PRESENTATION OF TYPHOID FEVER PATIENTS IN HAZARA DIVISION AND RESPONSE TO DIFFERENT TREATMENT REGIMENS

Hassan Shahzad Nazar, Aftab Rabbani, Adeel Riaz, Jasim Anwar
Department of Medicine, Ayub Medical College, Abbottabad

Background: Response to treatment can vary in patients with typhoid fever. This study was carried out on a group of typhoid patients who were treated in Medical B ward of Ayub Teaching Hospital. Resistance to antibiotic is commonly acquired by Salmonella typhi and is widely reported. Objective of study was to identify such resistance in patients coming from parts of Hazara Division. **Methods:** All patients who presented with typhoid fever and admitted to Medical B Unit from 1st July to 30th September 2002 were included in study. Out of 76 patients 46 (60%) were male. Epidemiological date, presenting symptoms, finding on physical examination, laboratory investigation and radiological examination were recorded. Then one of six commonly used treatment regimens were started. Response to treatment was studied. **Results:** Common presenting symptoms and signs were recorded. Headache and fever were seen in 100% of patients. Cough and hypotension were among presenting features in 65% of patients. Leucocyte count of Less than $4x10^3$/dl was seen in 11% of samples. Liver functions and Renal function were found alterd in 30% of patients. Study of response pattern to different regimens suggested relatively poor response to flouroquinolones. Fever of those patients who were treated with chloamphenicol and cefexime ,settled early as compared to patients on other regimens. **Conclusions.** In addition to well known presenting features of typhoid like headache, fever, cough, hypotension and leucopenia abnormalities of renal and liver functions were commonly seen. Response to quinolone was poor suggesting emergence of resistance of salmonella typhi in this area.

Key Words: Tyhpoid, Multiresistance in salmonella, Hazara, Quinolones, Chloroamphenicol.

INTRODUCTION

Typhoid Fever is common infectious condition and serious public health problem in Hazara division like many other parts of the world.[1] Patients report through out the year, in addition to these endemic cases, during months of summer clustering pattern is also observed suggesting epidemics similar to outbreaks reported by others.[2,3] In developed countries where the prevalence of enteric fever is quite low outbreaks are reported.[3] Standards of public health facilities is the main reason to be blamed for higher endemicity of typhoid fever in this area. Matter is made worse because modern laboratory techniques are not available which are needed to specifically identify responsible strains.[4] Almost every summer population of Hazara experiences several epidemics. Manifestation of typhoid fever and its complications are well described.[5] Response of enteric fever to various antibiotics has been changing.[6] Reports from parts of India, Far East and Pakistan are present which suggest that sensitivity pattern of salmonella is showing change.[1,6] Sensitivity of salmonella to different antibiotic in vitro and in vivo may differ which is one of the reason that resistant trend was not appreciated earlier.[7] An impression was there in this area about the reduced efficacy of quinolones in treating typhoid. Therefore a study has been carried out to compare different therapeutic options and identify any difference in efficacy of commonly employed therapeutic regimens. Presentation of typhoid has been reviewed in line with suggestion by some that patients infected with multiresistant strain could have different manifestations as compare to patients infected by sensitive strain [8,9].

MATERIAL AND METHODS

Study group included all patient admitted in medical (B) unit of Ayub Medical Complex between 01.07.2002 and 30.11.2002 in whom diagnosis of typhoid fever was made. Epidemiological data and clinical information were gathered on a proforma. Patients with negative blood cultures were not included. There were 76 patients admitted in the ward who satisfied the criteria for inclusion in to the study. Detailed history was taken from all the patients. Queries were made regarding previous vaccination. All the patients underwent complete physical examination. Every patient had x-ray chest, complete blood count, ESR and urine mircorscopy. Blood, urine and stool samples were sent for culture sensitivity studies. Six treatment regimens were designed and patients were started on any one of them haphazardly, taking care of hypersensitivity history or any other contraindication, with the view that groups of nearly same size should form.

Response to treatment was judged by improvement in symptoms and settling of fever. If temperature did not settle in 6 days of commencing treatment the antibiotic was changed. Patient who responded to initial treatment were treated with the same drug for 14 days. Six treatment regimens were as follow.

Oral or Inj. Ciprofloxacin 500mg IV (12 hourly)

Oral or Inj. Ofloxacin 200mg IV (12 hourly)

Oral or Inj. Chlormycetin 1-gm (8-hourly).

Oral or Inj. Amoxil 1 gm. (8-hourly)

Inj.Cefotrioxone 2-gm (O.D.)

Cap. Cefixime 400mg (O.D.)

RESULTS

Our patients were between the ages of 12 and 60 years. 22 (29%) patients were from Havelian 10 (13%) from Abbottabad and its immediate suburbs, 25 (33%) from Mansehra and 19 (25%) from the Galiat region. 46 (60%) patients were male and 30 (40%) were female.

Frequency of clinical suggestions and results of laboratory data and response to treatment are tabulated in table 1-5. Two (2.6%) patients expired during this study. These both developed multiorgan failure and disseminated intravascular coagulation. Rest of 74(97.4%) patient recovered on one treatment or the other. Fever clearance time of various regimen in cured group is given in table-5.

DISCUSSION

Typhoid is common infection of our area. Spread is through faeco-oral route. Therefore it is common in communities with poor standard of public health. In developing countries millions develop the disease and mortality is as high as 30%.[11] Presenting features seen in this study are comparable to what has been reported earlier.[5] Abnormalities of liver and renal functions seen can be explained on the basis of delay in seeking medical advice which has resulted in inclusion of relatively sick patients in this study. As observed by other workers patients infected by resistant strains are likely to have multi organ involvement and higher rate of complication.[13] This could be another explanation for higher number of patients with renal and hepatic involvement found in this study. Hypotension and cough were two common symptoms and when these two symptoms are present with headache and continuous fever, the possibility of typhoid becomes more likely. Very low number of patients who had been vaccinated show over all low status of vaccination in this community.

Several anti microbial agents have been tried and reported effective in treatment of enteric fever. These include chloramphenicol, ampicillin, co-trimaxazole, cefotraxione, cefixime, azithromycin and various quinolones like ciprofloxacin, oflaxacin, pefloxacin and many others.[1,6,12]

Table-1: Presenting features (n=76)

Features	Found in	%
Headache	76	100%
Fever	76	100%
Prostration and apathy	60	79%
Abdominal pain	55	71%
Palpable spleen	55	71%
Cough	50	65%
Hypotension	50	65%
Relative bradycardia	30	40%
Diarrhoea	20	26%
Constipation	15	20%
Rose spot	4	5%
Vaccination	3	4%

Table-2: Laboratory data (n=76)

Laboratory Investigation	Found in	%
Positive widal test	61	80%
ESR<20mm	56	74%
Hb >10gms%	52	68%
Leucocyt count 4-6x10^3	42	55%
Urea >50mg%	28	36.8%
Creatinine >2mg%	25	32.8%
Hb<10gms%	24	32%
Leucocyt count >6x10^3	23	30%
Raised ALT and Billirubin	23	30%
ESR >20mm	20	26%
Negative widal test	15	19.8%
Leucocyte count <4x10^3	11	14%

Table-3: Response to first treatment (n=76)

Drug	Number of patients	improved	%	Number of patients switched to other treatment
Cefixime	22	17	77%	5
Ciprofloxacin	20	8	40%	12
Chlormycetin	21	20	95%	1
Ofloxacin	5	2	40%	3
Ceftraxione	5	3	60%	1
Ampicillin	4	2	50%	2

Table-4: Result of second treatment

Drug	Number	Improved	percentage
Chlormycetin	8	8	100%
Cefixime	9	8	89%
Ciprofloxacin	4	2	50%
Ampicillin	1	1	100%
Ceftrioxone	1	0	0%
Ofloxacin	1	1	100%

Table-5: Fever clearance time

Drug	Fever clearance time
Chloramphenicol	2.5 days (range: 1-4 days)
Cefixime	3 days (range: 1-5 days)
Cefotraxione	3.5 days (range: 2-6 days)
Ciproxin	5.6 days (range: 3-7 days)
Ampicillin	5.7 days (range: 3-7 days)
Ofloxacin	5.9 days (range: 4-8 days)

As with any other infection, development of newer antibiotic agents has not in any way stopped development of resistance by the salmonella. It is interesting to find that antibiotics used twenty years back have more or less same efficacy when compared to newer agent.

Quinolones had been quite effective against salmonella for more than a decade.[10] Recent reports from India, Fareast, Africa and Pakistan showed that more and more salmonella strains are developing resistance to 4-quinolones and that sensitivity pattern of salmonella typhi has been changing.[6,7] Though the newer agents are available there has been no significant change in deffervescence periods reported, now a days ,as they were when older antimicrobial agents were employed. Therefore it can be inferred that there has been hardly any progress in terms of achieving rapid cure in patients with typhoid fever. Resistance to older treatment has been reported in case of enteric fever and various studies showed that resistance is emerging in vivo and in vitro to ampicillin, cotrimoxazole and cephalosporins. Sensitivity to chloramphenicol has been seen to improve which is probably because of reason that its use in last decade was much less as compare to that of quinolones. Potential for toxicity of chloramphenicol remains a concern but its efficacy justifies its use in typhoid fever. In this study no patient was found to have leucopenia and all the patients tolerated the drug well. An impression that patients who are treated with ciprofloxacin do not get well as quickly as they used to be several years ago, is supported by our observation. In this area such a higher rate of failure in quinolone is partly because of injudicious use of the compound in weakly indicated conditions, which has resulted in emergence of resistant strain probably. A study in sewerage water content and another one on poultry feed showed abnormally high quinolone content which are probably responsible for emergence of microorganism with resistance.[12]

Sensitivity of salmonella to cefixime has been reported.[14] This is safe and effective option in treatment of typhoid fever particularly in adolescent, children and during pregnancy. Treatment of complicated typhoid fever, where multiaorgan failure has taken over remains a challenge. Delay in diagnosis and emerging resistance to existing antimicrobial agents are two important factors leading to this life threatening situation in course of typhoid fever. It is recommended that trend of response we have experienced should be studied further with more meticulous bacteriological and laboratory support and then changing trend of sensitivity of salmonella typhi in our community can be understood with more precision and confidence.

CONCLUSION

Data showed that majority of patients suffering from typhoid were never vaccinated.

Clinical presentation of typhoid fever is more or less comparable with other studies. Patients of typhoid who are treated in Ayub teaching hospital are relatively more sick and have evidence of multiorgan involvement.

Almost half of the patients did not respond to quinolones and even when response was there, it took longer.

Response of enteric patients to chloramphenicol and cefixime is better.

There is an indication that samonella strains in this area have acquired resistance to quinolones and their sensitivity has improved for chloramphenicol and cefixime.

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Address for Correspondence:

Dr. Aftab Rabbani, Department of Medicine, Ayub Medical College, Abbottabad.

Email: draftabrabbani@hotmail.com