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Study of clinical profile and antibiotic response in typhoid fever: A study in a Dhaka shishu (children) hospital, Dhaka, Bangladesh

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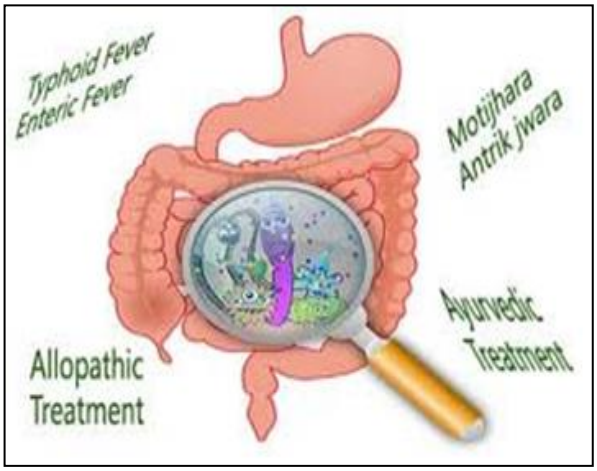
Abstract
The objectives of this Crosse sectional e analysis study is to gauge the clinical profile and pattern of varied medication employed in the treatment of infectious disease. A retrospective analysis of medicine patients littered with infectious disease was done at Department of Pediatric, Dhaka Shishu (Children) Hospital, and Dhaka throughout the year 2017-2018. Designation of patients was supported clinical options, agglutination test and blood culture. The mode of presentation, clinical course, treatment history, and laboratory investigations reports, antibiotic administered, response to medical care and also the complications were recorded. Total variety of 50 cases of infectious disease were studied. Out of those 23 (46%) were males and 27 (54%) were females. Average age of presentation was 8.2 years. Average length of hospital keep was 10.8 days. Fever was gift altogether patients. Resistance of S. typhi to ceftriaxone, Cipro, Azithromycin were considerably high. Antibiotic drug conjointly showed resistance in 21.4% of cases. Sensitivity to antibiotic was 100 percent in our study. Antibiotic drug was the foremost normally used antibiotic in our study (26 patients). Chloromycetin alone was employed in 2 patients and in 3 patients it had been given once 6 days of antibiotic drug treatment. Third generation antibiotic (ceftriaxone) alone were employed in ten patients. Indiscriminate use of medication in infectious disease ought to be discouraged. Acceptable antibiotic as indicated by sensitivity tests ought to use to forestall the event of resistant strains of S. typhi.

Keywords: typhoid fever, antibiotics, clinical profile

1. Introduction
Typhoid fever happens all told elements of the globe wherever there's substandard water system and sanitation. In endemic country together with Asian nation with morbidity starting from 102 to 2219 per 100,000 population [1]. Nowadays because of its dynamical modes of presentation, furthermore because the development of multidrug resistance, typhoid is turning into progressively troublesome to diagnose and treat. Improved standards of public health have resulted during a marked decline within the incidence of typhoid in developed countries [2]. The emergence of strains of typhoid bacillus proof against multiple antibiotics poses a heavy downside. Antibiotic drug was thought-about the antimicrobial gold customary for the treatment of typhoid until 19483. However within the last 20 years there has been increase within the resistance of strains of S. typhi to antibiotic drug. It absolutely was 1st according in GB, in 19504 and during this landmass in in 19725. Gradually, resistance to multiple antibiotics developed [6].



***Source*:** Google

Fig 1

The first major epidemic of multidrug resistant S. typhi was according in 19727 in North American country. Since then, AN increasing frequency of antibiotic resistance has been according from all elements of the globe, however a lot of thus from the developing countries [6]. The uses of antibiotic drug, Polycillin and co-trimoxazole became sporadic and quinolones became the primary line of treatment of typhoid. However, over the previous couple of years there has been increase within the abatement amount in patients treated with quinolones. Hence, this study was undertaken to judge the clinical profile and antibiotic response in typhoid.

2. Objective

To evaluate the numerous clinical shows, complications, and prognosis of typhoid fever.

3. Materials and Methods

A Crosse sectional analysis of medical specialty patients full of typhoid was done at Department of Pediatric Dhaka Shishu (Children) Hospital, Dhaka. The study throughout the year 2017-2018. Each males and female were enclosed within the study. Diagnosing of patients was supported clinical options, Widel test a look at and blood culture. The sensitivity pattern of blood culture was recorded. The mode of presentation, clinical course, treatment history, and laboratory investigations reports, antibiotic administered, response to medical care and therefore the complications were recorded. Abatement was outlined because the range of days needed for abatement of fever once beginning the antibiotics.

Pathogenesis

Pathogenesis Salmonella organisms penetrate the mucosa of both small and large bowel, coming to lie intracellularly where they proliferate. There is not the same tendency to mucosal damage as occurs with Shigella infections but ulceration of lymphoid follicles may occur. The evolution of typhoid is fascinating. Initially S. typhi proliferates in the second part of the Payer's patches of the lower small intestine from where systemic dissemination occurs, to the liver, spleen, and reticuloendothelial system. For a period varying from 1 to 3 weeks the organism multiplies within these organs. Rupture of infected cell occurs, liberating organisms into the bile and for a second time cause infection of the lymphoid tissue of the small intestine paticularly in the ileum. It is this phase of heavy infection that brings the classical bowel pathology of typhoid in its train. Invasion of the mucosa causes the epithelial cells to synthesise and release various proinflammatory cytokines including IL-1, IL-6, IL-8, TNF-β, INF, GM-CSF etc1. Pathology Huckstep4 refers to pathology in the Payer's patches assuming four phases. These phases correspond approximately to the weeks of disease if treatment has not been given.

Phase 1: Hyperplasia of lymphoid follicles.
Phase 2: Necrosis of lymphoid follicles during the second week involving both mucosa and submucosa. Phase 3: Ulceration in the long axis of the bowel with the possibility of perforation and haemorrhage. Phase 4: Healing takes place from the fourth week onward, and unlike tuberculosis of the bowel with its encircling ulcers, does not produce strictures. Although the ileum is the classical seat of typhoid pathology, lymphoid follicles may be affected in parts of the gastrointestinal tract, such as the jejunum and ascending colon. The ileum usually contains larger and more numerous Payer's patches than the jejunum, but this is not an invariable finding. It is not generally appreciated that such lymphoid follicles are also found in the large intestine. The number of solitary follicles in large intestine decreases with age. Ulceration during paratyphoid B infection may involve stomach and large intestine as well. Egglestone *et al*5 found typhoid perforations as usually being simple and involving the antimesenteric border of the bowel where they appear as punched out holes. In contrast to other types of perforation omental migration to the affected area does not occur. The reticuloendothelial system, enlargement and congestion of the spleen and mesenteric glands are characteristic finding. The so-called typhoid hepatitis has been described when a liver biopsy may show non-specific reactive hepatitis. The salient features on liver biopsy are focal liver cell necrosis with associated infiltration of mononuclears - typhoid nodules - sinusoidal congestion and dilation, and mononuclear cell infiltration of the portal area. Hepatitis should not be forgotten as one of the complications of typhoid and paratyphoid fever [6].

Laboratory diagnosis

The laboratory diagnosis of enteric fever is very important mainly because in post-antibiotic era most of the patients are treated empirically by the local medical practitioners and when the fever does not subside, these cases are labelled as pyrexia of unknown origin (PUO) and investigated for various causes of PUO including enteric fever. At this stage the typical signs and symptoms as described above are hardly observed. The presence of Salmonella typhi or S. paratyphi is detected either by culture of the organism or by the demonstration of specific antibodies or antigen in the serum or urine. The organism may be cultured from blood, bone marrow, stool or urine1-2. (i) Culture In addition to the usual two bottles inoculated with blood, a third bottle containing streptokinase bile salt broth can significantly increase the isolation rate of S. typhi. In 210 cases of enteric fever, whole blood conventional bile salt broth yielded the organism in 64% of cases but streptokinase bile salt broth inoculated with blood clot which was minced with scissors yielded a positive result in 92% of cases. Although the conventional wisdom is that S. typhi is obtained from blood during the first week of illness more frequently than from the stool, whereas the reverse applies during the second and third weeks of the illness, the clinician should be reminded that the organism can be cultured from blood as late as the fifth week of the disease, and the organism may be cultured from the stool throughout the disease. The organism is less frequently isolated from urine, but it is useful to determine whether a patient does excrete the organism in the urine because this could become a site for chronic carriage.

Culture of bone marrow or skin snips taken from rose spots might yield the organism once it cannot be obtained from blood, stool, or urine. The organism may be civilized from the bone marrow in as several as ninety six of patients even once antibiotics have already been given. In one cluster of patients; S.typhi was isolated from the blood in four-hundredth, from the stool in thirty seventh and from excreta in seven-membered, however from rose spots in sixty three of patients in an exceedingly case of infectious disease bone marrow cluture yielded the organisms although antibiotics had been administered. Generally the administration to a

patient with febricity of unknown origin of amoxycillin, ampicillin, or co-trimoxazole inevitably hampers the diagnosing of infectious disease fever1. The liquid and solid media that ar appropriate for isolation of Salmonella typhi and gastrointestinal disorder ar many. However, metal selenite broth is superior to selenite F broth for the isolation of S. typhi particularly once comparatively few infectious disease bacilli ar gift in excrement, for instance once antibiotic medical care or if stool specimens are left for prolonged periods at area temperature; and enterobacteria - enteric bacteria agar has been found to be superior to wood sugar essential amino acid deoxycholate agar for the isolation of S. typhi. Changed metal sulfate agar is superior to deoxycholate agar for the expansion of enterobacteria sp. and is necessary if the diagnosing of infectious disease is incredibly probably, or if a carrier is being investigated1, 3, 8. Automation in clinical biological science laboratories has been found to a boon during this direction. The recently introduced Organon-Teknika Bact-Alert machine-controlled culture system is one such device. The instrumentation includes of non-radioactive extremely enriched culture media as well as a proprietary rosin. This rosin will even neutralise the antibiotics within the blood sample, patient could be taking throughout the sampling time. This facility is additionally helpful as a result of its speed and pc generated reports and also the knowledge analysis. The entero bacteria culture will become positive as eraly as four hours once blood sampling. Our laboratory is having this facility, which is only government funded laboratory to have such automation. There are other automated devices like API, vitek etc. All these automated facilities are cost-effective in long run and can provide state-of-the art, prompt, and accurate diagnosis9. In conclusion, bone marrow is the gold standard for culturing the organism. It can yield positive results even if the patient has started antibiotics. The positivity rate from bone marrow can further be increased to almost 100% if FAN culture medium is used and growth is monitored in automated culture system such as Bact/Alert. Although blood culture is most likely to yield the organism during the first and third week, or septicaemic phases of the illness, the clinician is advised to order blood, stool, and urine cultures on one or more occasions to confirm or exclude the diagnosis.

4. Results

A total number of 50 cases of typhoid fever were studied. Out of those 23 (46%) were males and 27 (54%) were females. Average age of presentation was 08.2 years. Average duration of hospital stay was 10.8 days. Fever was present in all patients (100%). Vomiting was present in 18% patient. Diarrhea was seen in 18% patient. 10% patient had pain abdomen. Constipation was present in 8% patient. Hepatomegaly was detected in 18% and splenomegaly was present in 36% patient [Table 1]. A single estimation of Widal test was suggestive of enteric fever in significant titre in 88.6% cases (O titre of 1:160 or more). Blood culture was positive in 25% of cases. Malarial smear was positive patients and dengue antibody was positive in another patient. There was no luecopenia or thrombocytopenia in any patient. Antibiotic sensitivity pattern in culture proven cases [Table - HI] shows that resistance of *S. typhi* to amoxicillin, chloramphenicol, ampicillin and co-trimoxazole was significantly high. Ciprofloxacin also showed resistance in 21.4% of cases. Sensitivity to cephalosporin (ceftriaxone) was 100% in our study. In one of the patients, even though there was in vitro sensitivity to Ciprofloxacin, patient did not respond to it, suggesting in vivo resistance.

Table 1**:** Presenting symptoms of patients (N=50)

Symptom	Subjects	%
Fever	50	100
Vomiting	9	18
Diarrhoea	9	18
Headache	8	16
Pain abdomen	5	10
Body ache	1	2
Dry cough	3	6
Breathlessness	1	2
Weight loss	1	2
Constipation	4	8
Hepatomegaly	9	18
Splenomegaly	18	36

Bradycardia was observed in 12(24%) patients Bleeding per rectum was seen in no patient. No patient died due to disseminated intravascular coagulation [Table 2].

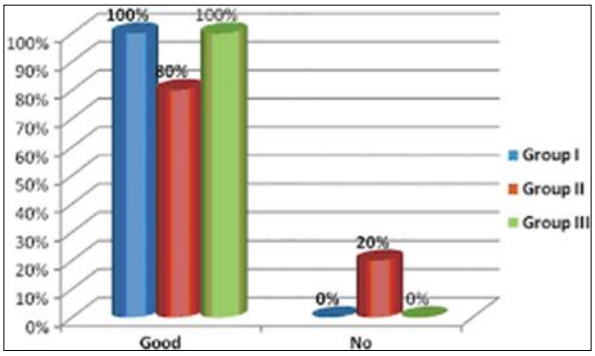


Fig 1: Treatment for antibiotic entice fever

Table 2: Complications observed during hosphalization (N=50).

Complications Number of subjects %		
Bradycardia	12	24
Bleeding per rectum	1	2
Jaundice	1	2
Disseminated intravascular	0	0
Coagulation followed by death	1	2

Table 3: Study Group Variation

Study Group	Typhidot-IgM Test positive (%)	Typhidot-IgM Test Negative (%)
Test Group (blood culture positive for S. Typhi) (n=111)	108 (97.29)	03 (2.7)
Control group I: (no enteric/typhoidal fever) n=57	02 (3.50)	55 (96.49)
Control group II: (normal healthy individuals) n=20	0(0)	20 (100)
Control group III: (blood culture positive for S. Partyphi –A) (n=20)	16 (80)	4 (20)

Table 4: Antibiotic sensitivity in culture proven cases (N=50)

Drugs	Sensitive n (%)	Resistant n (%)
Amoxicillin	3 (27.3)	8 (72.7)
Ampicillin	5 (45.5)	6 (54.5)
Co-Trimoxazole	4 (36.4)	7 (63.6)
Ciprofloxacin	11(78.6)	3 (21.4)
Third generation	00	00
Cephalosporin	14 (100)	0

Table 5: Clinical responses to antibiotics in all patients (N=50).

Antibiotics No.	Total treated of patients %	cases	Clinical response n (%)
Ciprofloxacin	26	52	12(46.2)
Chloramphenicol Chloramphenicol+	2	4.7	2(100)
Ciprofloxacin	3	6.8	3(100)
3^{r} generation Cephalosporin Ciprofloxacin +	10	20	10(100)
3^{r} generation Cephalosporin	9	20.4	9(100)

[Table 4] shows pattern of drug response. Ciprofloxacin was the most commonly used antibiotic in our study (26 patients). Chloramphenicol alone was used in two patients and in three patients it was given after six days of ciprofloxacin treatment. Third generation cephalosporin (ceftriaxone) alone were used in 10 patients. In nine patients it was given after six days of ciprofloxacin treatment as there was no clinical response. Average duration of treatment was 12 days with ciprofloxacin, 14 days with chloramphenicol and 10 days with third generation cephalosporin. Effervescence period was eight days with ciprofloxacin, 10 days with chloramphenicol and six days with third generation cephalosporin. [Figure 1] Treatment for antibiotic entice fever positive 80-100% and negative 0-20%.

5. Discussion

Drug resistance in typhoid fever is considered as one of the important factors in the morbidity and mortality of the disease. Since the introduction of antibiotic drug in 1948, it's been the drug of alternative within the treatment of infectious disease in most elements of the planet. But the indiscriminate use of the drug and acquisition of plasmid mediated R factor has led to the development of resistance to *S. typhi* against this drug [8]. Tropical countries like Bangladesh have shown widespread distribution of chloramphenicol resistant strains of *S. typhi*, the incidence varying from 38.6% to 83% [9-11]. The emergence of chloramphenicol resistance posed a big problem regarding the treatment of patients with typhoid fever. Alternative drugs suggested included co-trimoxazole, ampicillin and amoxicillin. During 1990, drug resistant *S. typhi* not responding to chloramphenicol, ampicillin and co-trimoxazole appeared in various parts of the country, the incidence varying from 50 to 52.9% [10]. In our study, incidence of chloramphenicol resistance was found to be 63.6%. Resistance to amoxicillin, ampicillin and co-trimoxazole was also present in significant number of patients. The quinolone group of drugs emerged as useful drugs for the treatment of multiple drug resistant cases of *S. typhi*. But unfortunately, the same factors of indiscriminate antibiotic use and cross resistance within the antibiotic group which led to the emergence of chloramphenicol resistant organisms are still operative. The resistance to quinolone is not plasmid coded but due to an altered DNA gyrase subunit. Resistance to ciprofloxacin is now being reported both from the Indian subcontinent and West [12-14]. In the present study *S. typhi* has shown resistance to ciprofloxacin in 18.1% of cases. The effervescence period for ciprofloxacin is about 3-5 days [15, 16] according to the literature and for cephalosporin is about three days. But in the present study we have observed that the defervescence period was comparatively longer; about eight days for ciprofloxacin and about six days for cephalosporin. In one patient, although there was in vitro sensitivity to ciprofloxacin patient did not respond to the drug. These findings suggest that sensitivity of *S. typhi* to ciprofloxacin is gradually decreasing. Indiscriminate use of drugs is one of the important factors leading to drug resistance and in case of ciprofloxacin, moderate cost, advantage of oral route, tolerability, convenient dosage schedule have contributed towards its indiscriminate use. In our study, sensitivity to third generation cephalosporin was 100%, although study done by Ranju*et al* [17] has shown significant decrease in the in vitro sensitivity to cephalosporin. High cost of cephalosporin may not permit its indiscriminate use for minor infection.

6. Conclusion

The indiscriminate use of medicine in typhoid ought to be discouraged. Acceptable antibiotic indicated by sensitivity tests ought to use to stop the event of resistant strains of S. typhi. In our study, sensitivity to third generation cephalosporin was 100%, although study done by Ranju*et al*[17] has shown significant decrease in the in vitro sensitivity to cephalosporin. High cost of cephalosporin may not permit its indiscriminate use for minor infection.

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Conflict of interest: The Author has no conflict of interest of the study.

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