

Clinical Presentation and Drug Resistance Patterns of Salmonellae Typhi and Paratyphi at a Tertiary Care Hospital of Sindh

1. Rukhsar Ali Shahani 2. Shazia Begum Shahani 3. Ghulam Mustafa Dahri
4. Haji Khan Khoharo

1. Asstt. Prof. of Community Medicine, Isra University, Hyderabad 2. M.Phil Student of Anatomy, Isra University, Hyderabad 3. Asstt. Prof. of Pharmacology, MMCH, Mirpurkhas 4. Asstt. Prof. of Medicine, Muhammad Medical College / Hospital Mirpurkhas

ABSTRACT

Objective: The aim of this study is to evaluate the clinical presentation and drug resistance patterns of Salmonellae typhi & paratyphi

Study design: Observational Descriptive Study.

Place and Duration: This study was conducted at the Muhammad Medical Hospital Mirpurkhas, from Jan 2010 to April 2011.

Materials and Methods: One hundred twenty six patients were studied, who satisfied the clinical and laboratory criteria of typhoid/paratyphoid fever. The blood samples, 5–10 ml from adults were inoculated directly into blood culture bottles. Subcultures were also performed. Antibiotic sensitivity was tested by the Kirby–Bauer technique according to Clinical and Laboratory Standards Institute guidelines. Statistical analysis was performed on SPSS version 10.0. (Chicago, Illinois, USA), using the chi-square test and student's t-test for the qualitative and quantitative variables respectively.

Results: The identified organisms were S.typhi observed in 91 (72.22%), both S typhi/paratyphi in 18 (14.28%) and S.paratyphi A and B in the rest 17 (13.49%). In 97 (76.98%) of patients, antibody O titers were $\geq 1:160$ and in 39 (30.95%) titers were $<1:160$. The overall multi-drug resistant isolates were found in $>80\%$ for the first line agent's i.e.; ampicillin, amoxicillin, cotrimoxazole and chloramphenicol. The highest sensitivity rate was found for the cefixime (98.41%) and the lowest one for the ampicillin (22.2%).

Conclusions: We found drug resistant and multi-drug resistant salmonellae in our study; this may be because of antibiotic use as self medication, medication by pharmacist and quacks

Key words: Salmonella typhi/ paratyphi, typhoid fever, drug resistance

INTRODUCTION

Enteric fever is a clinical syndrome characterized by constitutional and gastrointestinal symptoms and by headache. It can be caused by any Salmonella species. The term typhoid fever applies when serotype typhi is the cause. Infection is transmitted by consumption of contaminated food or drink. The incubation period is 5-14 days.¹ Pakistan is a hyper-endemic area for typhoid fever. According to WHO 2008 report the incidence of typhoid fever in 5-15 years children was 412 per million in 2002.² Early gastrointestinal manifestations include constipation, mild diarrhoea and abdominal pain. Approximately 50% of patients have hepatosplenomegaly and upto 3-10% develop intestinal perforation.³ A definitive diagnosis of typhoid fever can be made by isolation of Salmonella.typhi (S.typhi) or paratyphi from samples of blood, bone marrow, urine, stool, rose spots or intestinal secretions, and it is regarded as "gold standard method". While the alternative diagnostic methods include serologic testing. However, in countries where typhoid fever is endemic, the specificity of serologic tests is not reliable.⁴ The introduction of chloramphenicol since 1948 reduced the mortality rate to 4%. In the developing countries where

effective antibiotics are not readily accessible to public, mortality rates reach upto 10%, while the mortality rate in the developed countries hardly reaches 1%.⁵ Due to the increasing resistance to traditional antibacterial drugs used for therapy (ampicillin, amoxicillin, cotrimoxazole and chloramphenicol), the fluoroquinolones; such as the ciprofloxacin and ofloxacin became the drugs of choice for the treatment of these infections.⁶ The quinolone were reported to be effective in the treatment of adults with multidrug resistant typhoid with cure rates of 100% and third generation cephalosporins having 82-97% cure rates.⁷ But a number of resistance mechanisms to quinolone in certain parts of the world led to decreased susceptibility of S. typhi to these agents.⁶ Like many tropical areas, typhoid fever remains major public health problem in Sindh, and this compelled us to conduct a prospective study on clinical presentation and drug resistance patterns of typhoid/paratyphoid fever at a tertiary care hospital.

MATERIALS AND METHODS

Patients with a clinical diagnosis suggestive of typhoid fever, admitted at Muhammad Medical College Hospital

Mirpurkhas, Sindh from Jan 2010 to April 2011, were enrolled in the study. A detailed clinical and treatment history was elicited from all the patients. The full blood counts, Widal tests, Liver function tests and roentgenography were ordered. A case of enteric fever/typhoid fever was defined as an isolation of *S. typhi*/paratyphi A and B from a sample of blood in a hospitalized patient. Blood samples were collected from febrile patients whether taking or not an antibiotic therapy. The blood samples, 5–10 ml from adults were collected by venepuncture using aseptic technique, and inoculated directly into blood culture bottles containing 50 ml brain heart infusion broth. The samples were processed according to standard recommended techniques.⁸ The bottles were incubated at 37°C for 7 days and examined daily for bacterial growth. Subcultures were performed on the first, second, third, fifth and seventh day of incubation on 5% sheep blood agar and MacConkey agar.⁹ Suspected non-lactose fermenting colonies were screened biochemically and their identity was confirmed serologically. Antibiotic sensitivity was tested by the Kirby–Bauer technique according to Clinical and Laboratory Standards Institute guidelines.¹⁰ The following antibiotics were used: chloramphenicol (30ug), nalidixic acid (30ug), ampicillin (10ug), amoxicillin (10ug), amoxicillin/clavulanic acid (20/10ug), co-trimoxazole (25ug), ciprofloxacin (5 ug), ofloxacin (5ug), cefotaxime (10ug), ceftriaxone (10ug), cefpodoxime (30ug), sparfloxacin (5ug), azithromycin (15ug) levofloxacin (5ug), and cefixime (10ug). The study was approved by the ethics committee of institute. Statistical analysis was performed on SPSS version 10.0. (Chicago, Illinois, USA), using the chi-square test and student's t-test for the qualitative and quantitative variables respectively.

RESULTS

A total 126 patients including 59 male and 67 female, were studied. Clinical features at the time of presentation are shown in table I. The highest incidence rate for enteric fever was observed from August through November. Most of the patients were in their 2nd and 3rd decade (38.5% and 41.8%). The identified organisms were *S. typhi* observed in 91 (72.22%), both *S. typhi*/paratyphi in 18 (14.28%) and *S. paratyphi* A and B in the other 17 (13.49%) patients. In 97 (76.98%), antibody O titers were $\geq 1:160$ and in 39 (30.95%) titers were $< 1:160$. The drug resistance was observed to one or the other agent. The overall multi-drug resistant isolates were found in $> 80\%$ for the first line agent's i.e; ampicillin, amoxicillin, cotrimoxazole and chloramphenicol. The highest sensitivity rate was found for the cefixime (98.41%) and the lowest one for the ampicillin (22.2%). The drug sensitivity and resistance patterns are shown in table II. Upto 30% of patients were taking one or the other of the first line antibiotics as self medication, were running fever, and blood

cultures were found positive in 70% of them. Liver function tests were altered in 37.30% of patient. Mean bilirubin and SGPT levels were 1.9 ± 0.38 mg/dl and 59 ± 31 U respectively. Full blood counts revealed leukopenia in 74 (58.73%) and leukocytosis in 12 (9.52%).

Table No. 1: Clinical features at the time of presentation (n=126)

	No.	%
Fever	126	100
Chills	95	79.39
Headache	98	77.7
Anorexia	107	84.9
Abdominal pain	27	21.4
Diarrhoea	19	15.0
Constipation	39	30.9
Vomiting	57	45.2
Splenomegaly	71	56.3
Bloody diarrhoea	13	10.3
Leukopenia	74	58.7
Rose spots	19	15.0
Epistaxis	03	02.3
Sore throat	37	29.3
Respiratory symptoms	61	48.4
Meningism	53	40.0
Hepatomegaly	09	07.1
Coated tongue	09	07.1
Disorientation	45	35.7

Table No.2: Antibiotic sensitivity and resistance patterns (n=126)

Antibiotic	Sensitivity (%)		
	Sensitive (%)	Inter-mediate (%)	Resistance (%)
Ampicillin (10ug)	11.1	11.1	77.7
Amoxicillin (10ug)	22.2	9.52	76.19
Amoxi-Clav (20/10ug)	37.3	7.14	55.5
Chloramphenicol (30ug)	15.07	21.42	63.49
Nalidixic Acid (30ug)	19.04	23.01	57.93
Co-Trimoxazole (25ug)	16.6	13.49	69.84
Ciprofloxacin (5ug)	29.36	15.07	63.49
Ofloxacin (5ug)	24.60	16.66	58.73
Cefotaxime (10ug)	47.61	05.55	46.82
Ceftriaxone (10ug)	53.17	18.25	28.57
Cefpodoxime (30ug)	78.57	07.93	13.49
Sparfloxacin (5ug)	80.95	04.76	14.28
Azithromycin (15ug)	88.8	06.34	03.96
Levofloxacin (5ug)	95.23	02.38	02.38
Cefixime (10ug)	96.03	02.38	01.58

DISCUSSION

The antimicrobial resistance of *S. typhi* was rare prior to the 1980s. Chloramphenicol was the treatment of choice, but in the 1980s, resistance to chloramphenicol and alternative agents began to emerge in countries

where *S.typhi* was endemic. Thus ciprofloxacin became drug of choice for typhoid despite limitations to widespread use. Strains of *S.typhi* resistant to chloramphenicol, ampicillin, and co-trimoxazole were reported in South America, the Indian subcontinent, Africa and Saudi Arabia. At the same time, in Southern Vietnam, the multi-drug resistance became established by the early 1990s. Shortly after, isolates of *S.typhi* with reduced susceptibility to quinolone began to appear from the same areas with resistance to first line drugs, thereby threatening these agents for treatment of typhoid fever. Strains of *S.typhi* with decreased susceptibility to ciprofloxacin and resistant to nalidixic acid increased to 23% in the UK in 1999s, mainly in patients returning from travel to Asia who did not respond well to treatment with fluoroquinolones antimicrobials.⁶ A recent prospective population based study in five Asian countries confirmed that *S.typhi* resistance to Nalidixic acid is greater than 50% in both India and Pakistan. Our result of 57.93% Nalidixic acid resistance is comparable with this study.¹¹ Our study shows that >80% of *S.typhi*/paratyphi were multi drug resistant; (resistance to the chloramphenicol, ampicillin and cotrimoxazole). These results are similar to reported 100% resistance in one study from India.¹² The reason of high degree resistance even to quinolone and cephalosporins is because of self medication, medication by the pharmacist and quacks in our local community. The injudicious administration and sub-optimal drug dosaging has contributed to the reduced susceptibility and emergence of multi drug resistant *S.typhi*/paratyphi, not only to the first line drugs but also to the quinolone, azithromycin and cephalosporins. One study from Indonesia revealed 80-90% of typhoid patients were receiving antimicrobials as self medication at home and bed rest;¹³ other patients, those with more severe disease and those treated at home who then developed persisting complaints, presented at the health care centers and hospitals.¹⁴ In our study the crucial finding is that the 30% of patients taking antibiotic therapy yielded positive blood cultures in 70% of them, this reveals the existence of drug resistant salmonellae in the community. The self medication and availability of quinolone and 3rd generation cephalosporins without prescriptions is an illegal practice, it must be stopped. It is a challenge for the public health department, which is sleeping this moment.

CONCLUSION

We found drug resistant and multi-drug resistant salmonellae in our study. The usage of quinolone and cephalosporins as self medication, medication by pharmacist and quacks must urgently be prohibited. The public health department must take a strict action to prevent further drug resistant isolates of salmonellae.

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Address for corresponding author:

Dr Haji Khan Khoharo

Assistant Professor of Medicine.

Muhammad Medical College Hospital Mirpurkhas

B. No C-17/II, Anwer Villas, Phase I, New Wahdat

Colony Qasimabad, Hyderabad, Sindh.

Tel: 0321-3010577

drhajikhan786@gmail.com