TREATMENT OF ENTERIC FEVER - AN EXPERIENCE OF 57 CASES

Dr. Rashidul Hassan
MBBS, FCPS
Resident physician,
Shere Bangla Medical College Hospital, Barisal.

Dr. Nasiruddin Ahmad
MBBS, M. Phil
Asstt. Prof. Pathology
Shere Bangla Medical College, Barisal.

Dr. Ghulam Mahmood Selim
MBBS, FCPS.
Sr. Consultant
General Hospital, Barisal.

Dr. Jamaluddin Ahmad
MBBS, M. Phil.
Asstt. Prof. Pharmacology,
Shere Bangla Medical College, Barisal.

Abstract :
57 culture positive cases of enteric fever were collected and treated at Shere Bangla Medical College Hospital Barisal. Many of these cases were caused by samonella which is resistant to one or more antibiotics (chloramphenicol, ampicillin, amoxycillin) usually employed in the treatment of enteric fever. Results of the treatment shows that ciprofloxacin is the most effective antibitic in the treatment of enteric fever. The mortality rate of this series was 16% while complications were observed in 44% of cases.

Introduction :

Enteric fever has been virtually eliminated from the developed countries during the last several decades as a result of improved water supply and sanitation. But it continues to be a major public health problem in Bangladesh due to improper sanitation and poor socioeconomic conditions. In this region the disease is usually endemic but the incidence at times, increases to epidemic outbreaks. The scenario is further complicated because of emergence of strains of salmonella resistant to the commonly used antibiotics.

Since its introduction in 1947, Chloramphenicol brought about of a radical change in the course and prognosis of enteric fever. Amoxycillin and cotrimoxazol are also effective alternative agents for the treatment of enteric fever. But strains of salmonella resistant to these drugs are emerging in parts of the world including India (1,2,3,4). This study presents an experience of treatment of 57 cases of enteric fever at Shere Bangla Medical College Hospital, Barisal. Many of these cases, the isolated salmonella were found

resistant to the common antibiotics used to treat enteric fever namely chloramphenicol, cotrimoxazol and amoxycillin.

Patients and Methods :

The cases of enteric fever of this study were collected from the patients who attended Shere Bangla Medical College Hospital, Barisal, for treatment during the period extending from Feb '91 to Oct. '91 and also a few cases from the private chambers of some medical specialist of the town. All the cases were investigated as pyrexia of unknown origin and only those which yeilded positive blood culture for salmonella were included in this study.

Following the clinical diagnosis blood was sent for blood culture and sensitivity testing. As because it often take weeks to get the blood culture and sensitivity reports the treatment was strated with an antibiotic which is known effective against salmonella. The choice of the antibiotic was made depending on the antibiotic treatment the patient already received before admission. The antibiotics used are cotrimoxazol, chloramphenicol, ampicillin, amoxycillin, cephradine, ciprofloxacin, gentamycin, nalidixic acid, tobramycin, pivmecillinam and cefuroxime. The duration of treatment varied from 5 to 10 days. Those paients who failed to respond by remission of fever were given a combination antibiotic therapy. The antibiotic combination used is either, oral amoxycillin + cephradine or cotrimoxazol + chloramphenicol for 5 to 10 days. Patients still showing no response of fever were given treatment as indicated by the sensitivity report.

The cases presented or complicated by intestinal perforation were all taken in a group and were treated by a combination of Inj. cotrimoxazol (septrin), Inj. gentamycin and Inj. metronidazol.

Result and observation :

Age and sex : The age of the patients of our series varied from 6 to 62 yrs. The common age group involved was 21-30 yrs. Of the total 57 cases 47 (82.4%) were male and the rest 10 (17.6%) were female. The age and sex distributions are given in the following table.

Age group (in years)	Male	Female	Total
0-10 yrs	4	1	5
11-20	11	4	15
21-30	17	4	21
31-40	14	0	14
40 +	2	0	2
Total	48(84.2%)	9(15.8%)	57(100%)

Table 1 showing the age and sex distribution of the cases of enteric fever.

All the patients were treated emperically on the basis of provisional diagnosis by the general practitioners before the patients reported to us for treatment. These drugs included antibiotics, antimalarials and steroids. It appeared that the most frequently prescribed drug was cotrimoxazol (85.9%) followed by chloramphenicol and antimalarials. The duration of treatment varied widely. The following table tabulates the results of these treatments. (Table-2)

Name of the drug	No. of Patients treated (%)	Modeof therapy		Response
		Single	Combination	
1. Tab. Cotrimoxazol (960 mg bid)	49 (85.9%)	45 (78.9%)	4 (7.0%)	No response
2. Cap chloramphenicol (250/500mg tid)	41 (71.9%)	39 (68.4%)	2 (3.5%)	"
3. Cap Amoxycillin (250/500mg qid)	6 (10.5%)	6 (10.5%)	00	"
4. Cap Ampicillin (250/500 mg qid)	4 (7.0%)	4 (7.0%)	0	"
5. Tab Pivmecillinam (selixid)	8 (14.0%)	6 (10.5%)	2 (3.5%)	"
6. Cap Tetracycline (200/500 mg qid)	9 (15.8%)	0	9 (15.8%)	"
7. Cap cephradine (250 mg qid)	5 (8.8%)	5 (8.8%)	0	"
8. Cap Cephalexin (250 mg qid)	3 (5.3%)	3 (5.3%)	0	"
9. Cap Nalidixic acid (1000 mg qid)	5 (8.8%)	1 (1.8%)	4 (7.0%)	"
10. Tab Erythromycin (500 mg)	1 (1.8%)	1 (1.8%)	0	"
11. Tab Nitrofurantoin (50 mg qid)	1 (1.8%)	0	1 (1.8%)	"
12. Cap Rifampicin (450 mg/day)	1 (1.8%)	1 (1.8%)	0	"
13. Antimalarials				
14. Tab chloroquin (4 tab stat-2 tab after 6hr-1 tab bd for 3 days)	7 (12.3%)	3 (5.3%)	4 (7.0%)	"
15. Tab Fansidar (3 tab single dose)	10 (17.5%)	6 (10.5%)	4 (7.0%)	"
16. Mist Quinine sulph (10mg/kg tid)	24 (42.1%)	15 (26.3%)	9 (15.8%)	"
17. Tab corticosteroid	4 (7.0%)	0	4 (7.0%)	"

Table-2 pattern and mode of treatment received by the patient from their physicians before they reported to us.

Outcome of single drug therapy : 10 (ten) different drugs to which the salmonella is known sensitive areused as a single mode of treatment. It was found that ciprofloxacin gave the best results (100% response) followed by cephradine (57%). These are given in the following table. (Table-3)

Name of the drug used	duration of treatment (in days)	No. of the patients getting treatment	No. of patients showing remission of fever	No. of patient showing no remission of fever
1. Cap Amoxycillin (1gm qid)	10	4	2	2
2. Chloramphenicol (1gm tid/qid)	10	2	1	1
3. Cotrimoxazol tab. (2 tab tid)	10	5	0	5
4. Tab ciprofloxacin (500mg bid)	10	5	5	0
5. Cap cephradine (500 mg qid)	10	7	4	3
6. Tab pivmecillinam (400 mg qid)	10	11	3	8
7. Gentamycin inj. (80 mg im tid)	10	2	0	2
8. Nalidixic acid tab (1gm qid)	10	2	0	2
9. Inj. Tobramycin (80mg in tid)	8	5	2	3
10. Inj Cefuroxime (750 mg tid im)	10	8	2	4
Total		49	19	30

Table-3, showing the outcome of single antibiotic therapy.

Outcome of combination drug therapy : As stated earlier combination antibiotic were administered when the single antibiotic failed to produce remission of fever. The results are given in the following table (table-4)

Antibiotic combination used	duration of treatment (in days)	No. of the patients getting treatment	No. of patients showing remission of fever	No. of patient showing no remission of fever
1. Cap Amoxycillin (1 gm qid) + Cap Cephradine (250-500mg qid)	5	16	12	4
2. Tab Cotrimoxazol (2 tab tid) + Cap Cloramphenicol (50 mg/kg/day)	5	14	8	6
Total		30	20	10

Table-4, showing the out come of treatment by combination of antibiotics.

Patients who failed to show remission of fever following combination of antibiotic treatment were further treated by agents as indicated by sensitivity reports. The out come is given in the following table (table-5).

Total No. of patients	Out come
10	3 patients showed remission of fever following administration of ciprofloxacin
	2 patients showed remission of fever following treatment by combination of Inj Tobramycin + Inj Cephradine
	One patient showed remission of fever following stopping of all drugs
	three patients died

Table-5, showing out come of the patients who did not respond to both single and combination antibiotic treatment.

Case with perforation : Patients who presented with perforation or developed perforation at the hospital during the treatment were all treated in the surgery units by inj septrin bid, in combination with inj gentamycin (80mg im tid) and inj metronidazol (iv). Besides surgical toileting and operative treatment were done whereever the general condition of the patient permitted. It was observed that out of the eight patients 5 presented with perforation while the other 3 developed perforation while undergoing treatment. Of the total eight cases 5 cases died. The following table shows the outcome in the perforation cases.

Patients with perforation	No. of the patients	No. of patients cured	No. of patient died
Patients presented with perforation	5	2	3
Patients who developed perforation during treatment	3	2	1
Total	8	4	4

Table-6, showing outcome of perforation cases of this series.

During the course of illness 44% of the patients developed some form of complications ranging in severity from mere relapse to death. The following Table summarises these complications (Table-7). It is obvious that relapse following remission is the most frequent complications.

Name of the complications	No. of patients showing the complication (%)
1. Relapse after remission	21 (36.8%)
2. Paralytic ileus	9 (15.7%)
3. Perforation	8 (14.0%)
4. Gastrointestinal bleeding	6 (12.3%)
5. Pericarditis	1 (1.7%)
6. Acute renal failure	1 (1.7%)
7. Erythema multifomme	1 (1.7%)
8. Severe diarrhoea	3 (5.3%)
9. Acute abdominal pain	3 (5.3%)
10. Pneumonia	1 (1.7%)
11. Peripheral neuropathy	1 (1.7%)
12. Polyarthritis	1 (1.7%)
13. Severe wasting	1 (1.7%)
14. Death	7 (12.0%)

Table-7, showing the complications of enteric fever found in this study.

The ultimate outcome of the patients were analysed and found that 26 (45.66%) were cured without any complications and of the rest 24 (42.1%) patients developed complications (table-8) and of the later seven (12.2%) died. (see table-8).

Ultimate out come	No of patients
Cured without complications	26 (45.6%)
Cured following development of complications	24 (42.1%)
Death	7 (12.2%)
Total	57 (100%)

Table-8, showing the ultimate out come of the patients of enteric fever.

Antibiotic sensitivity of the isolated salmonella was done by disc diffusion method. The result of the sensitivity is given in the following table. (table-9). It is to be noted that sensitivity for all the antibiotics could not be done in each case. The results reveal that in majority of the cases the bacteria were resistant to chloramphenicol and ampicillin. More than half (53%) of the cases were resistant to chloramphenicol.

Name of the antibiotic disc used	No. of cases the antibiotic was tested	No. of cases sensitive	No of cases resistant
Ampicillin	52	03 (3.8%)	49 (94.2%)
Amoxycillin	38	18 (47.3%)	20 (52.7%)
Chloramphenicol	47	02 (4.2%)	45 (95.8%)
Chephalexin	15	10 (66.6%)	05 (33.4%)
Cephradine	49	44 (90.0%)	05 (8.8%)
Cefuroxime	17	17 (100.0%)	00 (0%)
Gentamycin	37	35 (94.5%)	02 (05.5%)
Nalidixic acid	27	24 (88.8%)	03 (11.2%)
Brulamycin	27	27 (100.0%)	00 (0%)

Table-9 showing the sensitivity pattern of the isolated salmonella.

Discussion :

Enteric fever continues to be major health problem in tropical and subtropical countries with high morbidity and mortality. for many years after its introduction. Chloramphenicol gave excellent results in the treatment of enteric fever and still is the drug of choice. But it is now apparent that resistant strains emerged and are emerging particularly in those parts of the world where enteric fever is endemic and indiscrminate use of antibiotics are prevailing [5]. Chloramphenicol resistance has been reported from many parts of the world [1]. In India salmonella strains resistant to multiple drugs has been reported by many investigators [2,3,4]. From the results of treatment it is apparent that ciprofloxacin is the most effective drug in enteric fever. Though unfortunately this antibiotic could

not be put in the sensitivity testing becasuse of unavailability of the disc. The other drugs which were also found clinically effective are amoxycillin, cephradine and pivmecillinam. The efficay of ciprofloxacin and other drugs has been reported by other investigators too [6,7,8]. However, on the sensitivity scale gentamycin cefuroxime, cephradine and nalidixic acid were found highly effective against the isolated salmonalla both in our study and also of others[8,9].

The proportion of the multiple drug resistant salmonella in our series is quite high (32%). Whether the drug resistant salmonella are also present in the community to a similar extent is a matter of further investigations. However, it appears very much likely to us that the resistant cases are over represented in this series than the real incidence in the community. As this observation is hospital based the resistant cases are more concentrated here, because many of the pts failure of the repeated bouts of antibiotic therapy led to hospitalisation.

During the course of illness 40% of the cases developed complications (table-7). The complications included wide variety of conditions of which relapse of fever after remission is the commonest (36%). The rate of relapse in our observations appears quite high in comparison to that reported by other investigators[6]. The exact cause of this higher relapse rate is not known for certain. Probably this is related to increased number of the severe form of the disease in our series.

One study in India reported the overall 79.4% complication rate in a series of 34 cases of enteric fever due to multi resistant salmonella typhae. In all these cases the isolated salmonella were found resistant to chloramphenicol, cotrimoxazol and amoxycillin. so it is probable that the more the number of drug resistant salmonellosis the more is the incidence of complications [6].

Some of the complications are related to management difficulties such as acute renal failure related to fluid and electrolyte balance, while some conditions, such as severe wasting, is in fact a sequlae of the disease.

Before the advent of chloramphenicol the fatality rate for enteric fever was in the range of 20-25%. But following its introduction this was reduced to about 5% [6]. Now a days the mortality rate from the condition is roughly 1% [6]. In this series the mortality rate is 16%. This may be because of the perforation cases which contributed more than half of all deaths as well as the dominance of severe and multiple drug resistant cases in this study series.

Finally it may be concluded from this study that in this region a significant proportion of cases of enteric fever is caused by salmonella resistant to one or more antibiotics. Therefore, an elaborate, preferably nation wide, epidemiological survey may be carried out to find out the exact incidence, the antibiogram, and the natural history of the enteric fever caused by the drug resistant salmonella.

References:

1. Dugoid JP, Marmion BP, Srain RHA. Mackie and McCartney, Medical Microbiology (13th ed) vol-1, Charchill Livingstone, Edinburg, 1987:317.

2. Gupta BL, Bhujwaka RA, Sriniwas. Multiresistant salmonella typhae in India. Lancet 1990. 336:252.

3. Panikar CK, Vimala KN,. Trasferable Chloramphenicol resistance in salmonella typhae. Nature 1972. 239: 109-110.

4. Ayyagari A, Pal N. Outbreak of typhoid fever due to multiresistant salmonella typhae. Trans Royal Soc Trop Med Hyg 1991. 85"302.

5. Editorial, Lancet, 1973 1:1008.

6. Adams EB. Typhoid and paratyphoid fevers in Weatherall DJ, Leadingham JGG, Warrell BA(eds) Oxford Text Book of Medicine (2nd ed) Oxford University Press Oxford 1987;:5.220.

7. Ferrecoi UC et al. Efficacy of ciprofloxacin in the treatment of chronic typhoid carrier. J Infect Dis, 1988. 157:1235.

8. Keusch GT. Antimicrobial therapy for enteric fever. State of the art. Rev Infect dis 1988, 10(suupl) :S199.

9. Soe GB etal. Treatment of typhoid fever and other systemic salmonellosis with cefotaxime, ceftriaxone, cetoperazone and other newer cephalosporins. Rev Infect Dis 1987; 9:719.