STUDY ON CLINICAL PROFILE AND LABORATORY PARAMETERS OF ENTERIC FEVER CASES WITH SPECIAL REFERENCE TO ANTIBIOTIC SENSITIVITY PATTERN

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ABSTRACT

BACKGROUND

Enteric fever is a serious infection caused by salmonella typhi and paratyphi. It is endemic in low and middle socio-economic conditions. It is transmitted mainly by feco-oral route. With the passage of time, the disease spectrum has undergone a sea of changes. Nowadays multidrug resistant infections are often encountered. These are very difficult to treat. In this study, we aimed to investigate the clinical features and laboratory features with special reference to the antibiotic sensitivity pattern. We undertook this study to identify the changing clinical scenarios, the laboratory parameters and above all the antibiotic sensitivity patterns which can guide us to initiate judicious treatment.

METHODS

90 clinically suspected cases of enteric fever were initially selected. Of these, 50 patients whose blood culture was positive for salmonella typhi infection, were selected. Their clinical features, laboratory findings and antibiotic sensitivity pattern were studied in detail. All the data collected were then analysed using descriptive statistics and Chi square analysis.

RESULTS

Fever was universally present along with hepatosplenomegaly. Majority of the patients responded to intravenous ceftriaxone. 90 case records of clinically suspected cases of enteric fever were initially selected, out of which 40 cases were discarded as blood culture was not done or turned out to be negative. Remaining 50 cases were blood culture positive for salmonella typhi. These 50 cases were selected, their data collected and analysed.

CONCLUSIONS

Enteric fever is a common cause of fever in developing countries. Early diagnosis and treatment with proper selection of antibiotics is necessary to avoid major complication, later on. In spite of this, ceftriaxone still remains the drug of choice in uncomplicated enteric fever. Oral Azithromycin and Cefixime also showed good efficacy and a high sensitivity pattern was noted with both of them.

KEY WORDS

Blood Culture, Hepatosplenomegaly

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BACKGROUND

Enteric fever caused by salmonella typhi and paratyphi is not very uncommon in the developing countries. With the passage of time, the disease spectrum has undergone a sea of changes. Nowadays multidrug resistant infections are often encountered. These are very difficult to treat. We undertook this study to identify the changing clinical scenarios, the laboratory parameters and above all the antibiotic sensitivity pattern which can guide us to judicious treatment.

3. Evaluate the haematological, biochemical and radiological parameters.
4. Study the antibiotic sensitivity pattern of the identified salmonella organism.

METHODS

Type of Study

Retrospective cross-sectional hospital based observational study.

Place of Study

Inpatient Paediatric Medicine department of Vivekananda Institute of Medical Sciences

Period of Study

January 2017 to June 2018.

Number of Subjects

50 blood culture positive enteric fever cases.

Inclusion Criteria

Febrile children <12 years of age diagnosed as enteric fever by blood culture, have been included in the study.

Aims and Objectives

1. To identify blood culture positive enteric fever cases.
2. Study of the clinical presentation.

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RESULTS

90 case records of clinically suspected cases of enteric fever were initially selected, out of which 40 cases were discarded as blood culture was not done or turned out to be negative. Remaining 50 cases were blood culture positive for salmonella typhi. These 50 cases were selected, their data collected and analysed.

Positive Blood Culture	No. of Cases (n=50)	Percentage (5)
S. typhi	50	100%
S. paratyphi	0	0%

Table 1. The Above Table Shows That All Blood Culture Positive Cases Showed Growth of Salmonella typhi

Age in Years	No. of Cases (n=50)	Percentage (%)
0-5	20	40
6-12	30	60
Total	50	100

Table 2. Age Distribution

Sex	No. of Cases (n=50)	Percentage %
Male	26	52
Female	24	48
Total	50	100

Table 3. Sex Distribution

The above data shows that there was no significant sex difference in our study.

Age in Yrs. (n=50)	Male	Female	Total
0-5	14	6	20
6-12	12	18	30
Total	26	24	50

Table 4. Age with Sex Distribution

Out of the 50 blood-culture positive cases, among 0-5 years age group, majority were males (70%) and among 6-12 years age group majority were females (60%).

Duration of Fever (Days)	No. of Cases (n=50)	Percentage (%)
1-6	0	0
7-14	47	94
>14	3	6
Total	50	100

Table 5. Duration of Fever at The Time of Admission

Serial No.	Symptom	0-5 yrs. (n=20)	6-12 (n=30)
1.	Fever	20(100%)	30(100%)
2.	Chills	3(15%)	2(6.6%)
3.	Headache	0	2(6.6%)
4.	Vomiting	12(60%)	13(43.3%)
5.	Pain abdomen	13(65%)	20(66.6%)
6.	Constipation	14(70%)	19(63.3%)
7.	Diarrhoea	3(15%)	3(10%)
8.	Skin rash	1(5%)	1(3.3%)
9.	Arthralgia	0	0
10.	Urinary symptom.	0	2(6.6%)
11.	Cough	0	0
12.	GI Bleed	0	0

Table 6. Clinical Symptoms in Different Ages

Sl. No.	Signs	0-5 Yrs. (n=20)	6-12 Yrs. (n=30)
1.	Pyrexia	20(100%)	30(100%)
2.	Coated tongue	20(100%)	28(93.3%)
3.	Rash, macula papular	1(5%)	1(3.33%)
4.	Relative Bradycardia	3(15%)	11(36.6%)
5.	Pallor	10(50%)	14(46.6%)
6.	Jaundice	2(10%)	0
7.	Hepatosplenomegaly	20(100%)	30(100%)
8.	Complications	3(15%)	6(20%)

Table 7. Clinical Symptoms in Different Age Groups

Widal Reaction	No. of Cases (n=50)	Percentage (%)
Positive	26	52
Negative	24	48

Table 8. Widal Test Result in Blood C/S Positive Patients (In all Cases Test Done After >= 7 Days of Starting of Fever)

		Blood Culture +	Blood Culture -	Total
Widal	Positive	26	9	35
	Negative	24	31	55
Total		50	40	90

Table 9. Comparison of Widal Test with Blood Culture

Antibiotic	No. of Cases (n=50)	Percentage (%)
Co-amoxiclav	45	90
Cefixime	47	94
Azithromycin	48	96
Ofloxacin	4	8
Ceftriaxone	48	96
Cefepime	48	96
Meropenem	49	98
Aminoglycosides	2	4
Nalidixic Acid	0	0

Table 10. Antibiotic Sensitivity Pattern

Antibiotic Sensitivity Pattern	Ranganathan et al	Madhavan et al	Chandrasekhar et al	Chungathu et al	R K Arora et al	Present Study
Co-amoxiclav	70%	88.2%	87%	96%	88%	90%
Cefepime	100%	90%	92%	96%	92%	94%
Azithromycin	60%	86%	84%	88%	90%	96%
Quinolones	87%	2.6%	97%	94%	90%	8%
Ceftriaxone	100%	90%	87.5%	100%	92%	96%
Meropenem	100%	98%	100%	96%	96%	98%
Aminoglycosides	20%	2.6%	100%	10%	16%	4%

Table 11. Comparison of Antibiotic Sensitivity Pattern with Other Studies

Exclusion Criteria

Febrile children who were clinically suspected to be enteric fever, but blood culture negative was not included in the study.

The case sheets of these patients were collected from the record section of the hospital.

Several data including clinical features, culture sensitivity pattern, laboratory parameters and antibiogram data were retrieved from the hospital records.

Blood culture was performed by BACTEC method, collecting 5 cc venous blood and diluting it 4 times under normal circumstances and 10 times if treated with antibiotics and then injecting into a bulb containing 20-30 cc of 5% bile broth. The bulb was incubated for 24-48 hours at 37 degree centigrade and subcultures were made on McCaskey's medium.

Cultures were declared negative after incubation for 5 days.

Antibiotic sensitivity pattern was assessed by the Kirby-Bauer disc diffusion method where discs containing antibiotics are placed on an agar plate on which bacteria were growing. If the bacteria are sensitive to the antibiotic, a zone of inhibition is seen around the disc.

Widal test was done by adding 0.5 ml of Salmonella typhi O, Salmonella Typhi H, Salmonella paratyphi A(H) and Salmonella paratyphi B(H) antigens respectively in test tubes with diluted sera of 1:30.1:60, 1:120, 1:240 and 1:480

concentration and also control of 0.5 ml normal saline. After shaking the rack well, it was incubated at 37 degree centigrade overnight. Then with naked eye, the highest dilution in which there is evidence of agglutination is noted.

All the data were collected and then analysed using mainly descriptive statistics and Chi square analysis.

Of the 50 cases included in the study, majority i.e., 30 were 6-12 years of age. This is the school going age group and increased occurrence of enteric fever in this cohort implies the importance of proper sanitary facilities and stresses the need of preventing the disease by timely immunization programs.

Of the 20 cases, <5 years of age, 7 were <1 year. It may be related to poor hygiene or changing food patterns in recent years like early use of formula food products etc.

Urban Versus Rural

Out of 50 cases, 31 (62%) were from rural area of West Bengal and the rest from urban area. The cause may be poor hygiene and improper sanitation.

Majority, 47 out of 50(94%) cases had fever lasting between 7-14 days, on admission. Only 3(6%) cases, at the time of admission, had fever lasting for more than 2 weeks.

Presenting Symptoms

All the patients were febrile at the time of admission. Among the associated symptoms, gastrointestinal symptoms predominated in the majority. 50% had pain abdomen and 66% complained of constipation. Only 2 cases had a skin rash and dysuria at the time of admission.

Pain abdomen and constipation occurred almost equally in both age groups. Vomiting and diarrhoea were more common in 0-5 year's age cohort, while urinary symptoms though very rare was noticed in 6-12-year age group.

Clinical Signs

All the cases had hepatosplenomegaly. Pallor was present in 24 (48%) cases, relative bradycardia in 14(28%) patients. Only 2 patients developed jaundice. Complications in the form of macrophage activating syndrome developed in 9 (18%) cases.

Jaundice and coated tongue were common in 0-5 year's age group. Relative bradycardia was seen more often in 6-12 years age group. Other signs were more or less equal in both age groups.

Laboratory Parameters

1. Hb-

In our study, majority had anaemia with Haemoglobin <11 gm/dl. Mean Hb was 10.27 with standard deviation of 1.7; minimum Hb was 4.6 and maximum was 13.3.

2. Total Leucocyte Count

Of the 50 cases normal leucocyte count was seen in 34(68%) cases. 12 patients had leukocytosis; the maximum count going up to 18300. Only 4(8%) had leucopenia<4000/cumm; the minimum count being 2600.

Regarding the differential count, 20 (40%) had normal neutrophil count but majority, 30(60%) had neutropenia. Mean neutrophil count was 3757.76 with minimum neutrophil count being 1200.

In our study, normal lymphocyte was seen in 38% cases; 58% had lymphocytosis. Mean lymphocyte count was 3864.2.

Platelet Count

In our study, 41(82%) had normal platelet count and thrombocytopenia was observed in 7(14%) cases. Thrombocytosis was rare, seen in only 2(4%) cases.

Erythrocyte Sedimentation Rate (ESR)-

Normal ESR was seen in 15 case while ESR >20 mm/hr was seen in 35(70%) cases.

Liver Function Test (LFT)

- Only 2 (4%) patients had raised bilirubin; maximum value being 4.3 mg/dl.
- Hemoglobinemia was noted in 7(14%) cases; the minimum level being 2.3 gm/dl.
- Transaminitis was seen in a good number of cases. SGOT (AST) was raised (mean value being 118.18 units/L) in 47(94%) cases. SGPT (ALT) was raised in 29(58%) cases. The mean value was 80.04 units/L.
- Altered coagulation profile (INR<=1.5) was seen in only 5(10%) cases.

Complications in the form of secondary HLH (Hemophagocytic lymphohistiocytosis) was seen in 9(18%) cases.

They had raised ferritin levels (>500 microgram/L). The maximum value of ferritin in such cases rose up to 4500 microgram/L. These patients also showed raised triglyceride (>265 mg/dl); the maximum being 650 mg/dl.

Hypofibrinogenemia (<150 mg/dl) occurred in these cases, the minimum being 13 mg/dl.

The Widal test was done 7 days or more after starting of fever, on all the 50 blood-culture positive cases. Widal test was positive in 26(52%) cases. TO was positive 1:160 titre in 30% of cases.

In the above 2x2 contingency table, the Chi-square is 8.13 for association between the Widal test and Blood culture is statistically significant ($P<0.005$) for $\alpha=0.05$, $df=1$.

It can be inferred that there is significant difference in the two tests. Out of 50 blood culture positive cases, Widal test was positive in 26 and negative in 24 cases. Of the 40 blood-culture negative cases, only 9 showed positive Widal test. The Widal test has sensitivity 52%, specificity 77.5%; positive predictive value of 74.28% and negative predictive value of 56.36% when compared with blood culture result.

Response to Therapy

Of the 50 cases, 46 were antibiotic naïve and after admission parenteral ceftriaxone was started in them. 4 were already on oral antibiotics at the time of admission, which was thereafter continued.

46 cases were started therapy with ceftriaxone. Remaining 4 were already on treatment with oral azithromycin and cefixime at the time of admission. Of the 46 cases on ceftriaxone, 36 cases out of 50 (72%) responded within 3-5 days of initiation of antibiotic therapy. 10 cases (20%) did not show defervescence even after 1 week of ceftriaxone injection.

They however responded to other antibiotics like meropenem (9 cases), 1 of each responded to co-amoxiclav, cefixime and ofloxacin. 2 responded to azithromycin.

The mean period of defervescence was 4.78 days. Minimum and maximum time taken to achieve defervescence was 2 and 13 days respectively.

Of the 10 cases which failed to show response to ceftriaxone, 9 achieved remission with meropenem and became afebrile 2-4 days after starting therapy with meropenem. Only 1 case continued to have fever even after 1 week of meropenem, and eventually responded to parenteral ofloxacin.

DISCUSSION

The above study was conducted as a retrospective observational study among the inpatient of VIMS, (Department of Paediatrics) whose blood culture was positive for salmonella typhi. This study spanned over a period of 18 months.

Of the cases included in the study, 20 cases (40%) fell in 0-5 years age group and 30 cases (60%) fell in 6-12 years age group. Of them 7 cases (14%) were less than 1 year. Walia et al⁽¹⁾ reported that 21.7% were children aged under 5 years and 6.1% were under 2 years. Yaramis et al⁽²⁾ reported that 17% of patients were children under 5 years and that school children were most affected.

In our study, 26 out of the 50 cases were males and amounted to 52% and 24 cases were females and amounted to 48%. Such male predominance was also noted in the studies by Garg et al⁽³⁾ and Raghuram et al.⁽⁴⁾ The male preponderance in our study was noted in the <5 years age group.

Like all other studies, fever in this study was the universal presenting feature. In 30 cases (60%) fever at the time of presentation, had a duration of <7 days. Only 3 cases (6%) it was >2 weeks duration.

Pain abdomen was seen in 66% cases, which was much higher than reported by R K Arora et al⁽⁵⁾ and Madhavan et al.⁽⁶⁾

Diarrhoea was seen in 12% cases, which was similar to that reported by R K Arora et al.⁽⁵⁾

Among gastro intestinal symptoms, vomiting and diarrhoea were common <5 years age, while urinary symptoms like dysuria was commoner >6 years of age. Pain abdomen and constipation occurred equally in both age groups.

Among the clinical findings, relative bradycardia was seen in 28% cases which is less than reported by Madhavan et al⁽⁶⁾ who cited it to be as high as 44.7%.

Pallor was seen in 48% cases, which is similar to R K Arora et al. In cases of severe fall in haemoglobin one should be alert of a massive GI bleed or other complications like secondary HLH.

Jaundice was seen in only 4% cases, which is similar to that reported by Chandrasekhar et al.⁽⁷⁾

Hepatosplenomegaly was a consistent feature of this study, which is similar to that reported by R K Arora et al.

Sinha et al⁽⁸⁾ reported that enteric fever may present in a dramatic form, 5 years of age who have higher percentage of complications and more frequent hospitalization.

In our study 68% had normal leucocyte counts and only 8% had leucopenia; leukocytosis was seen in 24% cases.

Almost similar incidence of leucopenia was also reported by R K Arora et al (10.7%) and Chungathu et al (8%).

58% cases in our study was reported to have relative lymphocytosis. A similar picture was also observed by Chungathu et al⁽⁹⁾ who cited lymphocytosis to the tune of 44%.

Thrombocytosis was seen in 14% cases; Madhavan et al reported it to be 27.6%.

Transaminitis -SGOT & SGPT were raised in 94 % and 58% cases respectively. This observation was however higher compared to Chandrasekhar et al (8%) and Madhavan et al.

Widal test was compared with blood culture in the initial 90 case records.

Chi-square 8.13 for the association between the Widal test and blood culture test is significant ($p < 0.005$).

Thus, it can be conferred that there is a significant difference in the two tests.

Out of the 50 blood-culture positive cases only 26 were Widal positive. Of the 40 blood-culture negative cases, 9 were Widal positive. Widal test has a sensitivity of 52% and specificity of 77.5 %. When compared to conventional blood culture, Widal test had a positive predictive value of 74.28% and a negative predictive value of 56.36%.

Of the 50 blood-culture positive cases, Widal was positive in 26 case, TO titre >1:160 was seen in 30% cases. This was in contrast to the observation made by Chandrasekhar et al (TO >1:160 seen in 92.3% cases).

Of the 50 cases, 46 were antibiotic naïve at the time of admission. Parenteral ceftriaxone was started in them. 36 responded to it. 10 continued to have fever even after 7 days of ceftriaxone; guided by the culture sensitivity reports, meropenem was initiated in these non-responsive cases. 9 became afebrile, one needed parenteral ofloxacin as fever did not remit even after 1 week of meropenem.

CONCLUSIONS

Out of the 50 blood-culture positive salmonella typhi enteric fever, 60% belonged to the school going age group of 6-12 years. Males outnumbered females <5 years age group. The consistent features were fever and hepatosplenomegaly. Majority had normal leucocyte count with relative lymphocytosis. Widal test though a simple, cheap and readily available test, it's reliability a diagnostic tool is questionable because not all blood culture positive patients showed a positive Widal test. Majority of the cases were resistant to quinolones and aminoglycosides and all were resistant to nalidixic acid. So, they cannot be recommended for therapy. Majority, 96% were sensitive to ceftriaxone but clinical response was seen in 78.3% cases. 21.7% did not respond/deteriorated further even after 1 week of treatment. Meropenem response was seen in 90% cases; only 10% showed resistance and later responded to ofloxacin. Of the 50 cases, 9 developed complications like secondary HLH even while on therapy with ceftriaxone. They later responded to meropenem. However, majority responded to ceftriaxone. In spite of this, ceftriaxone still remains the drug of choice in uncomplicated enteric fever. Oral Azithromycin and Cefixime also showed a good response and a high sensitivity pattern was noted with both of them.

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