenicol (7 of 20 cases). 3 cultures each were resistant for cotrimoxazole, ampicillin and azithromycin.

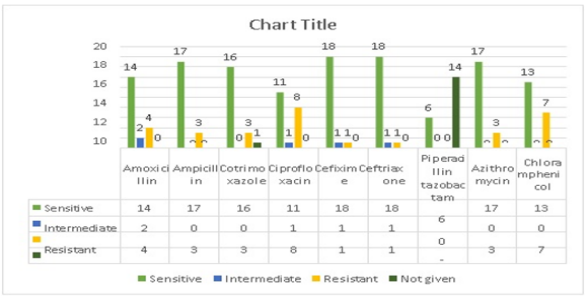

Figure 1: Blood culture and sensitivity pattern of isolated or ganisms

It was seen that prior antibiotic exposure reduced culture positive rates significantly. Table 2 shows difference in culture positivity among those who received antibiotics before drawing cultures and those who did not.

Table 2: Comparison of blood culture positivity among those with prior antibiotic exposure to those without prior antibiotic exposure.

Extramural antibiotics	Taken	Not taken	
Blood Culture			
Positive	7	13	P value 0.0001
Negative	43	4	
Total	50	17	

DISCUSSION:
Mean age of the patients included in this study was 9.2 years (Median- 9 years, SD 4.5 years) which is similar to that observed in previous studies(10, 11).

Of the 67 patients included in our study, 36 were males (53.7%) and 31 were females (46.3%). Other studies have found similar results, with slightly higher incidence of enteric fever among males(12, 13).

Geographical distribution of the included cases revealed 17 patients were from Uttar Pradesh (mostly from districts of Bijnor and

Saharanpur), 49 from Uttarakhand, and 1 patient was from Punjab (on vacation in Uttarakhand). This distribution was on expected lines and follows the demographics of patients attending our OPD.

Rapid card test for enteric fever, was positive in 54 of the 67 cases (80.6%) whereas Widal test was 81% cases. For our set up we took a cut off value of titre >1:80 based on previous study done in this geographical region(14, 15).

Microbiological growth was obtained in 20 cases, of which 19 were Salmonella typhi, while 1 was Salmonella paratyphi A. Blood culture was positive in only 14% of the patients who had received antibiotics prior to sampling for culture. In patients who had not received antibiotics till drawing culture samples, blood culture positivity increased to 76.5%. This shows that rampant antibiotic use can have impact on culture results. This has also been implicated in rise of antibiotic resistance(16).Most frequently, resistance was documented for ciprofloxacin (40%).

Most of the culture positive cases were sensitive to ceftriaxone and cefixime (18 of 20 culture positive cases). 3 cases were resistant to azithromycin. Other studies from the Indian subcontinent have also reported rising resistance to antibiotics like cefixime and azithromycin owing to indiscriminate use of these agents(8, 17, 18). In our study, we found 1 MDR isolate of Salmonella typhi, in a patient who was resident of Bijnor, Uttar Pradesh. A recent study has reported extended spectrum beta lactamase (ESBL) production by Salmonella typhi isolates from patients residing in Himalayan foothills(14). As such, isolation of MDR Salmonella in our study becomes significant.

CONCLUSION:

Enteric fever is still a public health challenge in India. Poor quantification of disease burden combined with emergence of resistance in Salmonella against commonly used antibiotics is a looming threat, against which our existing healthcare system is ill prepared. Nearly 1% patients presenting to our OPD were diagnosed with enteric fever. This value is suspected to be higher in community. Most of the patients can be managed on OPD basis with appropriate antibiotics. Antibiotic prescription also needs to be monitored in community for both patient welfare and checking the rise of antibiotic resistance. Resistance to ciprofloxacin was on expected lines. Emergence of resistance to Azithromycin is worrying. Another facet of the problem is spread of resistant salmonella strains to new areas, which includes sub-Himalayan region. Till now, no MDR strains have been reported from Uttarakhand. The one case we had, was resident of Bijnor, Uttar Pradesh, where there is high prevalence of resistant strains. Now, with large number of patients, coming to Rishikesh from western Uttar Pradesh, combined with tourist inflow from all over India, there is greater risk of spread of resistant strains in this region as well. Hence, we recommend caution in use of antibiotics, early identification and appropriate treatment of enteric fever cases in hospitals and community. Patient education, provision of safe drinking water and good sanitation facilities at community level will help control spread of the disease. For patients who can afford, typhoid vaccine (as recommended by IAP) should be given. Owing to endemicity of enteric fever in India, it would not be a bad idea to implement large scale vaccination strategies against typhoid, by incorporating typhoid vaccine in national immunization schedule. Further studies should be planned with bigger sample size to check resistance of Salmonella typhi to azithromycin and 3rd generation cephalosporins.

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