MULTI-DRUG RESISTANT TYPHOID FEVER WITH DIARRHEA

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Objective: *To provide information about the characteristics of diarrheal stool in multi-drug resistant typhoid fever and observe the clinical course after treatment with furazolidone or ciprofloxacin.* ***Setting****: Hospital based. Subjects and* ***Methods****: Twenty one male children who were positive for multi-drug resistant S. typhi by blood and stool cultures, having diarrhea at the time of hospitalization comprised the subjects. Serum and stool electrolytes were estimated. Stool samples were also processed to detect established enteropathogens, leukocytes and red blood cells. Children were treated either with furazolidone or ciprofloxacin and evaluated till recovery.* ***Results:*** *Mean (± SD) pre-admision duration of fever and diarrhea of these cases were 19.1 (±5.6) and 15.8 (±4.6) days, respectively. Stool character in 81% of the patients was watery with mean (±SD) volume of stool 51.4 (±25.1) ml per kg body weight in the first 24 hours of observation. Leukocyte count varied between 20-49 per high power field in 66.7% stool samples. Occult blood was present in only 19% cases. Fecal red blood cells in high power field were detected in 52.4% cases. Mean fecal electrolytes (mmol/liter) were as follows: sodium-53.8, potassium-51.4, chloride-41.6 and total* Co_2*-24.3. Most of the children (71.4%) had no dehydration and had normal serum electrolytes. The isolated strains of S. typhi were multi-drug resistant. These children were treated successfully either with furazolidone or ciprofloxacin.* ***Conclusion:*** *The stools of multi-drug resistant typhoid fever patients were watery with little blood. Their electrolyte contents were more similar to the diarrheal stool seen in shigellosis rather than cholera. Uncontrolled observations revealed that children recovered with furazolidone or ciprofloxacin therapy.*

Key words: *Diarrhea, Multi-drug resistant, S, typhi, Typhoid fever.*

TYPHOID fever remains prevalent in the developing countries that lack adequate sanitation and water supply.Although, accurate information is hard to obtain, conservative data estimates that more than 12 million cases occur annually in the developing world (except China), of which as many as *7.7* million cases occur in Asia alone(l). The emergence of drug resistance in typhoidal *Salmonellae* has been the major concern in recent years. Several epidemics of typhoid fever caused by multi-drug resistant (MDR) *S. typhi* have been reported from different parts of the world from time to time(2-4). Recently, Calcutta city and its suburbs witnessed an epidemic of MDR

typhoid fever(5,6). In that epidemic, the nonspecificity of clinical presentation of MDR typhoid fever and association with diarrhea have been reported in large number (37%) of cases (7). Although diarrhea is a common finding of typhoid fever, it is not regarded as a diagnostically useful clinical criterion. This study was an attempt to provide information about the characteristics of diarrheal stool in MDR typhoid fever and observe the clinical course after treatment.

Subjects and Methods

Children aged upto 12 years admitted in the Dr. B.C. Roy Memorial Hospital for Children, Calcutta during the period between February 1990 to January 1992 with clinical diagnosis of typhoid fever were included in the study. Patients who did not receive any drug before hospitalization or received drugs known to have no effect either on typhoid fever or diarrhea were included in the study. Typhoid fever was suspected clinically in patients who had sustained temperature (>39°C) for 5 or more days but did not have signs and symptoms suggesting other infection except diarrhea. Diarrhea was defined as passage of 3 or more loose or liquid stools in the preceding 24 hours.

Exclusion criteria from the study were as follows: Patients: (i) having severe malnutrition defined as ≤50% Harvard Standard weight for age; (ii) who had downgrade trend of temperature and decreased frequency of stool; and *(iii)* having other obvious illness requiring use of other antimicrobials. After selection, a complete history was obtained either from the patients or their parents. A thorough physical examination was done and findings were recorded in a specially designed form. Patients were weighed nude to the nearest 100 g.

Examination of Blood and Stool

On admission, 10 ml blood was drawn aseptically from each patient of which 5 ml was collected in tryptic soy broth for isolation of *S. typhi* using standard techniques(8). The remaining 5 ml was used for Widal test by conventional agglutination method(9), for estimation of plasma specific gravity using Total Solid Meter, American Optical Company and for estimation of serum electrolytes using Auto Analyzer, Nova-4, Automated Electrolyte Analyzer.

Only male children (for ease of collection of stool and urine separately) suffering from suspected typhoid fever having diarrhea at the time of hospitalization were selected.

Stool sample was collected immediately after admission in sterile McCartney's bottle by sterile rectal catheter and examined macroscopically for character and presence of blood and mucus. It was examined microscopically to estimate fecal leukocytes, red blood cells and to detect parasites and occult blood with guaiac test. Centrifuged supernatant stool was obtained to estimate electrolytes by flame photometry. Stool sample was also processed for detection of established bacterial enteropathogens using standard techniques(8). An aliquot of sample was kept at - 30° C and subsequently examined for rota virus(8). Antimicrobial susceptibility testing of the *S. typhi* isolates was done by Kirby-Bauer disc diffusion technique(10). Resistant strains of *S. typhi* were also tested for their minimum inhibitory concentration (MIC) by agar tube dilution method(11). Phage typing of *S. typhi* strains was done at the National Salmonella Phage typing center, Lady Hardinge Medical College, New Delhi.

Treatment

Patients who were suffering from clini-

cally suspected typhoid fever less than 3 weeks duration without having an abnormal state of consciousness or intestinal or extra intestinal complications were treated with furazolidone at the dose of 7.5 mg/kg body weight/day in four divided doses for 14 days. Patients having high temperature for more than 21 days received ciprofloxacin orally at the dose of 10 mg/kg body weight/day in two divided doses for 14 days. Antimicrobials were initiated after 24 hours of collecting stool to measure the baseline stool volume. However, during this period patients received antipyretic and oral rehydration solution or intravenous fluid for replacement of fluids and electrolytes. When there was no improvement in clinical signs and symptoms inspite of 8 days drug therapy, the drug was changed. This treatment schedule had been followed inspired by the encouraging results of clinical trials of furazolidone and ciprofloxacin for the treatment of MDR typhoid fever conducted in this hospital (12,13). Patients were discharged on 15th day of hospitalization after receiving medicines for 14 days, or on 7th day after remission of temperature and cessation of diarrhea. Remission of temperature was considered when the maximum body temperature (axillary) was 37.5° C for 48 hours or more. Cessation of diarrhea was defined as passage of semisolid or formed stool or no stool passed for 12 hours. All patients received the normal hospital diet. Patients who had diarrhea, also received oral rehydration therapy as recommended by the World Health Organization (WHO) or intravenous fluid (Ringer's lactate).

Clinical Follow-up

Investigators monitored the clinical response daily by recording the following parameters: temperature, frequency of stool, character of stool, presence of blood in stool, anorexia, vomiting, abdominal pain and development of any complication. Stool was collected separately only for the first 24 hours after admission, volumes were measured 8 hourly by weighing the preweighed diapers in small children and by weighing bucket in to which older children were instructed to defecate.

Results

A total of 592 hospitalized children, clinically suspected as typhoid fever were screened, of which 221 (37.3%) were positive for *S. typhi* by blood culture. Of these 221 *S. typhi* strains isolated, 204 (92.3%) strains were resistant to two or more antimicrobial agents (MDR) and the cases were finally diagnosed as MDR typhoid fever. However, 14 children had jaundice and another 18 had abnormal state of consciousness on admission. One hundred seventy two children were positive for MDR *S. typhi* by blood culture and did not have any complication during admission except diarrhea in 64 (37.2%) cases. However, only 27 cases were initially selected for this study who were male and were positive for MDR *S. typhi* by both blood and stool culture. Six cases were further excluded as they were infected with other co-enteropathogens. Finally, 21 male children who were positive for MDR typhoid fever by blood and stool culture and had diarrhea but no other complication at the time of hospitalization became the subjects of our presentation.

Clinical Characteristics

Table I shows the clinical characteristics of the children who suffered from bacteriologically confirmed MDR typhoid fever and had diarrhea. Most of the children (71.4%) had no dehydration at the time of admission and had normal serum electrolytes.

TABLE I— *Clinical Characteristics of* 22 *ChildrenSuffering from Bacteriologically Confirmed Multi-Drug Resistant Typhoid Fever Associated with Diarrhea.*

Characteristics	Observed value (Mean ± SD)	Range *
Age (years)	6.4 ±1.23	5-8.4
Body weight (Kg)	16.1 ±3.7	11.4-26.2
Dehydration (%)	28.6	
Plasma specific gravity	1.024 ± 0.002	1.023-1.028
Concentration of electrolytes in blood (mmol/liter)		
Sodium	131.0 ±4.3	126.5-145.0
Potassium	3.1 ± 0.4	2.7-4.0
Chloride	94.7 ± 3.1	90-100.5
TCO_2	20.5 ± 0.8	19-22.2

TCO_2-Total carbon dioxide

Stool Character

Table II shows the findings of different parameters of diarrheal stool in MDR typhoid fever. Stool character in most of the patients (81%) was watery with the frequency ranging between 8-20 times and volume between 15-120 ml/kg of body weight during first 24 hours of observation. Fecal leukocytes were present in all diarrheal stool samples. The small osmotic gap inferred from the sodium, potassium concentrations of stool indicate that the diarrhea is not osmotic in nature.

Bacteriological Profile

All *S. typhi* strains isolated from blood and stool culture, were resistant to chloramphenicol, ampicillin, amoxicillin, trimethoprim-sulphamethoxazole and tetracycline. However, they were uniformly susceptible to furazolidone, gentamicin, amikacin, norfloxacin, ciprofloxacin and nalidixic acid. Minimum inhibitory concentration (MIC) values of chloramphenicol, ampicillin, trimethoprim-sulphamethoxazole and tetracycline ranged between 200-400, 400-1600, 400->1600 and 400-800 µg/ml, respectively.

S. typhi isolated from both blood and stool culture of these patients belonged to several phage types which indicate that no single phage type could be implicated in the causation of diarrhea in MDR typhoid fever. However, the predominant phage type was 0 (42.8%). Other phage types were Vi negative (23.8%), A (19.0%), El, UVS and C9 in 4.8% strains in each group. Antibody titre against *S. typhi* O antigen of 1:160 or more was observed in all the patients by single Widal test.

Clinical Course of Illness

Out of these 21 MDR typhoid fever cases associated with diarrhea, 15 were treated with furazolidone and 6 with ciprofloxacin orally. The mean (± SD) time required for defervescence and cessation of diarrhea were 6.0 (±0.4) and 5.3 (±0.3) days, respectively in the furazolidone treated group, in contrast to 3.1 (± 0.3) and 2.2 (± 0.2) days in the ciprofloxacin recipients. Clinical response was observed with

TABLE II-*Parameters Related to Diarrheal Stool of MDR Typhoid Fever Cases.*

Parameters	Observed value (Mean ± SD)	Range
Pre-admission duration of fever (days)	19.1+5.6	12-31
Pre-admission duration of diarrhea (days)	15.8 ± 4.6	8-25
Stool frequency during 24 hours of observation (No.)	10.7 ± 3.3	8-20
Character of stool (%)		
Watery	81.0	
Bloody	9.5	
Soft	9.5	
Quantity of stool passed during first 24 hours of observation (ml/kg body weight)	51.4 ±25.1	15-120
Positive for occult blood (%)	19	
pH	6.4 ± 1.0	4.5-8
Fecal RBC > 10 per high power field (%)	52.4	
Fecal WBC > 20 per high power field (%)	76.2	
Stool electrolytes (mmol/liter)		
Sodium	53.8 ± 26.1	15-105
Potassium	51.4 ±25.6	14-110
Chloride	41.6 ±24.2	8-82
TCO_2	24.3 ±13.1	4-40

RBC - Red blood cells; WBC-White blood cells;
TCO_2- Total carbon dioxide

an average of 24 and 48 hours after starting ciprofloxacin and furazolidone, respectively.

Discussion

Twenty one male children were described in this study who had bactenoloeicaily confirmed MDR typhoid fever with diarrhea. They also had high antibody titer against S. typhi O antigen (> 1: 160) which corroborate our earlier observation(14).

To avoid selection bias, all the male children suffering from bacteriologically confirmed (isolation of S. typhi by both blood and stool culture) MDR typhoid fever associated with diarrhea were studied. However, 6 patients were excluded from the final analysis as two of them were infected with Shigella spp, 2 with enteropathogenic E. coli and one each with Giardia lamblia and rotavirus.

Several studies showed that initial clinical presentations or MDR typhoid fever were often nonspecific and the disease could manifest as dysfunchon of any organ system including gastrointestinal tract (7,15,16). A1ong with fever, diarrhea is one of the most common clinical presentations of typhoid fever (7,17-19). Diarrhea was associated in 37% of MDR typhoid fever cases in our present study which could be compared to the incidence of diarrhea in typhoid fever from other parts of India (17,18) and Pakistan(19). However,

fairly high incidence of diarrhea in typhoid fever had been reported from other developing as well as developed countries like African nations(20-22), Jordon (23), Ethiopia(24), Sweden(25) and USA(26).

In this study, nature of stool was watery in majority (81%) of the cases which confirms the earlier findings (27,28). In contrast, Stuart and Pollen described the diarrheal stool of typhoid fever as foul-smelling with a consistency of pea-soup(29). Typhoid fever patients, in our series, passed stool as much as 51.4 (± SD, 25.1) ml/kg of body weight within first 24 hours of observation which was more than the volume passed (mean ± SD; 45.2 ± 5.3) by the typhoid fever patients in an earlier study conducted at Bangladesh (27). The mean (± SD) sodium and potassium losses in diarrheal stool in this study were 53.8 (±26.1) mmol/liter and 51.4 (±25.6) mmol/liter, respectively which was comparatively more than the fecal loss of sodium (mean ± SD; 47 ± 5 mmol/liter) and potassium (mean ± SD; 48 + 5 mmol/liter) by the patients of Bangladesh (27). This could be explained by the fact that the volume of stool passed by our patients was more as compared to that of the patients of Bangladesh, which might be the reflection of more fecal loss of sodium and potassium in our study. The loss of sodium in diarrheal stool was lower and loss of potassium was higher as compared to the loss of sodium and potassium in the stool of pediatric cholera patients infected either by *V. cholerae* 01 or 0139 (30,31). In typhoid fever, fecal potassium loss was higher and sodium loss was similar to that of patients infected with *Shigellae(32)* and other enteropathogens except *V. cholerae(33)* which might be due to differences in stool character in typhoid fever and in invasive diarrhea caused by *Shigellae* spp.(32,34).

This study showed that diarrhea in typhoid fever developed on an average of 3 days after the onset of fever which confirms the earlier findings from Bangladesh(27,28)". However, the previous view was that diarrhoea usually started on the second week or even later in typhoid fever (29,35). Majority of the patients in our series (71.4%) did not have dehydration as they received normal diet and water even at home. Resolution of temperature and cessation of diarrhea occurred within a very short marginal time difference, depending upon the therapy used. Furazolidone therapy took little longer time than ciprofloxacin therapy for complete defervescence (6.0 vs 3.1 days) and cessation of diarrhea (5.3 vs 2.2 days).

Uncontrolled observations revealed that though ciprofloxacin appeared to be the superior drug (13,36,37), furazolidone was also an effective drug for the treatment of typhoid fever associated with diarrhoea(12,38-40).

The pathogenesis of diarrhea in typhoid fever is not well understood. S. *typhi,* the causative agent for typhoid fever, usually causes systemic intracellular infection of reticuloendothelial cells. However, before entering into the blood stream, it causes hyperplasia of Peyer's patches in the ileum and inflammation and ulceration of the overlying tissue. Ulceration in the proximal colon is also common. Inflammatory changes in the intestine may have a role in causation of diarrhea in typhoid fever. Presence of fecal leucocytes and red blood cells proves the presence of inflammation in the intestine. However, some workers(27) have hypothesized that the mechanism of diarrhea in typhoid fever may be related to the mechanism of fever which usually occurs due to the release of endogenous pyrogen or interleukin-I, from mononuclear phagocytic cells and is mediated through prostaglandin(41,42). Others

have indicated the role of cyclic AMP for production of diarrhea in experimental salmonellosis(43).

A low osmotic gap in diarrheal stools indicated that it was not osmotic diarrhea and there is no need of alteration of diet. Oral rehydration therapy recommended by the World Health Organization was sufficient to tackle the fluid and electrolyte loss in these cases. Uncontrolled observation indicated that furazolidone is a safe, cheap and effective drug for the treatment of MDR typhoid fever associated with diarrhea in the pediatric age group.

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