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ORIGINAL ARTICLE

Clinical and Laboratory Profile and Response to Antibiotics in Typhoid Fever

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ABSTRACT

Objective: To study the clinical and laboratory profile and response to antibiotic therapy in typhoid fever.

Study Design: Quasi experimental study

Place and Duration of Study: The Children's Hospital, Lahore from December 2019 to May 2020.

Material and Methods: Total of 200 patients between 01 to 15 years of age who fulfilled the criteria of confirmed and clinically suspected cases. Data was analyzed by SPSS 20.

Results: There were 120 males and 80 females. 52% of patients were under 5 years of age. Only 6% were using boiled water. Mean duration of fever was 14 ± 6 days. The most common symptom was anorexia (57%) and clinical sign was coated tongue (52%). Blood cultures were positive in 21%. All isolates were 100% sensitive to azithromycin and meropenem. None were sensitive to ciprofloxacin, ampicillin and chloramphenicol. 28% were sensitive to co-amoxiclav, 14% to Co-trimoxazole, 9.5% to ceftriaxone and cefixime each, 85% to amikacin and 81% to piperacillin-tazobactam. 37% patients responded to ceftriaxone, 35% to azithromycin and 25% to meropenem.

Conclusion: Sensitivity pattern has revealed a significant proportion of multidrug and extensively drug resistant strains. Continued surveillance of resistance patterns and formulation of antibiotic therapy for a step wise approach accordingly as in our study for their judicious use is the need of hour.

Key Words: *Typhoid fever, Antibiotics, Sensitivity*

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INTRODUCTION

Typhoid fever caused by *Salmonella typhi* remains a serious public health problem in developing countries. Main source of infection is contaminated food, water and poor hygiene. It is endemic in Pakistan where burden of typhoid is significant and occurs largely in children with the highest rates occurring in children under five years of age especially in resource limited overcrowded communities with poor sanitation facilities.[1]

Typhoid fever can involve various organs leading to wide range of presentation from uncomplicated to complicated typhoid fever. The diagnosis poses challenges because of diversified clinical presentation and manifestations as well as resemblance with many other febrile illnesses. Bone marrow culture offers the greatest sensitivity at upward of 80%. However, it is expensive, invasive and not commonly used. Consequently, although less sensitive, blood culture remains the practical standard for typhoid fever diagnosis.[2] Because sensitivity is less than 100%, and has the potential to be influenced by over-or under-fill of sample vials and contaminants within samples, case detection with a single-blood culture underestimates typhoid fever incidence. Antimicrobial use can produce false-negative blood cultures also results in underestimating typhoid fever prevalence in febrile patients. Additional diagnostic challenges in low-resource settings include capacity limitations (i.e., shortages in trained staff, diagnostic tools, quality control etc.) that make it difficult to distinguish typhoid from paratyphoid fever and other causes of acute febrile illness.[3]

Alarming increase in antibiotic resistance and emergence of multidrug resistant strains severally limit the therapeutic options available and has the potential to drive increased burden and case fatality. Asia continues to be the crucial hub for enteric fever. Multidrug-resistant strains (MDR), defined as strains resistant to ampicillin, chloramphenicol, and trimethoprim sulfamethoxazole emerged in the 1980s.[4] This led to the adoption of fluoroquinolones and third generation cephalosporins as an alternate and resistance to them also began to emerge because of widespread indiscriminate use resulting in extensively drug resistant (XDR) typhoid. Treatment options have narrowed down to only two drugs; oral azithromycin and intravenous carbapenems.[5]

Unlike Sindh province, there are paucity of studies on drug susceptibility patterns in Punjab which are direly needed to formulate antibiotic protocols accordingly thus making sure their judicious use. This will reduce the burden of drug resistant strains.

MATERIALS AND METHODS

This quasi-experimental study was done in Pediatric Medical Ward of The Children's Hospital, Lahore on 200 patients between 01 to 15 years of age, with confirmed and clinically suspected cases of typhoid fever. Patients presenting with encephalopathy and intestinal perforation or hemorrhage were excluded. Confirmed cases of typhoid fever were those with *Salmonella typhi* isolated from blood culture while the clinically suspected cases were those with documented fever of fever 38 ^{0}C and above for at least three days prior to presentation in hospital and having no other focus to explain the cause of fever along with one or more of the following; coated tongue, hepatomegaly or rise in alanine aminotransferase (ALT) levels. Response was defined as the patient becoming afebrile within 5 days of starting antibiotics therapy or there is a decrease in the intensity and frequency of fever along with subjective improvement like return of appetite and decreasing need for regular antipyretics

A proforma was used to enter all the information. Demographic data, patient's source of drinking water, knowledge about typhoid vaccination, duration of fever along with signs and symptoms and history of prior courses of antibiotic therapy were noted. Complete blood counts, liver function tests (total bilirubin, ALT) and blood cultures were sent for all patients. Leucopenia was defined as white blood cell counts less than 4×10^{9}/ L and thrombocytopenia as platelets less than 150×10^{9}/ L. Malaria and dengue infections were ruled out. If blood culture turned out to be positive, its sensitivity pattern to empirical antibiotics as well as other commonly used antibiotics was accounted for.

All the patients were started on 75 mg/kg/day of intravenous ceftriaxone as first line drug and if the patient didn't respond in 5 days, oral azithromycin was added in a dose of 20 mg/kg/day while stopping the first line drug. If the patient responded to ceftriaxone it was continued to complete 14 days. Azithromycin responsive patients completed 10 days of therapy. If patient did not respond to azithromycin alone, intravenous meropenem in a dose of 60 mg/kg/day was added and continued for 10 days. If any time during treatment, culture and sensitivity patters became available, antibiotic therapy was modified accordingly.

Test of significance was applied and value less than 0.05 (p = 0.05) was considered significant. Data was analyzed by SPSS 20.

RESULTS

A total of 200 patients were enrolled in this study.

There were 120 (60%) males and 80 (40%) females. Majority of patients (n=104, 52%) were under 5 years of age. None of the patients had any knowledge about typhoid vaccination. Only 12 patients (6%) were using properly boiled water. There was history of prior intake of antibiotic therapy before hospital admission in 60% of patients. Mean duration of fever was 14 ± 6 days. Fever was found in 100% of patients followed by anorexia (57%), abdominal pain (42%), vomiting (32%) and diarrhea (31%). The most common clinical sign was coated tongue (52%) followed by hepatomegaly (9%). Thrombocytopenia was found in 28 (14%), leucopenia in 10 (5%), leukocytosis in 3 (1.5%) while ALT derangement was noted in 62 (31%) patients. Blood cultures were positive in 42 (21 %) patients (table 1).

TABLE 1: Demographic, clinical and laboratory profile of typhoid patients

	Number	Percentage
Males	120	60.00
Females	80	40.00
Age:		
1 – 5 years	104	52.00
6 – 10 years	64	32.00
11 – 15 years	32	16.00
Use of filtered water	102	51.00
Use of boiled water	12	06.00
Use of tap water	86	43.00
History of prior antibiotic therapy	120	60.00
Knowledge about typhoid vaccination	0	0.00
Symptoms:		
Fever	200	100.00
Anorexia	114	57.00
Abdominal pain	84	42.00
Vomiting	64	32.00
Diarrhea	62	31.00
Constipation	12	6.00
Cough	20	10.00
Signs:		
Coated Tongue	104	52.00
Hepatomegaly	18	9.00
Jaundice	04	02.00
Lab Parameters:		
Thrombocytopenia	28	14.00
Leucopenia	10	05.00
Leukocytosis	03	1.50
Raised alanine aminotransferase (ALT)	62	31.00
Positive blood culture	42	21.00

In the positive isolates, all were found to be 100% sensitive to azithromycin, meropenem and imipenem. None of the isolates were sensitive to ciprofloxacin, ampicillin and chloramphenicol. Among third generation cephalosporins, only 4 isolates (9.5%) were sensitive to Ceftriaxone and cefixime each. Among miscellaneous antibiotics, 36 isolates (85%) were found to be sensitive to amikacin while 34 isolates (81%) were sensitive to piperacillin-tazobactam. Seventy-four patients (37%) responded to ceftriaxone alone, 70 patients (35%) responded to azithromycin while fifty-six patients (28%) responded to meropenem (table 2).

TABLE 2: Sensitivity pattern of Salmonella Typhi

Antibiotic	Number of Sensitive Isolates	% of Sensitivity	Number of resistant isolates	% of Resistance
Empirical antibiotics:				
Ceftriaxone	04	9.5	38	90.0
Azithromycin	42	100.0	0	0.0
Meropenem	42	100.0	0	0.0
Miscellaneous:				
Cefixime	04	9.5	38	90.0
Co-amoxiclav	12	28.5	30	71.0
Ampicillin	0	0.0	0	0.0
Co-trimoxazole	6	14.0	36	85.7
Chloramphenicol	0	0.0	0	0.0
Ciprofloxacin	0	0.0	0	0.0
Piperacillin-Tazobactam	34	81.0	8	19.0
Amikacin	36	85.7	6	14.0

Total blood culture = 200 Positive blood culture = 42

DISCUSSION

Typhoid fever is considered as one of the most serious infectious diseases and threat to public health on global scale especially in developing countries with serious concerns over the fast-emerging *Salmonella typhi*.

Most of our patients (52%) were between 01 to 05 years of age. None of patients had any knowledge of typhoid vaccine. Only 6% patients were using properly boiled water. Consumption of unsafe water along with poor sanitation and hygiene, inappropriate food handling and limited surveillance are known risk factors for contracting the disease.[4] So, actions should be taken at all health care levels to implement preventive strategies like safe water, improved sanitation and widespread vaccination.

Fever was the presenting complaint in 100% of patients followed by anorexia (57%), abdominal pain (42%), vomiting (32%) and diarrhea (31%). Comparable results were shown by an Indian study[5] where majority of patients (61%) presented with anorexia followed by vomiting and abdominal pain. In our study the most common physical sign was coated tongue (52%) followed by hepatomegaly while the same Indian study showed toxic look as the most common sign followed by coated tongue and hepatomegaly.[5]

The most common hematological abnormality in our patients was thrombocytopenia (14%) followed by leucopenia (5%). In contrary to our results two Indian studies had leucopenia as the most common abnormality in complete blood counts[5,6]. Additionally 62 of our patients (31%) had raised alanine aminotransferase (ALT).

Out of 200 blood cultures, 42 (21%) were positive for *Salmonella typhi*. Local study by Javed et al has reported comparable results of 23.2%.[7] Another study from Pakistan has shown good yield of 83.7% out of 129 blood cultures.[8] Two Indian studies have reported comparable results of 20% and 27.9%.[5,6] Isolation of salmonella from blood still remains a challenge due to prior indiscriminate use of antibiotics and thus a low yield due to over the counter availability, poor quality control and inability of general practitioners to use antibiotics rationally and in proper dosages and duration. Majority of patients (60%) in our study had history of taking at least one or two courses of antibiotics before hospital admission.

Our study showed that majority of *Salmonella typhi* were multi drug resistant (MDR) and extensively drug resistant (XDR).Only 14% were sensitive to co-trimoxazole while 28.5% showed sensitivity to co-amoxiclav. None of the salmonella were sensitive to ampicillin and chloramphenicol. In a latest study from Karachi, similar poor sensitivities to first line of antibiotics were noted.[9] Comparable results were reported from a study in Bangladesh where 11% sensitivity was found for co-trimoxazole and 38% for ampicillin.[10] Contrary to our results Patel et al from India reported 100% sensitivity to all the above mentioned first line antibiotics.[11] This shows a wide variation in the region with some centers reverting to chloramphenicol and co-trimoxazole and hence the importance of ongoing studies. Possible reintroduction of older first line antibiotics in future which are showing somewhat sensitivity can be considered at some point. Though these agents have the advantage of being inexpensive and easily available but also have the demerits of higher relapse rates and need of longer duration of therapy.

Salmonella typhi showed only 9.5% sensitivity to ceftriaxone and same results were found for cefixime. Wide variations in results of local studies were noted. A study from Lahore showed isolates to be 100% sensitive[12] and same was the case with regional studies from Bangladesh and India.[10,11] Recent study from Karachi reported 3.64% sensitivity[13] while another one from Civil Hospital Karachi showed 24% sensitivity.[9]

There was 0% sensitivity of isolates to ciprofloxacin. Comparable results were shown in a study in Karachi by Siddique et al.[9] A study done in Lahore reported 7% sensitivity.[12] Contrary to our results study done in India showed better sensitivity patterns of 81%.[11]

An interesting observation was noted in the sensitivity patterns of isolated salmonella as 85% of them showed good sensitivity to piperacillin-tazobactam and 80% for amikacin. These might be considered the agents of choice for hospitalized patients in future and thus reducing the burden on azithromycin and carbapenems.

Our study demonstrated 100% sensitivity to azithromycin, meropenem and imipenem. Local study in a tertiary care center in Karachi showed 100% sensitivity too.[14] Regional studies are also showing promising results for Azithromycin. Nair et al reported 100% sensitivity of salmonella to azithromycin and thus 100% clinical cure rate.[15] Ali et al from Bangladesh showed 88.4 % sensitivity to azithromycin.[10]

Prior use of antibiotic therapy before making a definitive diagnosis of typhoid fever is one of the known factors responsible for negative outcome of cultures and our study showed a significant association between these two variables (p = 0.001). Hence the stress is to rationally use antibiotics and taking culture samples before the first dose.

Different centers are using different antibiotic protocols for the treatment of typhoid patients. There are multiple reports on monotherapy as well as dual therapy. Nagarag et al[16] from India reported oral azithromycin to be as effective as intravenous ceftriaxone while other studies showed oral azithromycin to be more efficacious in uncomplicated typhoid fever.[15,17] In our study Seventy-four patients (37%) showed clinical response to ceftriaxone alone while 70 patients (35%) had to be switched over to azithromycin due to failure of ceftriaxone. Fifty-six patients (28%) went on to have meropenem in addition to azithromycin. Hussain et al has reported the same results with meropenem.[18] High intracellular concentration of azithromycin along with long half-life, easy dosing schedule, shorter duration of therapy, less or no relapses and being cheap are the reasons it is fast replacing conventional choices.

Our opinion is that there is a need for step wise approach in introduction of antibiotics and to start with already in use older drugs for hospitalized patients like ceftriaxone while keeping in mind that many salmonella isolates are still sensitive though in small numbers and a clinical cure is achieved in a good percentage of patients like in our study thus leaving azithromycin and carbapenems as a last resort as this is what is left for *XDR Salmonella typhi.*[19,20]

CONCLUSION

Sensitivity pattern of *Salmonella typhi* has revealed a significant proportion of MDR and XDR strains. Continued surveillance of resistance patterns and formulation of antibiotic therapy for a step wise approach accordingly for their judicious use is the need of hour. Additionally, public health awareness campaigns regarding safe drinking water, sanitation, hygiene and vaccination need to be employed to reduce disease burden and prevent drug resistant infections.

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