The sensitivity pattern of different antibiotics used in the treatment of typhoid fever in hospitalized children

Abora Ettela
ID: 2005-3-70-028
Department of Pharmacy
East West University
Dhaka, Bangladesh

DECEMBER 2009

Supervisor

Farhana Rizwan

Senior Lecturer

East West University

The sensitivity pattern of different antibiotics used in the treatment of typhoid fever in hospitalized children

A thesis paper submitted to the Department of Pharmacy, East West University in partial fulfillment of the requirement of the Degree of Bachelor of Pharmacy.

A collaborative study between Department of Pharmacy, East West University and Institute of Child Health & Shishu Sasthya Foundation Hospital, Dhaka, Bangladesh.

Certificate

This is to certify that the thesis submitted to the Department of Pharmacy, East West University, Mohakhali, Dhaka in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy was carried out by Abora Ettela, ID: 2005-3-70-028, under our guidance and supervision and that no part of the thesis has been submitted for any other degree. We further certify that all the sources of information and laboratory facilities availed of this connection is duly acknowledged.

Farhana Rizwan 23.12.09

Farhana Rizwan
Supervisor
Senior Lecturer
Department of Pharmacy
East West University
Mohakhali, Dhaka

20-12-09

Dr. Forhad Monjur
Co-supervisor
Laboratory medicine specialist
Department of Pathology
ICH&SSF
Mirpur, Dhaka

23/12/09

Dr. Chowdhury Faiz Hassain
Chairperson
Department of Pharmacy
East West University
Mohakhali, Dhaka

Dedication - This thesis paper is dedicated to my parents and my sister

LIST OF TABLES

LIST OF FIGURES

LIST OF CHARTS

LIST OF CONTENTS

ACKNOWLEGEMENT

I would like to express my deepest appreciation to all those who gave me the opportunity to write this paper. First of all I would like to thank my supervisor, Farhana Rizwan, Senior Lecturer, Pharmacy Department of East West University for encouraging, supporting and assisting me throughout the program. I would also like to thank Dr. Sufia Islam – Associate Professor, Pharmacy Department of East West University, for guiding us in the initial stages of the project.

I would also like to express my respect and gratitude to Dr. Chowdhury Faiz Hossain – Chairperson of the Pharmacy Department and Professor Dr. Muniruddin Ahmed – Pro Vice Chancellor of The East West University for always inspiring us in our pursuit of knowledge.

I would like to express my gratitude to Professor Dr. A. F. M. Salim – Department of Pediatrics and Dr. Forhad Monjur – Assistant Professor, Department of Pathology, at the Institute of Child Health & Shishu Sasthya Foundation Hospital. They helped me immensely. Dr. Forhad Monjur guided us through all our work at the hospital. Dr. A. F. M. Salim showed us how to approach research work with an open mind and how to organize the data in a meaningful way.

I would like to give special thanks to the Mr. Salauddin Ahmed, the librarian at the Institute of Child Health & Shishu Sasthya Foundation Hospital, who provided us with all the necessary data of the patients and let us collect the information from there.

Lastly I would like to thank Almighty Allah for guiding me through each step in my endeavor for education. Finally I express my appreciation for my parents and younger sister for their heartfelt prayers and support.

ABSTRACT

Typhoid fever is caused by the gram-negative bacteria called *Salmonella typhi*. It is transmitted by ingesting food or drink contaminated by the faeces or urine of infected people. Symptoms develop after 1 – 3 weeks. Around 10% of people infected can excrete the virus for up to 3 months. Nearly half become permanent carriers and are capable of infecting other people. Complications that may occur are intestinal perforations, hemorrhages and ulcers. Typhoid fever is common in endemic areas such as Asia, Africa and South America. It is however rare in the developed countries especially in North American countries and Europe. Bangladesh happens to be one of the endemic regions due to its poor sanitary and sewage systems.

It can be diagnosed by certain blood, bone marrow, and/or stool tests that look for the bacteria. Widal tests are the specific tests for typhoid. But very often physicians diagnose by clinical examination.

Typhoid fever is treated by antibiotics. Chloramphenicol was the drug of choice earlier. Other drugs successfully used were ampicillin and cotrimoxazole. But recently these drugs have become resistant. This is known as multi-drug resistance. Currently other antibiotics such as ciprofloxacin and cephalosporins e.g. ceftriaxone are being used successfully.

It is believed that typhoid fever can be eradicated by proper and hygienic water and sanitary facilities. Vaccination is another good option for inoculating the current masses. Some of the vaccines are Vi Polysaccharide vaccine (composed of purified polysaccharide from *S. typhi* capsule), a live attenuated strain of *S. typhi*, and inactivated whole cell vaccine.

CHAPTER 1

INTRODUCTION

1.1 TYPHOID FEVER

Typhoid fever is a systemic infection. It is an infectious disease caused by *Salmonella enterica* serotype Typhi (*S. typhi*) (Ganjewala, Khan, & Rao, 2008). Because of high infectivity and significant disease burden, typhoid fever constitutes a major global health problem (Borsutzky, Collioud, Dietrich, Favre, Griot-Wenk, Guzman, Metcalfe, & Pearman, 2005). It remains an important worldwide cause of morbidity and mortality. It is a prolonged febrile illness and continues to be a health problem in developing countries where there is poor sanitation, poor standard of personal hygiene and prevalence of contaminated food (Ganjewala, Khan, & Rao, 2008).

1.2 HISTORICAL BACKGROUND

Until the first quarter of the 19th century, typhoid fever was not recognized as a separate clinical entity and was often confused with other prolonged febrile syndromes such as typhus fever of rickettsial origin. '*Typhos*' in Greek means 'smoke' and typhus fever got its name from smoke that was believed to cause it. Typhoid means typhus-like and thus the name given to this disease. It was only in late 19th century that the disease was finally established as a distinct clinical entity (Singh, 2001).

In 1829, Dr. P. Ch. A. Louis in Paris described typhoid fever, clearly separating it from other fevers, and associated the clinical expression of the infection with the essential pathologic lesions in the intestines, mesenteric lymph node, and spleen. Dr. Louis discussed rose spots, intestinal perforation, and hemorrhage. It can be argue that since 1829 no important clinical or gross pathologic facts have been added. Also about this time, Drs. M. Bretonneau in France and N. Smith in the United States recognized the spread of the disease by contagion and insisted that immunity was conferred by an attack of the illness (Edelman & Levine, 1986).The term enteric fever was introduced in 1869 and now includes both typhoid fevers and paratyphoid fevers (Singh, 2001).

William Budd, an Englishman, wrote his epidemiologic masterpiece in 1873, providing evidence that bowel discharge were the main source of infection; that the disease was waterborne; that milk, food, contaminated linen, and other deformities were sources of dissemination; and insisted without direct proof that a specific germ caused typhoid and deduced its capacity for multiplication (Edelman & Levine, 1986).

1.3 INFECTIOUS AGENT

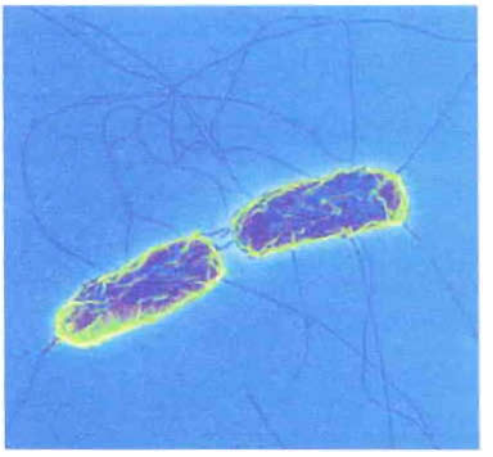


Figure 1: Salmonella typhi

Link: http://www.biosci.utexas.edu/ib/ScienceUnderStars/index.html

1.3.1 Microbiological characteristics

The genus *Salmonella* belongs to the family *Enterobacteriaceae*. They are motile, Gram negative bacilli. (Guidelines for drinking water quality, 2004) *Salmonella typhi* cells are rod shaped 2-3 μm long and 0.4-0.6 μm diameter (Ganjewala et al., 2008). They do not ferment lactose, but most produce hydrogen sulfide or gas from carbohydrate fermentation (Guidelines for drinking water quality, 2004). Originally, they were grouped into more than 2000 species (serotypes) according to their somatic (O) and flagellar (H) antigens. It is now considered that this classification is below species level and that there are actually no more than 2–3 species (*Salmonella enterica* or *Salmonella choleraesuis*, *Salmonella bongori* and *Salmonella typhi*), with the serovars being subspecies. (Guidelines for drinking water quality, 2004)

1.3.2 Virulence

Salmonella have flagellar, somatic, and outer coat antigens (named H, O and Vi antigens) (Cotran, Kumar, & Robins, 1989). These antigens play a role in its virulence. Vi is a capsular

antigen that can be destroyed at 100°C (Chan, Krieg, & Pelczar, 1993). They lack enterotoxins but are capable of invading intestinal mucosal cells to cause degenerative changes in the brush border and apical cytoplasm (Cotran, Kumar, & Robins, 1989). When they reach the bloodstream some of the bacteria undergo cell lysis by combined action of antibodies and the complement system. This results in the liberation of endotoxin which causes many of the characteristics symptoms of the disease (Chan et al., 1993).

1.4 MODE OF TRANSMISSION

Salmonella typhi is spread by the faecal–oral route. Infection by typhoid species is associated with the consumption of contaminated water or food, with direct person-to person spread being uncommon. (Guidelines for drinking water quality, 2004) During the early days when there was no treatment typhoid was greatly feared because of its contagiousness. Whenever someone was sick with the disease, everyone in the household was at great risk to develop the fever (Ray, 2002).

They are usually acquired by ingestion of contaminated food or water. Polluted water is the most common source of typhoid. In addition, shellfish taken from sewage contaminated beds, vegetables fertilized by night soil and eaten raw, and contaminated milk are another important sources of Salmonella typhi contraction (Singh, 2001). Transmission may be direct by means of the fecal to oral route, it may be airborne, 85-41"48 and it may be indirect by means of foods, toys, towels, contaminated toilet seats, and many other objects. All these avenues of transmission may occur in the household, between families, in restaurants, and in institutions including hospitals. (An Evaluation of the Salmonella Problem, 1970)

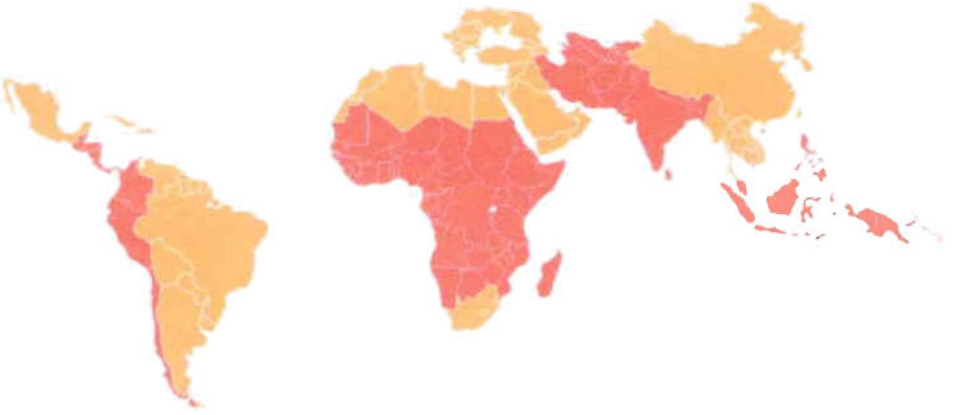
1.5 EPIDEMIOLOGY

It is a disease of poor environmental sanitation and hence occurs in parts of the world where water supply is unsafe and sanitation is substandard (Singh, 2001). The disease remains an important public health problem in developing countries. In 2000, it was estimated that over 21.6 million episodes of typhoid occurred worldwide, resulting in 216 000 deaths, and that more than 90% of this morbidity and mortality occurred in Asia (Acosta et al., 2008).

Few established surveillance systems for typhoid exist in the developing world, especially in community settings, so the true burden is difficult to estimate. This is shown by recent

revisions in the global estimates of the true burden of typhoid. In contrast to previous estimates, which were 60% higher, investigators from the US Centers for Disease Control and Prevention estimate that there are 21.6 million typhoid cases annually, with the annual incidence varying from 100 to 1000 cases per 100 000 population. The global mortality estimates from typhoid have also been revised downwards from 600 000 to 200 000, largely on the basis of regional extrapolations (Bhutta, 2006).

According to 22 eligible studies, regions with high incidence of typhoid fever (>100/100 000 cases/year) include south-central Asia and south-east Asia. Regions of medium incidence (10-100/100 000 cases/year) include the rest of Asia, Africa, Latin America and the Caribbean, and Oceania, except for Australia and New Zealand. Europe, North America, and the rest of the developed world have low incidence of typhoid fever (<10/100 000 cases/year) (Crump et al., 2004). Developed countries have brought down the incidence of typhoid fever to very low levels. For example, in UK, the incidence of this disease is reported to be just one case per 100 000 population (Singh, 2001). The figure below shows the prevalence of typhoid fever.



Highly endemic Endemic Low incidences

Figure 2: Geographical distribution of typhoid fever

Link: http://www.richardstupart.com/2009/07/01/things-you-can-die-from-between-cape-town-and-cairo/

Recent population based studies from South Asia suggest that the incidence is highest in children aged less than 5 years, with higher rates of complications and hospitalization, and may indicate risk of early exposure to relatively large infecting doses of the organisms in these populations (Bhutta, 2006). Typhoid fever may occur at any age but it is considered to be a disease mainly of children and young adults. In endemic areas, the highest attack rate occurs in children aged 8-13 years. In a recent study from slums of Delhi, it was found that contrary to popular belief, the disease affects even children aged 1-5 years. Older people appear to be relatively immune, presumably because of frequently reinforced (Singh, 2001).

One of the first community-based epidemiological data on typhoid disease burden from Bangladesh indicates a high burden of disease in the urban population. The greatest incidence of infection was in children <5 years of age. Community-based surveillance for typhoid fever in Kamalapur during 2001 found that 49 (5.5%) blood cultures grew *Salmonella* Typhi. *S.* Typhi isolations represented 75% of all positive blood cultures; 53% were in children <5 years of age. The overall incidence of typhoid fever was 3.9 cases per 1,000 populations per year; in children <5 years of age, the rate was 18.7 per 1,000 children per year. Children <5 years of age had an 8.9-fold increased likelihood of infection when compared with all others (Incidence of Typhoid Fever, Dhaka, 2001).

There may be other factors that affect the changing epidemiology of typhoid. Although the overall ratio of disease caused by *S typhi* to that caused by *S paratyphi* is about 10 to 1, the proportion of *S paratyphi* infections is increasing in some parts of the world. Also, in contrast to the Asian situation, the HIV and AIDS epidemic in Africa has been associated with a concomitant increase in community acquired bacteraemia due to nontyphoidal salmonellae such as *S typhimurium*, an illness that may be clinically indistinguishable from typhoid. The exact reasons for these differences in the epidemiology and spectrum of salmonella infections between Asia and Africa remain unclear (Bhutta, 2006).

1.6 PATHOLOGY

Typhoid fever occurs only in humans. The disease begins in the small intestine. When *Salmonella typhi* is ingested, it enters the small intestine. It attaches itself to the epithelium of the intestinal wall (Chan et al., 1993). It is followed by luminal proliferation, mucosal penetration, and uptake by macrophages and dissemination to the lymphatic structures of the

gut and mesentery. They multiply in the mesenteric lymph nodes. These are the earliest events in typhoid fever and are completed within the incubation period of one to two weeks. Bacteremia then ensues during the first week of clinical disease (Cotran et al., 1989).

The organisms cause enlargement of reticulo endothelial and lymphoid tissue throughout the body. Proliferations of phagocytes cause swelling of the lymphatic submucosal nodules of the entire gut i.e. mainly Peyer's patches of the terminal ileum. These become sharply delineated, plateau-like elevations up to 8 cm in diameter, bulging into the intestinal lumen. Concomitantly, the mesenteric lymph nodes, the spleen and often the liver increases in size. In untreated cases, during the second week, the mucosa over the swollen ileal lymphoid tissue is shed, resulting in oval ulcers with their long axes in the direction of bowel flow, a pattern seen only in typhoid fever and Yersinia infections. Bleeding from typhoidal ulcers is usually scant, but it can sometimes become uncontrollable. Perforation, although rare, has been the cause of fatalities. Once past the peak of the disease, the ulcers heal slowly and the lymphatic structures amazingly regenerate without permanent scarring (Cotran et al., 1989).

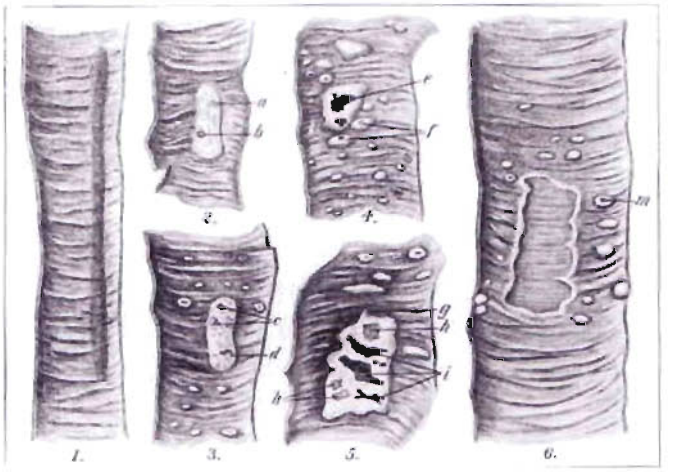


Figure 3: Ulceration and hemorrhages in the Peyers patch
Link: www.pathguy.com/lectures/infect.htm

Histologically, there is both local and systemic mobilization and accumulation of mononuclear phagocytes. The macrophages form nodular aggregates rather than full- fledged tuberculoid granulomas. They are filled with red blood cells and nuclear debris, during the height of the disease. There is also neutropenia in the peripheral blood (Cotran et al., 1989).

The spleen is enlarged, soft and bulging with uniformly pale red pulp and obliterated follicular markings. Splenic ruptures occur but are uncommon. The liver shows small, randomly scattered foci of parenchymal necrosis in which the hepatocytes are replaced by a phagocytic mononuclear cell aggregate called typhoid nodule. Treatment can of course arrest or modify all these classic lesions. Fatty change may appear in the liver of patients kept on prolonged liquid diets. Tetracyclin treatment may result in microvesicular fatty liver change and in hepatic failure with jaundice. A more frequent complication is pneumonia. S. typhi can localize in many sites including conjunctivae, meninges, joints kidneys and gallbladder (Cotran et al., 1989).

Table 1

Pathological changes in typhoid fever

S.No	Organ	Pathological Changes
1.	Heart	Heart may get enlarge and affected by fatty degeneration.
2.	Skin	Skin changes with collection of bacilli, which cause the classical rose spots.
3.	Liver	Liver get enlarged with fatty changes.
4.	Peyer patches	Peyer patches vary from hyperplasia and ulceration, through to frank ulceration and typhoid perforation.
5.	Spleen	Spleen becomes large and soft.
6.	Kidney	Kidney show cloudy swelling which may results in albuminuria.
7.	Lungs	Bronchitis is common in typhoid fever.
8.	Gall bladder	Cholecystitis may lead to the formation of infected gall stones in the gall bladder which may be a potent source of infection in the typhoid carrier.

(Ganjewala et al., 2008)

1.7 CLINICAL FEATURES

The onset may be insidious. The temperature rises in a stepladder fashion for 4 or 5 days. The following symptoms are seen with the progression of time.

Table 2

Clinical Features

First week	
• Fever	• Relative bradycardia
• Headache	• Constipation
• Myalgia	• Diarrhea and vomiting in children
End of first week	
• Rose spots on the trunk	• Abdominal distention
• Splenomegaly	• Diarrhea
• Cough	
End of second week	
Delirium, complications, then coma and death if left untreated	

(Boon, Colledge, Hunter, & Walker, 2006)

At the end of the first week a rash may appear on the upper body and on the back as sparse, slightly raised, rose-red spots, which fade on pressure. It is usually visible only on white skin. By end of the second week, the patient may be profoundly ill unless the disease is modified by antibiotics. In the third week toxemia increases and the patient may pass into coma and die. The bacteria may live in the gallbladder of carriers for months or years after clinical recovery and pass intermittently in the stool and less commonly in the urine. Such patients may develop gallbladder disease (Boon et al., 2006).

1.8 DIAGNOSIS

Although the mainstay of diagnosing typhoid fever is a positive blood culture, the test is positive in only 40-60% of cases, usually early in the course of the disease. Stool and urine cultures become positive after the first week of infection, but their sensitivity is much lower. In much of the developing world, widespread antibiotic availability and prescribing is another reason for the low sensitivity of blood cultures. Although bone marrow cultures are more sensitive, they are difficult to obtain, relatively invasive, and of little use in public health settings (Bhutta, 2006).

Diagnostic test	Sensitivity range (%)	Specificity range (%)	Comments
Microbiological tests			
Blood culture	40-80	NA	Widely regarded as the gold standard, but sensitivity may be low in endemic areas with high rates of antibiotic use—hence true specificity is difficult to estimate
Bone marrow cultures	55-67	30	Greater sensitivity but invasive and thus of limited clinical value, especially in ambulatory management
Urine culture	0-58	NA	Variable sensitivity
Stool culture	30	NA	Sensitivity lower in developing countries and not used routinely for follow-up
Molecular diagnostics			
Polymerase chain reaction	100	100	Promising, but initial reports indicated similar sensitivity to blood cultures and lower specificity
Nested polymerase chain reaction	100	100	Promising and may replace blood culture as the new "gold standard"
Serological diagnosis			
Widal test (tube dilution and slide agglutination)	47-77	50-92	Classic and inexpensive. Despite mixed results in endemic areas, still performs well for screening large volumes. May need standardisation and quality assurance of reagents
Typhidot	66-88	75-91	Lower sensitivity than Typhidot-M
Typhidot-M	73-95	68-95	Higher sensitivity and specificity than classic Typhidot in some series, but other evaluations suggest that the performance may not be as robust in community settings as in hospital
Tubex	66-88	63-89	Promising initial results but has yet to be evaluated in larger trials in community settings
Others			
Urine antigen detection	65-95	NA	Preliminary data only

NA=Not available.

Other haematological investigations are nonspecific. Blood leucocyte counts are often low in relation to the fever and toxicity, but the range is wide; in younger children leucocytosis is a common association and may reach 20 000-25 000/mm Thrombocytopenia may be a marker of severe illness and accompany disseminated intravascular coagulation. Liver function test results may be deranged, but significant hepatic dysfunction is rare (Bhutta, 2006).

The classic Widal test measures antibodies against O and H antigens of *S. typhi* and is more than 100 years old. Although robust and simple to perform, this test lacks sensitivity and specificity, and reliance on it alone in areas where typhoid is endemic may lead to over diagnosis. Newer diagnostic tests have been developed—such as the Typhidotor Tubex, which directly detect IgM antibodies against a host of specific *S. typhi* antigens—but these have not proved to be sufficiently robust in large scale evaluations in community settings. A nested polymerase chain reaction using *H1-d* primers has been used to amplify specific genes of *S. typhi* in the blood of patients and is a promising means of making a rapid diagnosis. Table 2 compares the performance of the various tests for typhoid (Bhutta, 2006).

Despite these new developments, the diagnosis of typhoid in much of the developing world is made on clinical criteria. This poses problems, since typhoid fever may mimic many common febrile illnesses without localizing signs. In children with multisystem features, the early stages of enteric fever may be confused with conditions such as acute gastroenteritis, bronchitis, and bronchopneumonia. Subsequently, the differential diagnosis includes malaria; sepsis with other bacterial pathogens; infections caused by intracellular organisms such as tuberculosis, brucellosis, tularaemia, leptospirosis, and rickettsial diseases; and viral infections such as dengue fever, acute hepatitis, and infectious mononucleosis. There is thus an urgent need to develop a multipurpose "fever stick" that may allow the rapid and specific diagnosis of common febrile illnesses, especially malaria, dengue fever, and typhoid (Bhutta, 2006).

1.9 COMPLICATIONS

A summary of the possible complications are given in Table 3. Hemorrhage from, or a perforation of the ulcerated Peyer's patches may occur at the end of the second week or during the third week of the illness. A drop in temperature to the normal or subnormal levels may occur in those with intestinal hemorrhage. This can be falsely reassuring as it occurs

even before there is clinical evidence of bleeding such as melaena. Additional complications may involve almost any viscus or system because of the septicemia present during the first week; these include cholecystitis, pneumonia, myocarditis, arthritis, osteomyelitis and meningitis. Bone and joint infection is especially seen in children with sickle-cell disease (Boon et al., 2006).

Table 4:
Complications of Typhoid Fever

Bowel	
• Perforation	• Hemorrhage
Septicaemic foci	
• Bone and joint infection • Meningitis	• Cholcystitis
Toxic phenomena	
• Myocarditis	• Nephritis

(Boon et al., 2006)

1.10 TREATMENT

1.10.1 Treatment with antibiotics

There was no specific treatment for typhoid fever for thousands of years. Doctors could only try to make patients comfortable or suggest methods to reduce fever, such as by drinking fluids and resting. As the fever rose and the person's other symptoms worsened, there was no treatment available. If he or she was lucky, enough bacteria would be shed from the body to reduce the severity of the disease. Sometimes the patient would feel well enough to go back to daily life activities. Frequently though, the symptoms would return. In many cases, the patients died (Ray, 2002). The mortality of untreated typhoid can be as high as 30%, whereas with appropriate antimicrobial chemotherapy it is < 1 % (Beechmg, Hart, & Mirza, 1996).

Early diagnosis of typhoid fever and prompt institution of appropriate antibiotic treatment are essential for optimal management, especially in children. Although most cases can be managed at home with oral antibiotics and regular follow-up (this may include confirmation of stool clearance in non-endemic areas or in high risk groups such as food handlers), patients

with severe illness, persistent vomiting, severe diarrhoea, and abdominal distension require hospitalisation and parenteral antibiotic treatment. In addition to antibiotics, supportive treatment and maintenance of appropriate nutrition and hydration are crucial. Appropriate antibiotic treatment (the right drug, dose, and duration) is critical to curing typhoid with minimal complications. Along side adequate rest, hydration, and correction of fluid-electrolyte imbalance is to be maintained. Antipyretic therapy can be given as required (such as paracetamol 120-750 mg taken orally every 4-6 hours). Adequate nutrition: a soft, easily digestible diet should be given (Bhutta, 2006).

Several antibiotics are effective in enteric fever. Chloramphenicol was the first antibiotic to be effective in typhoid fever and remains the most commonly used drug in this disease. It has the great advantage of being cheap and readily obtainable throughout the world. However, its serious, although rare, bone marrow toxicity together with a relatively slow clinical response and significant incidence of relapse and carrier state following treatment has prompted a search for alternative agents (Geddes, 1977).

The indiscriminate use of the drug and acquisition of plasmid mediated R factor has led to the development of resistance to *S. typhi* against chloramphenicol. The emergence of chloramphenicol resistance posed a big problem regarding the treatment of patients with typhoid fever. Drug resistance in typhoid fever is considered as one of the important factors in the morbidity and mortality of the disease. Alternative drugs suggested included co-trimoxazole, ampicillin and amoxicillin (Chowta & Chowta, 2005).

Ampicillin is effective in enteric fever but the response to treatment is extremely slow. Amoxycillin is superior to ampicillin and one study has suggested that it is as good as chloramphenicol. The present lack of an injectable preparation of amoxycillin is a distinct disadvantage in a disease in which vomiting is common (Geddes, 1977).

The emergence of multidrug resistant typhoid (resistant to all three first line inexpensive antibiotics, chloramphenicol, amoxicillin, and co-trimoxazole) in the 1990s led to widespread use of fluoroquinolones as the treatment of choice for suspected typhoid, especially in South Asia and South East Asia where the disease was endemic (Boon et al., 2006). Fluoroquinolones are recommended as first line therapy for children and adults infected with

sensitive as well as multidrug resistant (Azmatullah, Critchley, Madni, Thaver, & Zaidi, 2009).

Ciprofloxacin has recently been suggested as the preferred treatment for traveller's diarrhoea and multiresistant Salmonella typhi infection (Dodd, Mellersh, Nelson, Simpson, & Watson, 1991). But a recent Cochrane review of antimicrobial treatment of typhoid fever concludes that there is little evidence to support administration of fluoroquinolones to all cases of typhoid and that satisfactory cure rates can be achieved in drug sensitive cases with first line agents such as chloramphenicol. And again the emergence of resistance to quinolones has placed tremendous pressure on public health systems in developing countries as treatment options are limited (Bhutta, 2006). The resistance to quinolone is not plasmid coded but due to an altered DNA gyrase subunit.

The fact that sensitivity to the ciprofloxacins and cephalosporins is decreasing has been proven by a study. According to literatures published years before the study the defervescence period for ciprofloxacin was about three to five days and for cephalosporins was about 3 days. But in the study done in 2005 the defervescence period was considerably longer i.e. about eight days for ciprofloxacin and about six days for cephalosporins. In one patient, although there was *in vitro* sensitivity to ciprofloxacin patient did not respond to the drug. According to the paper these findings suggest that sensitivity of S. typhi to ciprofloxacin and cephalosporins is gradually decreasing (Chowta & Chowta, 2005).

Fluroquinolones have been studies various times in comparison with other antibiotics in the treatment of typhoid. In comparison with ceftriaxone, the meta-analysis showed significantly lower odds of clinical failure with fluoroquinolones but there was no difference in microbiological failure or relapse. Fever clearance time was significantly lower with fluoroquinolones. In a fluoroquinolones versus azithromycin study, there were no significant differences in clinical failure, microbiological failure, or relapse. There was a significant increase in convalescent faecal carriage with fluoroquinolone use. This was measured early on days 2-3 after end of treatment.

One study was done on children comparing fluoroquinolones with cefixime. Reduction in clinical failure was of borderline significance in favour of fluoroquinolones. There were no significant differences in microbiological failure or relapse. Although a trend favouring

fluoroquinolone can be seen. There was a significant reduction in fever clearance time and length of hospital stay with fluoroquinolones. Another trial used gatifloxacin which is active against nalidixic acid resistant strains.

Azithromicin vs ofloxacin was done with paediatic patients. With ofloxacin there was a significant increase in clinical failure, no significant differences in microbiological failure, and no relapses at one month followup. Ofloxacin use significantly increased fever clearance time and convalescent faecal carriage and a borderline increase in length of hospitalisation. In the trial of gatifloxacin versus azithromycin there were no significant differences in clinical or microbiological failure, relapse, fever clearance time length of hospital stay or convalescent faecal carriage, although confidence intervals were wide. (Azmatullah et al., 2009).

Interestingly in one study, treatment of typhoid with ciprofloxacin and cefuroxime induced interstitial nephritis causing non-oliguric renal failure. There have been no cases reported in children. Although the patients also received cefuroxime, there never have been any cases of interstitial nephritis induced by cefuroxime given either alone or with other drugs. All patients with ciprofloxacin associated renal failure described by the time of writing had maintained a urine output. It was suggested that renal function should be monitored during treatment with ciprofloxacin. In addition, ciprofloxacin should be added to the long list of drugs that may cause interstitial nephritis (Dodd et al., 1991). Another downside of quinolones unfortunately is that quinolones are contraindicated in pediatric patients and pregnant woman due to the potential damage to the articular cartilage (Benavente, García, E., García, G., & Santillán, 2000).

Apart from this clinical studies have shown excellent efficacy of cefixime and ceftriaxone against typhoid fever. Cefixime, the first oral extended-spectrum cephalosporin, has strong activity against serovar Typhi and its clinical usefulness has also been proven in several studies. It was concluded that a fair amount of cefixime can enter mammalian cells and inhibit the growth of bacteria inside cells when the bacteria are sensitive enough to cefixime. Cefixime accomplishes the desired characteristics of an antibiotic and may be the treatment of choice of MDR and non-MDR typhoid fever, particularly in children from endemic areas with high prevalence of MDR typhoid fever. Its activity is comparable to those of ceftriaxone and the new quinolones (Ikeda, Ikemoto, Matsumoto, K., Matsumoto, Y., Tawara, & Wakai,

2001). Parenteral ceftriaxone was associated with higher rates of relapse (Bhutta, 2006). Although the cephalosporins and ceftriaxone are useful against MDR typhoid fever, but the required intravenous route of administration renders them impractical for some patients. (Butler, Daga, Johnson, Khakhria, Pandit, Pathak, Potkar, Sridhar & Zelasky, 1999).

Mecillinam, an amidino-penicillanic acid is extremely active against salmonellae, and well-excreted in bile (Geddes, 1977). Mecillinam is a new antibiotic related to the penicillins but more active than ampicillin against salmonellae, including Salmonella typhi. Mecillinam must be administered parenterally, but the ester, pivmecillinam, is absorbed from the gut. Eight patients suffering from typhoid fever and one suffering from paratyphoid fever were treated with the antibiotic, and seven responded satisfactorily. One patient could not tolerate pivmecillinam because of vomiting but there were no other adverse reactions. Serum and bile levels of mecillinam were many times the mninimum inhibitory concentrations for most salmonellae. The antibiotic is a promising addition to the agents available for treating typhoid (Clark, Geddes, McGhie & Wall, 1976) However, its *in vitro* promise has not yet been confirmed by a large enough clinical study (Geddes, 1977).

Chloramphenicol (500mg, 6 hourly), Ampicillin (750mg 6-hourly) and Cotrimoxazole (2 tablets or IV equivalent 12 hourly) may be given (Boon et al., 2006). Appropriate antibiotic treatment (the right drug, dose, and duration) is critical to curing typhoid with minimal complications. Standard treatment with chloramphenicol or amoxicillin is associated with a relapse rate of 5-15% or 4-8% respectively, whereas the newer quinolones and third generation Cephalosporins are associated with higher cure rates (Boon et al., 2006). The cephalosporins, ceftriaxone and cefixime are useful against typhoid fever but the required intravenous route of administration renders them impractical for some patients. Azithromicin (500mg once daily) has been shown to be an alternative where fluoroquinoline resistance is present but have slightly increased treatment failure rate (Boon et al., 2006).

1.10.2 Spread of Resistance to antibiotics

Bacterial resistance is attributable to 3 general mechanisms

1. The drug does not reach its target:

Drugs mostly enter the cell through porin channels. Absence, mutation or loss of favored porin channel can slow or inhibit the rate of drug entry. The bacterial cell may also have

efflux pumps to throw out the drug molecules. Resistance to chloramphenicol and fluroquinolones occur by this way.

2. The drug is not active

Many drugs such as aminoglycosides and beta-lactams become resistant this way.. This occurs by variation in the enzymatic conditions which fail to activate the drug

3. The target is altered

Fluroquinolone, macrolides and tetracycline resistance occur by this way. This is due to the mutation of the drugs natural target e.g. ribosome protection from macrolides.

The drug resistant traits often also pass onto the progeny. This acquired resistance may also be done by transferring the information through transferable plasmids.

As mentioned, *S. typhi* has slowly become resistant to many antibiotics over time. Chloramphenicol-resistant S. Typhi emerged first in the UK within 2 years of the successful use of chloramphenicol in typhoid. Subsequently, isolates carrying transferable chloramphenicol resistance were described from Greece and Israel. Two *S.* Typhi isolates from Aden and Cairo carrying transferable resistance to chloramphenicol, ampicillin and tetracycline were found in 1967. However, it was not until 1973 that epidemics of typhoid with resistant strains were reported from Mexico and India. Other epidemics occurred subsequently in Vietnam, Korea and Peru. Most of these resistant strains carried transferable resistance to chloramphenicol, tetracycline, aminoglycosides and sulphonamides (Beechmg et al., 1996).

Multi-drug resistant *S. Typhi* was first described in India in 1990. Multiresistant strains have also been isolated in Malaysia, Bangladesh and Vietnam, and the epidemic zone in Asia now appears to stretch from Pakistan in the west to China in the east. In addition, there is a 'pseudo-epidemic' zone in the Middle East. Between 30% and 40% of the population of Persian Gulf states are expatriate workers, mainly from the Indian sub-continent and the Far East. These workers travel repeatedly from their home countries to work and 70-80% of multiresistant *S. Typhi* strains in Bahrain, Kuwait, Qatar and Oman are imported. In this region 5- 30% of *S. Typhi* isolates are multi-drug resistant (Beechmg et al., 1996).

Surprisingly, multi-drug resistance does not seem to have had a major impact in Africa, or South and Central America. In Africa, cases have been described in Egypt and a cluster of six cases of multiresistant *S. Typhi* infection was reported from northern Natal. Elsewhere in Africa and America, *S. Typhi* remains sensitive to one or more of the first line agents, although large outbreaks of infection due to strains resistant to chloramphenicol and some of the other antimicrobial agents continue to occur. In the UK, multiresistant strains now represent >18% of *S. Typhi* isolates, mostly acquired in the Indian sub-continent or the Middle East. Three such strains have been isolated in Spain but their origin is unclear (Beechmg et al., 1996).

1.10.3 Carrier state

Individuals who excrete *S typhi* for more than three months after infection are regarded as chronic carriers. However, the risk of becoming a carrier is low in children and increases with age, but in general it occurs in less than 2% of all infected children (Bhutta, 2006). Formerly, it was thought that persons with gastroenteritis caused by unadapted serotypes of *Salmonella* excreted the bacteria in large numbers while symptomatic, and that the causative agents persisted in the intestine only for short periods after symptoms disappeared. There was little information on the role of the symptomless excretor who had no history of intestinal infection. It is now known that some convalescents, as well as persons without history of symptoms, may excrete salmonellae for long periods. This is not to imply that most such persons are permanent carriers, as is the case with those who excrete *S. typhi* because of chronic infection of the biliary or urinary tract. Occasionally cultures of *Salmonella* are isolated from gallstones, as *S. typhi* so often is, and the persons from whom these stones were removed were undoubtedly permanent carriers. It is clear that permanent carriers of unadapted salmonellae are rare, however, probably representing a small percentage of those persons in whom bloodstream invasion occurred. (An Evaluation of the *Salmonella* Problem, 1970)

Conversely, the long-term carrier state (six months or more) following disease occurs more often than is commonly realized. Many investigators have reported on the frequency of long-term carriers, particularly among children, on familial spread from such carriers, and on the fact that excretion of the bacteria is intermittent. (An Evaluation of the *Salmonella* Problem, 1970)

Similarly, the literature is replete with references to asymptomatic carriers who have no history of diarrheal disease. Many of these asymptomatic excretors of salmonellae have been discovered through routine examination of fecal specimens from food handlers. Estimates of the numbers of carriers in various countries are available (range, 2-50 per thousand), but it should be recalled that in the majority of asymptomatic carriers, the bacteria persist for relatively short periods of time and excretion of salmonellae is intermittent. (An Evaluation of the *Salmonella* Problem, 1970)

Persons become asymptomatic carriers through having had the disease or from exposure to infection without development of symptoms. The duration of the carrier state is variable in different age groups. In persons with acute gastroenteritis, the bacteria are excreted in large numbers, but as most such patients recover, the numbers of *salmonellae* excreted diminishes, so that after three or four weeks the bacteria usually cannot be demonstrated in stools. Infants frequently become long-term carriers and may harbor the bacteria for longer periods than older persons. Further, they transmit infection to other members of their families. (An Evaluation of the *Salmonella* Problem, 1970)

1.11 PREVENTION

Improved sanitation and living conditions is the ultimate solution in prevention of typhoid fever. Waterborne typhoid fever outbreaks have devastating public health implications. Within a WSP, control measures that can be applied to manage risk include protection of raw water supplies from animal and human waste, adequate treatment and protection of water during distribution. (Guidelines for drinking water quality, 2004).

1.11.1 Control of infected patients

But this can be achieved only after long time effort. In the meantime efforts should be given to prevent typhoid from spreading in the current population. Some measures that can be taken are isolation of a patient suffering from typhoid fever. The patient's urine and faeces are highly contagious, as may be his vomit. Patient as well as the people attending to him must carefully scrub their hands using soap. The patient's eating utensil should preferably be disposable; otherwise they should be reserved for him and be sterilized by boiling after use. Another obvious method is to avoid taking food or drinks that might be contaminated with the bacteria e.g. the food from the roadside vendors etc (International Medical Guide for Ships, 1988).

1.11.2 Control of drug use

Indiscriminate use of drugs in typhoid fever should be discouraged. Appropriate antibiotic indicated by sensitivity tests should be employed to prevent the development of resistant strains when treating patients (Chowta & Chowta, 2005).

1.11.3 Control by Vaccination

Inoculation by vaccination is a good option for immunization. The original concept of a vaccine to protect against typhoid fever was introduced in 1897, by Almorth Wright; a British scientist (Ray, 2002).Wright took *Samonella typhi* bacteria and allowed it to multiply in a controlled laboratory setting. Next, he took the bacteria and preserved it in a solution. Finally, he heated the solution to a high temperature that killed the bacteria. What was left was a solution that contained dead typhoid bacteria. When the solution was injected into humans, the body reacted and released lymphocytes to fight the infection. Sometimes the person developed mild symptoms but not serious enough. This vaccination allowed the body to develop immunity and if faced to live *Salmonella typhi*, it could fight the disease on its own. This was a big breakthrough. It was used to protect soldiers stationed in India where typhoid incidences were very high (Ray, 2002).

During the 1960s and 1970s, randomized controlled field trials of inactivated parenteral whole cell vaccines were sponsored by the World Health Organisation (WHO) in Eastern Europe and Guyana. These studies demonstrated the efficacy of vaccines consisting of *S. Typhi* inactivated by heat and phenol or by acetone ranged from 51% to 88% in children and young adults and protection persisted for up to 7 years. Although these early parenteral vaccines were clearly able to confer protection against typhoid fever, their global use as public health tools for routine vaccination was undermined by their high reactogenicity: the parenteral whole cell vaccines caused fever (6–30% of the recipients), headache (10%) and severe local pain (up to 35%). Furthermore, up to 10% of the vaccines missed work or school owing to the vaccination.

Consequently, the whole cell vaccines have been replaced by the well tolerated Vi-based parenteral subunit vaccine and the oral attenuated live bacterial vaccine Ty21a (Borsutzky et al., 2005). Age-specific infection rates suggest that vaccination would be most beneficial in

the first year of life, before infection rates become high during the second and subsequent years of early childhood (Incidence of Typhoid Fever, Dhaka, 2001).

Another approach is the use of subunit vaccines that are generated using purified Vi capsular polysaccharide of *S. Typhi*. Immunisation with Vi-antigen results in the induction of anti-Vi antibody titres in vaccinees in endemic and nonendemic areas (a fourfold rise in anti-Vi antibodies is defined as seroconversion). Previous exposure to *S.* Typhi does not seem to influence the immune response. The efficacy of the VI polysaccharide was assessed in the late 1980s in field trials in typhoid-endemic areas in Nepal and South Africa. In South Africa, the vaccine was given to more than 11,000 children 6–14 years of age and exhibited a protective efficacy of 64% during the first 21 months after vaccination and an efficacy of 55% over 3 years (Borsutzky et al., 2005). Routine immunisation of school-age children with VI or Ty21a vaccine is recommended for countries endemic for typhoid. VI vaccine should be used for 2–5 year-old children in highly endemic settings (Bahl, Bhan & Bhatnagar, 2005).

The use of attenuated live bacterial vaccines (LBV) constitutes another typhoid vaccine strategy. Attenuated strains administered orally mimic the mucosal and systemic immune responses elicited by natural infection. Oral vaccination is generally associated with lower rates of side-effects and higher acceptance by vaccines and can be logistically simpler (Borsutzky et al., 2005).

CHAPTER 2

Objective of the study:

Typhoid fever is an old disease and has been plaguing the lives of humans for thousands of years. In the ancient times people did not know the cause, nor could they treat it properly. Only in the recent years has the treatment proven to be satisfactory. This came about after the discovery of antibiotics. Typhoid fever can now be successfully treated. Typhoid fever is more prevalent in developing countries like Bangladesh. And here in the urban areas, children form a large segmented of those afflicted with this disease. Keeping this in mind the study was carried out to find the antibiotics used in the treatment of typhoid fever. It was done to see which of the antibiotics are most effective, especially in children below the age of twelve.

In spite of good treatments, carrier states and the growing resistance of the bacteria *Salmonella typhi* against the currently used antibiotics prove to be a challenge. Therefore the study also aims at comparing their sensitivities and to see whether any of the commonly used antibiotics are becoming resistant. The objectives of the study can be summarized as:

- To determine the most effective antibiotics for treating typhoid fever in children.
- To compare the relative of sensitivities of the antibiotics used.
- To determine if any of the antibiotics are becoming less sensitive.
- To see whether the most common and effective antibiotics are becoming resistant.

Significance of the study:

Typhoid fever affects a significant number of people worldwide. As seen in 22 studies, regions with high incidence of typhoid fever include south-central Asia and south-east Asia. Regions of medium incidence include the rest of Asia, Africa, Latin America and the Caribbean, and Oceania, except for Australia and New Zealand. Europe, North America and the rest of the developed world have low incidence of typhoid. In 2004 it was estimated that typhoid fever caused 21 650 974 illness and 216 510 deaths during 2000 (Crump, Luby, Mintz, 2004).

Bangladesh is one of the endemic regions of typhoid. It is one of the developing countries and as such lacks many of the proper and hygienic facilities especially in the poor urban areas. In one study the municipal water supply was used by all 41 cases and 81of 82 controls. In multivariate analysis, drinking water that was not boiled at home was a significant risk factor. Twenty-three (56%) cases and 21 (26%) controls reported that water from the primary source was foul-smelling. Even eating papaya was associated with illness (Breiman, Brooks, Hossain, Luby, Mintz, Naheed, Ram, 2007).

It can be seen that a large population of Bangladesh is prone to infection by *S. typhi*. Though the ultimate solution is proper sanitary and water systems, treatment of current cases have to be done by the most effective use of the available antibiotics. Also the emergence of multi-drug resistance has caused major concern. Typhoid today is a treatable disease. With proper planning of prevention and vaccination, it may even be eradicated. But the other side also exists. If the *Salmonella typhi* bacteria become resistant to our current antibiotics, it could turn into a major threat. For this the knowledge of the individual drug's efficacy against *S. typhi* and its growing resistance needs to be monitored periodically.

Amongst the people affected a large segment are children. This study can provide information related to the treatment of typhoid fever in children which may differ from the adults. This includes the antibiotics efficacy, commonly used antibiotics and their sensitivities. It will be significant to the health sector of Bangladesh. It may also be informative to other endemic areas of the world. The study is especially reflective of the *salmonella* strains in poor urban areas of Dhaka.

CHAPTER 3

MATERIALS AND METHODS

3.1 Place of study:

The retrospective study was carried out at the Institute of Child Health & Shishu Sasthya Foundation Hospital, Mirpur, and Dhaka, Bangladesh. Here the information was collected from the library.

3.2 Study period:

The data collected was over a period of one year.

3.3 Research Design:

The study was retrospective. Data from 50 patients were collected below the age of 12 years.

3.4 List of Drugs

A list of antibiotics either currently or previously used in typhoid fever treatment was made. The antibiotics were chloramphenicol, amoxicillin, ciprofloxacin, cefotaxime, azithromycin, ceftriaxone, cefoperazone, ofloxacin and levofloxacin. The following information was collected for each individual antibiotic.

- Drug Name
- Adult Dose
- Pediatric Dose
- Adult Dose
- Contraindications
- Interactions
- Pregnancy
- Precautions

3.5 Protocol

A protocol was prepared and it consisted of the following:

- Project title
- Background information

- Introduction
- What is typhoid fever
- How does it spread
- Clinical features of typhoid fever
- Summary of complications of typhoid fever
- Investigations
- Treatments available
- Management
- Preventions
- Prevalence
- Significance of the study
- Hypothesis
- Objective
- Place of study
- Materials and methods
- Inclusion criteria
- Exclusion criteria
- Study period
- Data collection procedure
- Treatment given
- Statistical analysis
- Outcome variables

3.6 Data Collection and Sample Characteristics

The data was collected from the Institution of Child Health & Shishu Sasthya Foundation Hospital, Mirpur, and Dhaka from 1st January to 30th June, 2008. Information from patients who met the inclusion criteria was included.

3.7 Inclusion Criteria:

The following was included

- Male and female children diagnosed with typhoid fever.

- Patients within the age of 0 to 12 years.
- Children who were admitted in the hospital for the treatment i.e. indoor patients.

3.8 Exclusion Criteria: The following was not included in the study

- Patients who did not develop typhoid fever.
- Patients who had typhoid fever but was not admitted in the hospital i.e. outdoor patients.
- Patients that were not admitted within the time period of the study i.e. July 2007 to July 2008.

3.9 Data collection paper

A data collection paper was made in order to compile all the information and data of the patient in an organized manner.

3.10 Laboratory Investigation

Most of the laboratory tests done on the children were by collecting blood samples and stool. The analysis was done at the Institution of Child Health & Shishu Sasthya Foundation Hospital, Mirpur, Dhaka. The procedures involved were isolation of the organism, CBC, Urine Diazo Test, blood culture, clot culture, culture of faeces, urine culture, cultural characters, slide agglutination, antimicrobial susceptibility testing, detection of antibodies, carrying out Widal test, preparation of antigen and diagnosis of chronic typhoid carriers.

3.11 Demographic history of the patient

The demographic history consisted of the patient's family history, patient's personal information and use of antibiotic and history of present illness at admission. Data about demographic characteristics of children and their family was collected at the beginning of the study. A follow up questionnaire (data collection paper) was developed and filled correctly from the documents of the hospital's library.

3.12 Patient's Family History

The family history of the patient contained:

- ✓ Length of formal education of mother
- ✓ Length of formal education of father

- ✓ Mother's occupation
- ✓ Father's occupation
- ✓ Socioeconomic status
- ✓ Hygienic conditions
- ✓ Condition of the surrounding environment
- ✓ Sanitation
- ✓ Consumption water condition
- ✓ Nutrition/ supplements
- ✓ Any other family member who have same type of illness during past 21 days

3.13 Patient's Personal Information

Patient's personal information contained the following features:

- Name
- Age
- Sex
- Weight
- Education
- Address
- Date of admission
- Discharge date
- Maximum temperature reached
- Day the fever started
- Day the fever ended

- Hand washing practice
- Nail cutting practice
- Personal cleanliness
- Vaccination status
- Outer food habits (street or open food)
- Sanitation and hygiene

3.14 History of present illness (complains during admission)

The data collection paper (DCP) also includes the history of present illness during the period of patient admission and which contain the following data:

- Type of diarrhea
- Duration of diarrhea prior to admission (hours)
- Dehydration status
- Number of stools/day
- Constipation
- Vomiting
- Duration of vomiting prior to admission (hours)
- Number of vomits/day
- Fever
- Duration of fever in hours
- Cough
- Duration of cough in hours
- Unable to drink
- Duration of unable to drink in hours

- History of convulsion
- Other problems
- Feeding history
- Hours before passed last urine
- What vaccine has the child received (dose and booster)
- Drugs/ antibiotics (dose) received before admission

3.15 Antibiotics taken by the patient before admission

Some of the patients used antibiotics before admission to the hospital. The names of the antibiotics are:

- Ciprofloxacin
- Cephradine
- Ceptazidime
- Ceftriaxone
- Ampicillin
- Azithromycin

Other than this normally used drugs were paracetamol, antihistamine, pain killer, expectorant, oral saline, vitamins and mineral supplements, etc.

3.16 Hospital treatment and courses

Selection of antibiotics for therapy depended on patient's age, renal and hepatic function and also on the spectrum and sensitivity of drugs. Single and combination of antibiotics both are used for the treatment of patients. Usually multiple drugs were used in case of severe complication and resistance cases.

3.17 Use of Different Antibiotics during treatment course

All patients did not receive the same antibiotics or the same dosage forms. Receiving of the antibiotics to the patients mainly depended on the patient's condition. In most of the cases antibiotics that were given are:

- Ciprofloxacin I.V & suspension,
- Ceftriaxone injection,
- Cefixime (third generation broad spectrum),
- Azithromycin
- Gentamycin.

3.18 Sensitivity Chart:

The sensitivity tests of the antibiotics were compiled into charts like the sample below.

Name / ID	Bishowoy 15939	Atia 15963	Simran 16231	Siam 17212	Saccho 17300	Borshea 17380	Ayesha 17463
Ceftazidime (CAZ)			S		S	S	
Netilmicin (NET)				S			
Ceftriaxone (CRO)			S	S	S	S	
Ciprofloxacin (CIP)			S	S	S	S	
Nitrofuratoin (NI/F)							
Imipenem (IMI/IPM)				S			
Azithromycin (ATH/AZM)			R			M	
Cephradine (CE/CRD)							
Nalidixic Acid (NA)			R	R		R	
Cotrimoxazole (TS)					S		
Aztreonam (ATM)							
Cephalexin (CL)				M			
Ampicillin (AMP)			R	S	S	R	
Gentamicin (GN/CN/GM)				S			
Chloramphenicol (C)			R	S	S	R	
Sulphamethoxazole Trimethoprim (SXT)							
Sulfamethoxazole (RL/ SXT)			R				
Cefotaxime (CTX)				S			

3.19 Data summary from data collection sheet:

Data collected from data collection sheet was summarized into a table form. This was done so that information could easily be analyzed. The following is the table outline.

Name / ID	Liana 24157	Siam 24166	Joyonto 24901	Nabila 24915	Jebin 25018	Sabrina 25090	Tina 25148
Age:							
Weight (kg)							
Sex							
Fever (days)							
Abdominal Pain							
Vomiting							
Diarrhea							
Constipation							
Respiratory Distress							
Highest temperature reached in °F							
Others							
Medicine given before admission							
Treatment given							
Sensitivity pattern							
Widal test							
Day at which temperature became afebrile							
Day of discharge							

3.20 Statistical and graphical representation of data

The data found was first organized into tables. From these tables the data was turned into percentage and means. They were then represented using both bar charts and pie charts were used. These charts were made using Microsoft Word.

3.21 Analysis and drawing conclusion

The results found were analyzed. Studying about typhoid from various journals and books and the results of our own study, various observation were made. From these observations conclusions were drawn.

3.22 Data collection sheet

Information included in the data collection paper:

DATA COLLECTION PAPER

STUDY PLACE: SHISHU SASTHYA FOUNDATION, BANGLADESH

Study Name: Investigation on the sensitivity of various antibiotics against TYPHOID FEVER

PATIENT HISTORY

01. PARTICULARS OF THE PATIENTS:

File Serial No:.....
Name of Month:.....
Name of the patient:.....
Age:.....
Address:.....
Sex:.....
Date of Admission.....
Time:.....
Date of Discharge:.....
Weight:.....

02. PRESENT COMPLAINTS:

1. .....
2. .....
3. .....

03. HISTORY OR PRESENT ILLNESS (Elaborate history):

.....
.....
.....

04. FEEDING HISTORY:

Breast Milk ☐ Milk Formula ☐ Mixed Feeding ☐

Semisolid ☐ Solid ☐ Weaning (.....months)

05. IMMUNIZATION HISTORY:

1. BCG ☐ 2. DPT + Polio ☐ 3. Measles ☐ 4. Hepatitis - B ☐

5. MMR ☐ 6. Chicken pox ☐ 7. Others ☐

06. HISTORY OF PAST ILLNESS: .....

.....

07. HISTORY OF PAST MEDICATION (*if any*): .....

.....

08. SOCIO-ECONOMIC HISTORY: .....

.....

09. GENERAL EXAMINATION:

I..... VI.....

II..... VII.....

III..... VIII.....

IV..... IX.....

V..... X.....

10.PROVISIONAL DIAGNOSIS:.....

.....

.....

11. DIFFERENTIAL DIAGNOSIS:.....

.....

.....

12. INVESTIGATIONS: .....

.....

.....

.....

13. FINAL DIAGNOSIS:

.....

.....

.....

.....

14. TREATMENT		DOSE
01. Ciprofloxacin	(Inj / Syr / Tab / Cap) ☐	.....
02. Cefixime	(Inj / Syr / Tab / Cap) ☐	.....
03. Ceftriaxone	(Inj / Syr / Tab / Cap) ☐	.....
04. Ceftazidime	(Inj / Syr / Tab / Cap) ☐	.....
05. Cotrimoxazole	(Inj / Syr / Tab / Cap) ☐	.....
06. Cephalexin	(Inj / Syr / Tab / Cap) ☐	.....
07. Cefotaxime	(Inj / Syr / Tab / Cap) ☐	.....
08. Chloramphenicol	(Inj / Syr / Tab / Cap) ☐	.....
09. Ampicillin	(Inj / Syr / Tab / Cap) ☐	.....
10. Azithromycin	(Inj / Syr / Tab / Cap) ☐	.....
11. Amoxicillin	(Inj / Syr / Tab / Cap) ☐	.....
12. Aztreonam	(Inj / Syr / Tab / Cap) ☐	.....
13. Gentamicin	(Inj / Syr / Tab / Cap) ☐	.....
14. Imipenem	(Inj / Syr / Tab / Cap) ☐	.....
15. Levofloxacin	(Inj / Syr / Tab / Cap) ☐	.....
16. Ofloxacin	(Inj / Syr / Tab / Cap) ☐	.....
17. Netilmicin	(Inj / Syr / Tab / Cap) ☐	.....
18. Others:	(Inj / Syr / Tab / Cap) ☐	.....

15. IDENTITY OF DATA COLLECTOR:

Name:..... Signature:.....

Date of data collection: .....

CHAPTER 4

RESULTS

4.1. OCCURRENCE OF TYPHOID FEVER AT DIFFERENT AGES IN CHILDREN

a) Mean age of children: 3.38 years

b) Percentage distribution according to age

Age	No. of Children	Percentage
0-3 years	23	46.94%
3-6 years	17	43.69%
6-9 years	7	14.29%
>9 years	2	4.08%

Table 5: Typhoid fever at different ages

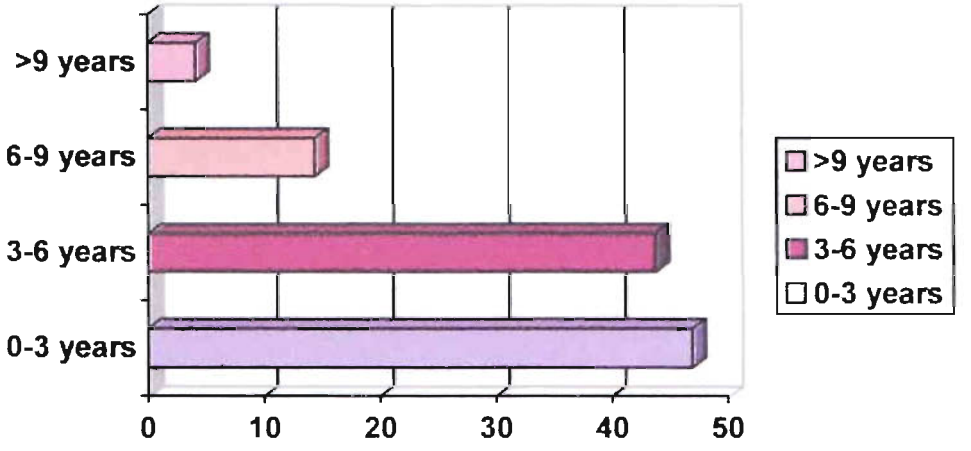


Chart 1: This figure shows that children below 5 years were more frequently admitted with typhoid fever than the children above five years.

4.2. OCCURRENCE OF TYPHOID FEVER AT DIFFERENT WEIGHT IN CHILDREN

a) Mean weight of children: 13.28 kg

b) Percentage distribution according to weight

Weight	No. of Children	Percentage
≤10 kg	14	34.16%
> 10 kg	27	65.84%

Table 6: Typhoid fever at different weight

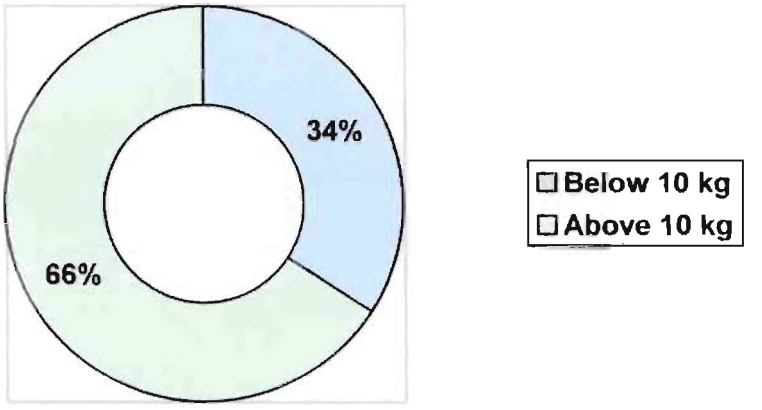


Chart 2: The chart shows that more children above 10 kg were admitted with typoid than below 10 kg.

4.3. PERCENTAGE DISTRIBUTION OF MALE AND FEMALE

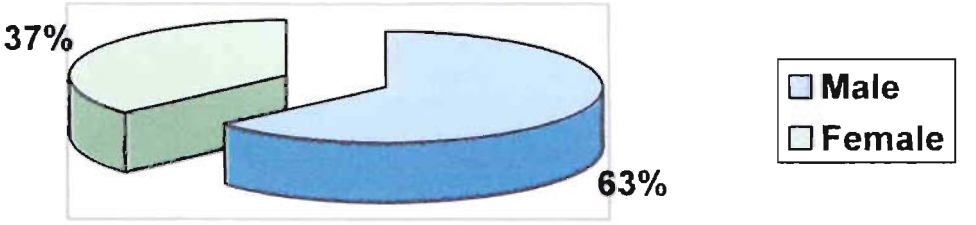


Chart 3: Percentage distribution of Male to female ratios of the children included in the study in percentage. It was seen that more male children came to the hospital with typhoid then females.

4.4. AVERAGE STAY OF PATIENTS IN HOSPITAL

Average days that patient stayed admitted in the hospital = 6.91

Male to female distribution

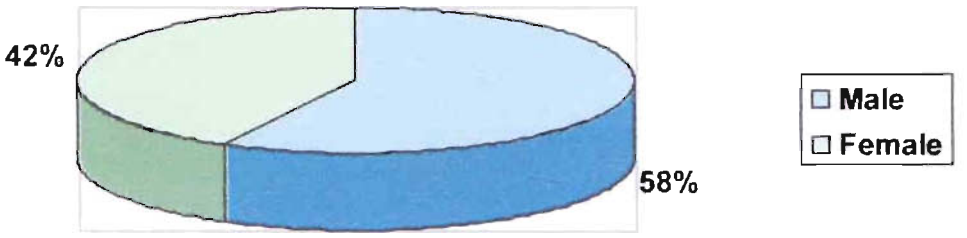


Chart 4: Percentage distribution of Male to female ratios of the average number of days that the children stayed admitted at the hospital.

4.5. SENSITIVITIES OF SOME INDIVIDUAL ANTIBIOTICS

a) NETILMICIN

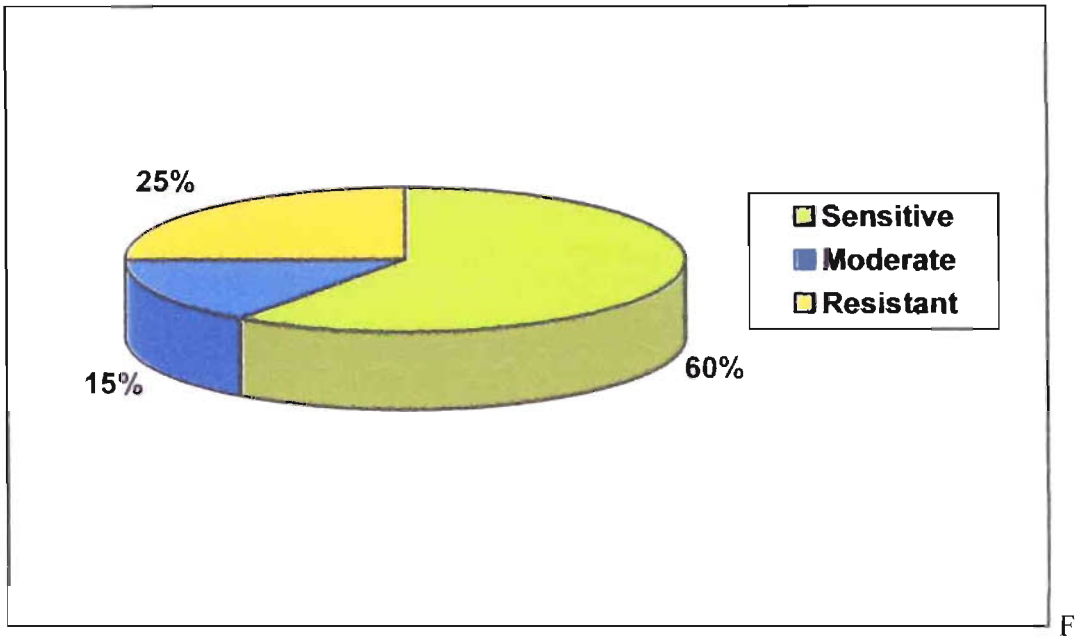


Fig 4:

Chart 5: Percentage Distribution of sensitivity pattern of Netilmicin

Netilmicin is 60% sensitive, 15% Moderate and 25% resistant.

b) IMIPENEM

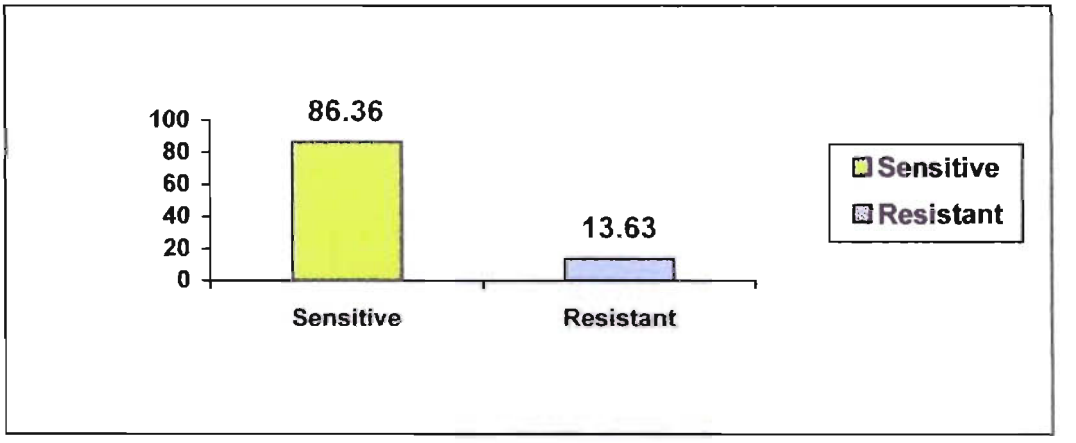


Chart 6: Percentage Distribution of sensitivity pattern of Imipenem

Imipenem is 86% sensitive, 14% resistant.

c) CEPHALEXIN

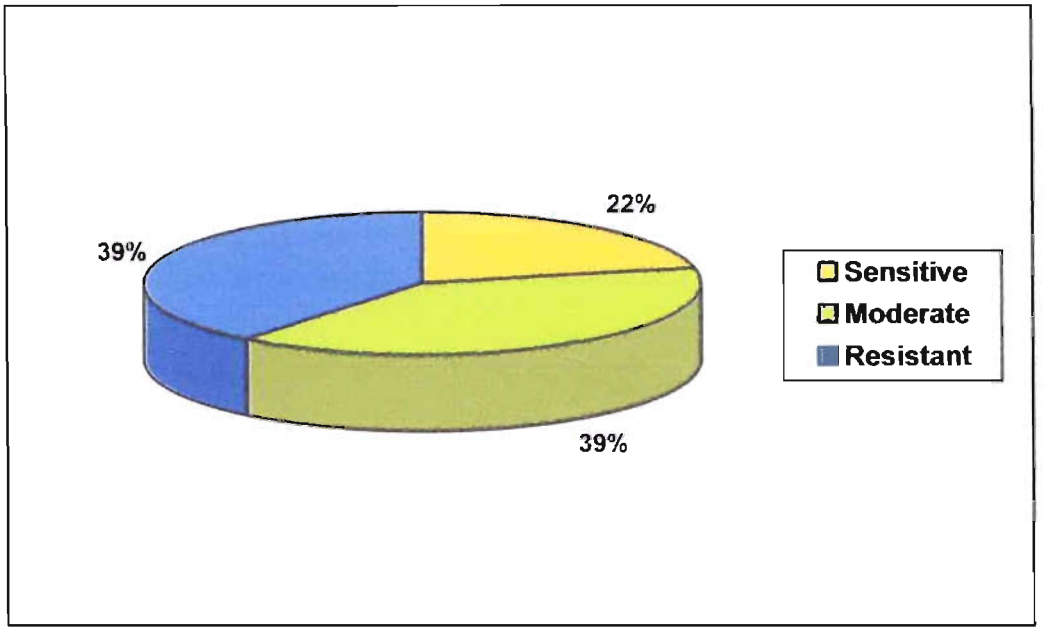


Chart 7: Percentage Distribution of sensitivity pattern of Cephalexin

Cephalexin is 22% sensitive, 39% Moderate and 39% resistant.

d) AMPICILLIN

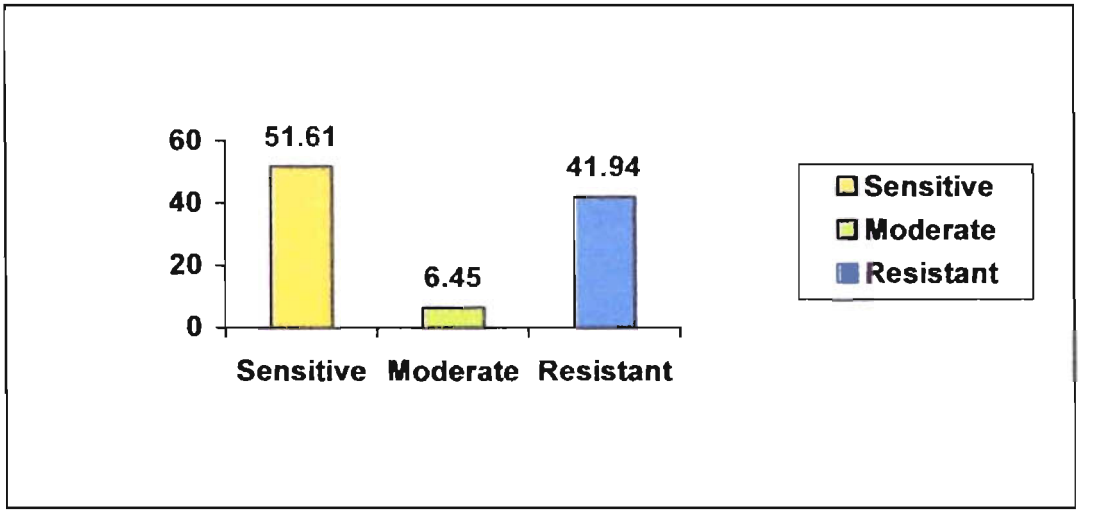


Chart 8: Percentage Distribution of sensitivity pattern of Ampicillin.

Ampicillin is 52% sensitive, 6% Moderate and 42% resistant.

4.6. COMPARISON OF SENSITIVITIES BETWEEN DIFFERENT ANTIBIOTICS

a) The following graph shows the relative degree of sensitivity between Cotrimoxazole, Cephalexin, Ampicillin, Gentamicin, Chloramphenicol and Cefotaxime.

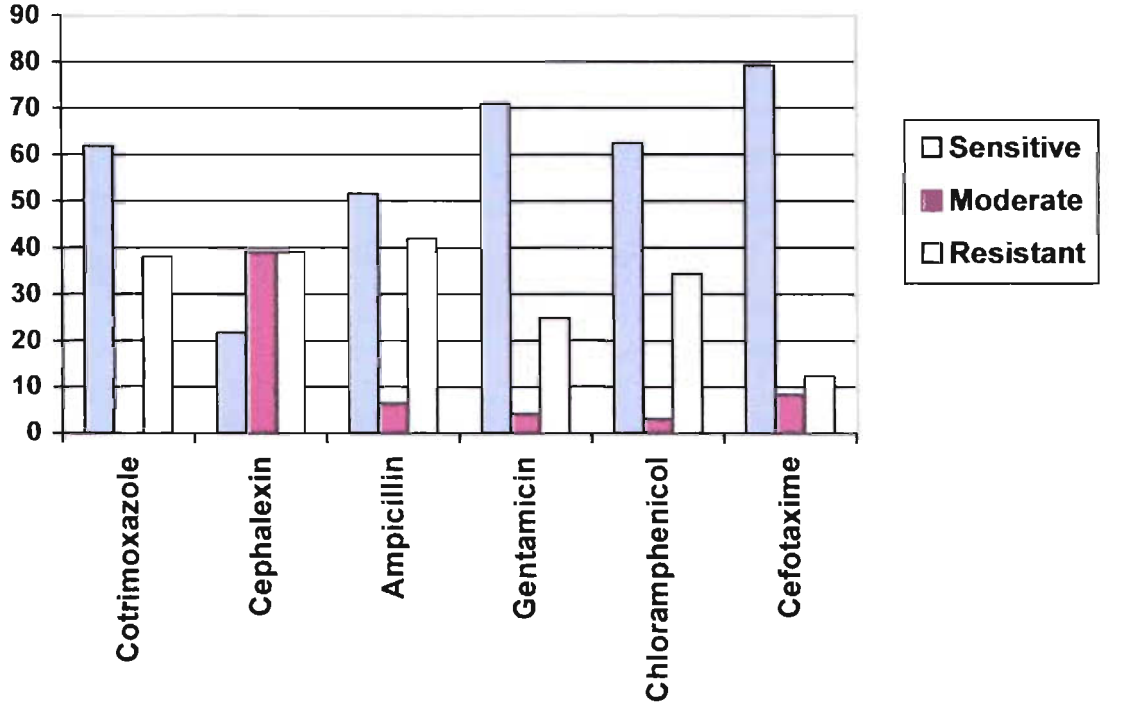


Chart 9: Sensitivity chart 1. It was seen that Cefotaxime and Gentamicin showed good sensitivity. Cotrimoxazole showed moderate resistance. Cephalexin and Ampicillin on the other hand showed high resistance.

b) The following graph shows the relative degree of sensitivity between Netilmicin, Ceftriaxone, Ciprofloxacin, Imipenem, Azithromycin and Ceptazidime.

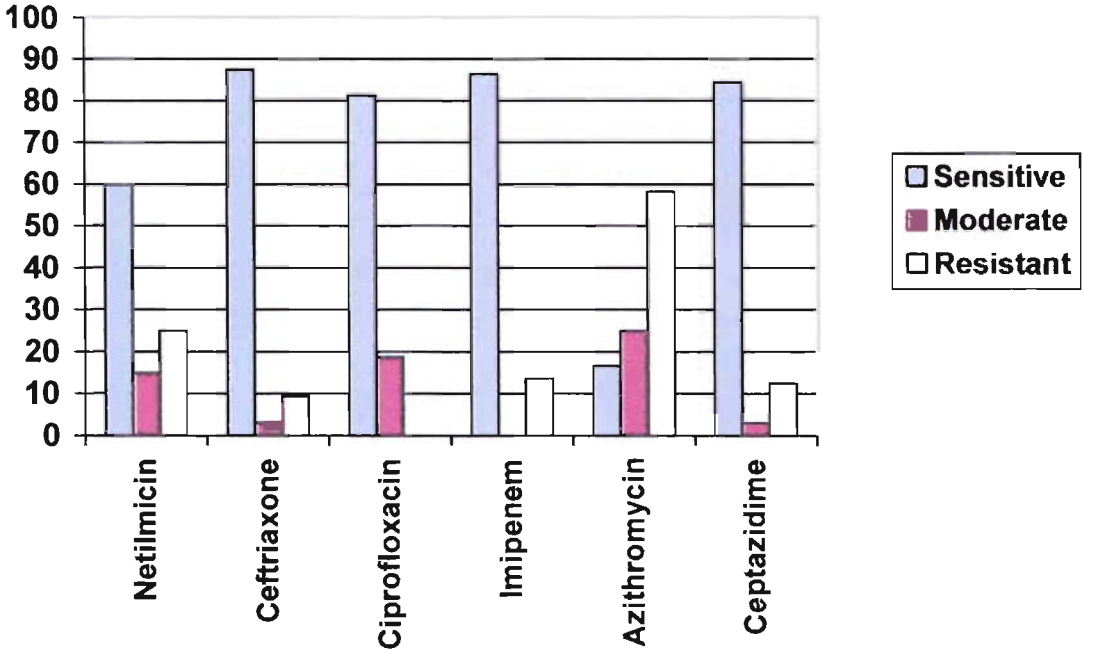


Chart 10: Sensitivity chart 2. This chart shows that Azithromycin is most resistant. All the other drugs showed good sensitivity against typhoid.

Combining the results of a) and b) Cefotaxime, Gentamicin, Ceftriaxone, Ciprofloxacin, Imipenem and Ceftazidime showed good sensitivity. Cotrimoxazole and Netilmicin were moderate. Cephalexin, Amipicillin and Azithromycin showed poor sensitivity.

4.7. NO. OF DAYS OF FEVER – DEFERVESCENT PERIOD

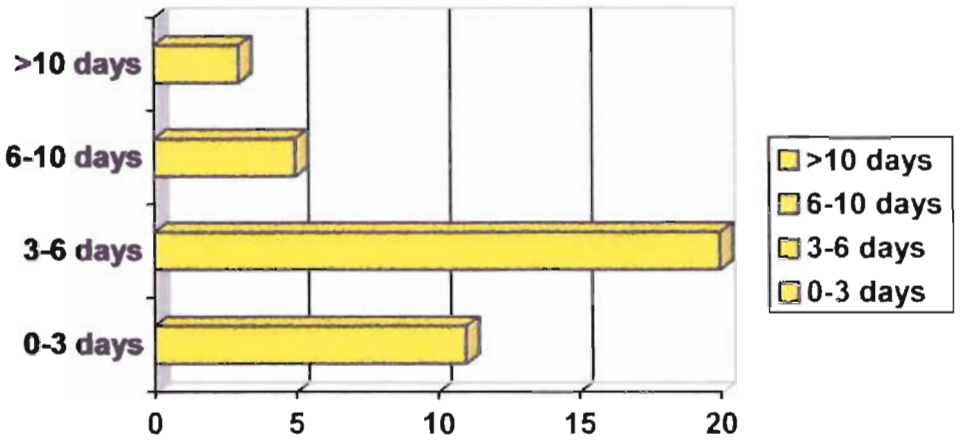


Chart 11: The relation between the number of days of fever continuation and the number of patients or the frequency. The graph shows that the fever stayed for usually 3-6 days for most patients.

4.8. MAXIMUM TEMPERATURE REACHED

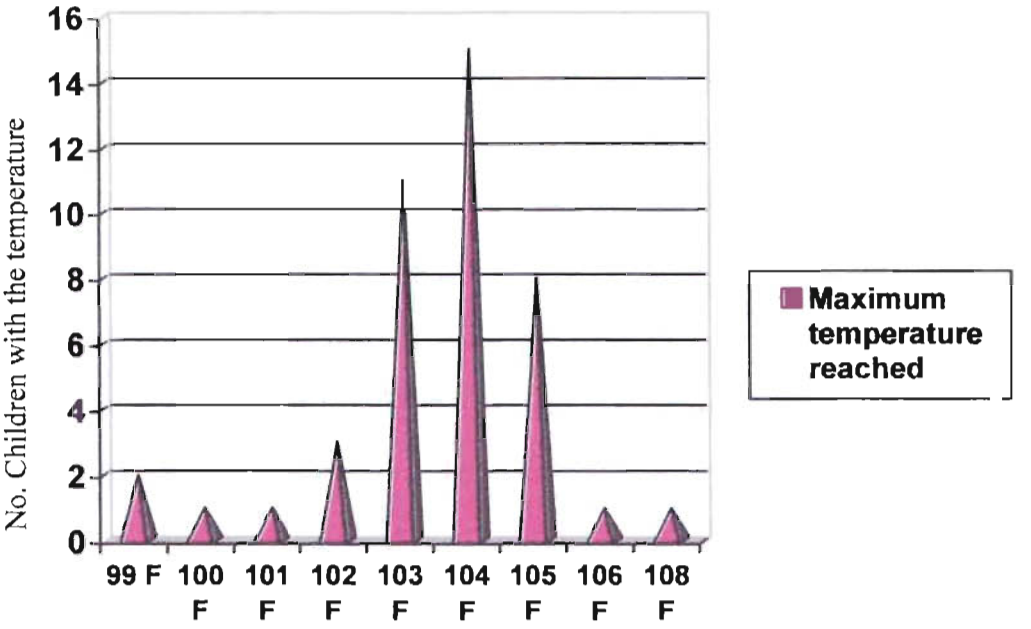


Chart 12: Maximum temperature reached during typhoid fever. It shows the Maximum temperature reached while the children were kept admitted at the hospital. The graph shows that in typhoid the fever usually went up to 104°F.

4.9. ANTIBIOTICS USED AND THE DAY AT WHICH PATIENTS BECAME AFEBRILE

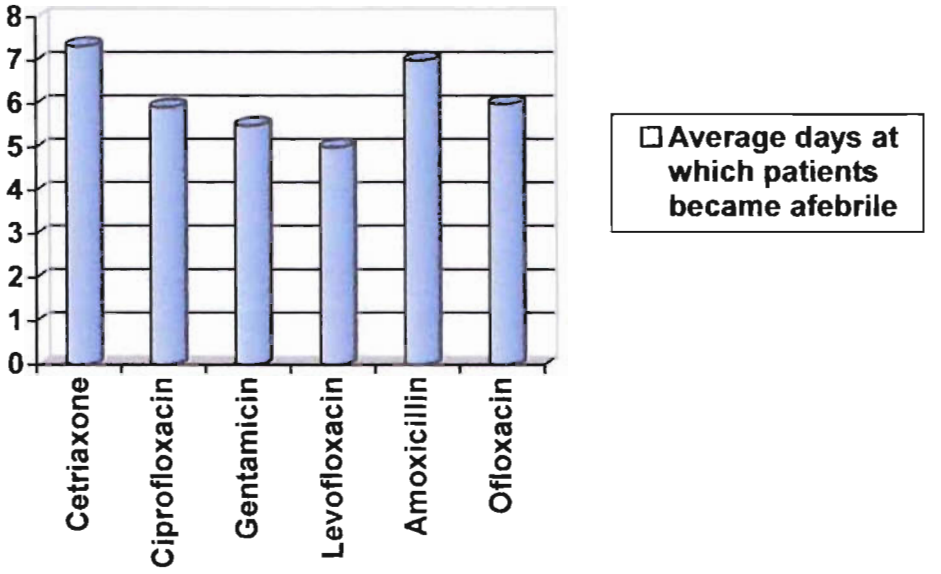


Chart 13: The average number of days it took for the patients to become afebrile. The graph shows the comparison of the different drugs used in the treatment and the average days it took for the patients to become afebrile.

4.10. ANTIBIOTICS USED AND THE LENGTH OF HOSPITAL STAY.

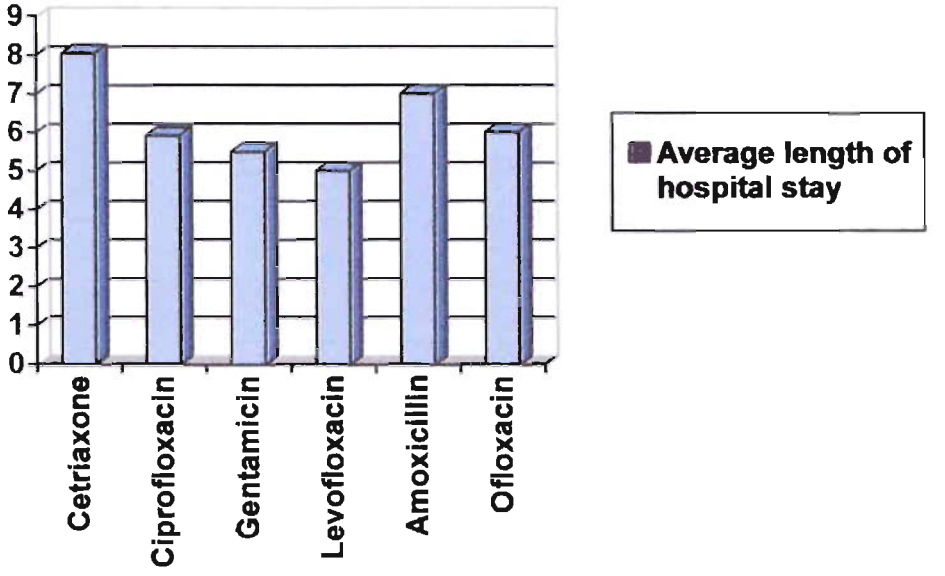


Chart 14: The average number of days that patients stayed in the hospital and the treatment given. The graph shows the comparison of the different drugs used in the treatment and the average days the patient stayed at the hospital.

CHAPTER 5

DISCUSSION

The advent of antibiotics was an important milestone and without which we would be completely defenseless against a great number of common diseases. Typhoid fever is one of them. But recently the growing resistace of *S. typhi* to the antibiotics is a matter to be concerned about. A transferable plasmid encoding resistance to chloramphenicol, co-trimoxazole, and ampicillin has spread to *Salmonella typhi* in many countries. This changing trend in the antibiotic susceptibility of serovar *typhi* has encouraged the use of new agents, such as oxyimino-cephalosporins and quinolones, for treatment of typhoid fever caused by multidrug- resistant strains. Although resistance to these agents has been observed in some cases, it is lower than that of *S. typhi* to the older agents (Ikeda et al., 2001).

The retrospective study was done using 50 patients. The results of this study show considerable differences in their sensitivity towards *Salmonella typhi*. Most of the antibiotics were sensitive in greater than 50% of the cases except cephalexin and azithromycin whose sensitivity was 39% and 18% respectively. This is contrary to studies which show that azithromycin may be as good as ciprofloxacin for treatment. It indicated that the two treatments were effective and comparable in that they gave clinical cures of all patients within 10 days and produced bacteriological eradication of *Salmonella* from the blood cultures of all of the patients (Brown, Butler, Frenck, Girgis, Khakhria, Sultan, & Tribble, 1999).

Ciprofloxacin is currently the drug of choice (Frost, Kelleher, & Rowe, 1996). The study supports this as ciprofloxacin was the only drug out of 12 drugs which did not give a single case of full resistance though it showed moderate resistance in 18.75% cases. It was sensitive in the rest. A study showed that though ciprofloxacin has not become resistant, it is slowly growing so. This was established by the increase in defervescent period (Chowta & Chowta, 2005). This study shows that the average defervescent period was around 6 days compared to 8 days in our study. Though not exactly same, 6 days is still greater than previous literatures on ciprofloxacin which states 3-5 days (Chowta & Chowta, 2005). This means that ciprofloxacin is probably slowly gaining resistance. The study showed good sensitivity against the cephalosporins such ceftriaxone, cefotaxime and ceptazidime but overall they may not be better than ciprofloxacin.

Imipenem isn't a popular drug in the treatment of typhoid but it showed good sensitivity i.e. 86% sensitive, 14% resistant. Overall it can be said that gentamicin, imipenem, ceftriaxone, cefotaxime, ciprofloxacin and ceftazidime showed very good sensitivity. Netilmicin, cotrimoxazole and chloramphenicol showed moderate sensitivity. Cephalexin, azithromycin and ampicillin were resistant.

CHAPTER 6

CONCLUSION

yphoid fever in Bangladesh is widespread. And the effective treatment for this is antibiotics. n this study the mean age of the children admitted was 3.38 years. It was seen that children elow 3 years were more frequently admitted due to typhoid than older children. This could uggest that younger children may be more susceptible to *S. typhi*. The mean weight of the hildren was 13.28 kg. Children with weight greater than 10 kg were affected more by yphoid fever. Male to female percentage distribution showed that male children admitted ere more than female i.e. 67% to 37% respectively. The fever stayed mostly for 3-6 days. Most of the fever reached up to 104°F, though for 2 patients it went up to 106°F and 108°F

As seen from the discussion above ciprofloxacin may be becoming resistant. This is a serious natter as it is one of most widely used drug for the treatment with success. The growing esistance may cause typhoid to become a very difficult disease to treat. And thus more lternative antibiotics for the treatment of typhoid should be looked into and found.

n comparison of ampicillin, cephalexin, imipenem and netilmicin, cephalexin and ampicillin ere resistant. Imipenem was the most sensitive. Enough studies have not been done in hildren in the treatment of typhoid using imipenem. It may be pursued further and it may rove to be a good treatment option. levofloxacin seems like another good drug. Though its ensitivity has not been seen, it gave the least defervescent time amongst amoxicillin, floxacin, gentamicin, ciprofloxacin and ceftriaxone. Similarly hospital stay was least for atients treated with levofloxacin.

Though treatment with antibiotics is a very crucial factor, spreading awareness especially mongst the lower socio-economic class is very vital. So, it may be concluded that revention, awareness, and prompt treatment with antibiotics that S. typhi are sensitive to emains the way to control and prevent this disease.

REFERENCE

1. Acosta, C. J., Agtini, M. D., Albert, M. J., Ali, M., Baiqing, D., Bhattacharya, S. K., Bhutta, Z. A., Canh, D. G., Clemens, J. D., Danovaro-Holliday, M. C., Elyazeed, R. A., Farrar, J., Galindo, C. M., Ochiai, R. L., Page, A.L., Pang, T., Seidlein, L. V., Shin, S., Wain, J., & the Domi Typhoid Study Group. (2008). A study of typhoid fever in five Asian countries: disease burden and implications for controls. Bulletin of the World Health Organization. 86(4), 260-8.
2. An Evaluation of the Salmonella Problem - A Report of the U.S. Department of Agriculture and the Food and Drug Administration, U.S. Department of Health, Education, and Welfare., 1970. Washington D.C.: Printing and Publishing Office, National Academy of Sciences.
3. Azmatullah, A., Critchley, J., Madni, S. A., Thaver, D., & Zaidi, A. K. M., 2009. A Comparison of Fluoroquinolones versus Other Antibiotics for Treating Enteric Fever: Meta-Analysis. *BMJ journal, 338*:b1865.
4. Bahl, R., Bhan, MK., & Bhatnagar, S., 2005. Typhoid and paratyphoid fever. *The Lancet, 366*(9487), 749 - 762.
5. Beechmg, N. J., Hart, C. A. & Mirza, S. H., 1996. Multi-drug resistant typhoid: a global problem. *Journal of Medical Microbiology, 44*, 317 -- 319.
6. Benavente, I. H., García, E. M., García, G. R. & Santillán, R. M., 2000, Efficacy of cefixime in the therapy of typhoid fever. *Proceedings Western Pharmacology Society 43*, 65-66.
7. Bhutta, Z. A., 2006. Current concepts in the diagnosis and treatment of typhoid fever. *BMJ journal, 333*, 78-82.
8. Boon, N. A., Colledge, N. R., Hunter, J. A.A., & Walker, B. R. (Eds.)., 2006. Davidson's Principles and Practice of Medicine (20th ed.). New Delhi: Elsevier.
9. Borsutzky, S., Collioud, A., Dietrich, G., Favre, D., Griot-Wenk, M., Guzman, C. A., Metcalfe, I. C., & Pearman, J., 2005. Vaccines against typhoid fever. *Vaccine, 24*, 3804–3811.
10. Breiman, R. F., Brooks, W. A., Hossain, M. A., Luby, S. P., Mintz, E. D., Naheed, A., Ram, P. K., 2007. Risk factors for typhoid fever in a slum in Dhaka, Bangladesh. *Epidemiology and Infection, 135*, 458-465
11. Brown, F. M., Butler, T., Frenck, R. W., Girgis, N. I., Khakhria, R., Sultan, Y., & Tribble, D., 1999. Azithromycin versus Ciprofloxacin for Treatment of Uncomplicated

Typhoid Fever in a Randomized Trial in Egypt That Included Patients with Multidrug Resistance. *Antimicrobial Agents and Chemotherapy, 43(*6), 1441-1444.

12. Butler, T., Daga, M. K., Johnson, R. B., Khakhria, R., Pandit, R. B., Pathak, K., Potkar, C. N., Sridhar, C. B. & Zelasky, M. T., 1999. Treatment of typhoid fever with azithromycin versus chloramphenicol in a randomized multicentre trial in India. *Journal of Antimicrobial Chemotherapy, 44,* 243–250.
13. Chan, E. C. S., Krieg, N. R. & Pelczar, M. J., 1993. Microbiology. (5th ed.). New Delhi: Tata McGraw-Hill Publishing Company Limited.
14. Chowta, MN., & Chowta, MK., 2005. Study of clinical profile and antibiotic response in typhoid fever. *Indian Journal of Medical Microbiology, 23*(2), 125-127.
15. Clark, P. D., Geddes, A. M., McGhie, D., & Wall, J. C., 1976. Mecillinam: a new antibiotic for enteric fever. *British Medical journal, 2,* 14-15.
16. Cotran, R. S., Kumar, V., & Robins, S. L., 1989. Robbins Pathologic Basis of Disease. (4th ed.). Canada: W. B. Saunders Staff.
17. Crump, J. A., Luby, S. P., Mintz, E. D., 2004. The global burden of typhoid fever. *Bulletin of the World Helath Organization, 82*(5), 346-353.
18. Dodd, K., Mellersh, A., Nelson, C. S., Simpson, J. & Watson, A. R., 1991. Typhoid fever, ciprofloxacin, and renal failure. *BMJ Journal, 66,* 1083-1084.
19. Edelman, R. & Levine, M. M., 1986. Summary of an International Workshop on Typhoid Fever. *Reviews of Infectious Diseases, 8*(3), 329-349.
20. Frost, J. A., Kelleher, A., & Rowe, B., 1996. Increasing ciprofloxacin resistance in salmonellas in England and Wales 1991–1994. *Journal of Antimicrobial Chemotherapy, 37*(1), 85-91.
21. Ganjewala, D., Khan, K. H. & Rao, K. V. B., 2008. Recent advancement in typhoid research. *Journal of Advanced Biotechnology, 7*(4), 35-41.
22. Geddes, A. M., 1977. The antibiotic treatment of typhoid fever. *Journal of Antimicrobial Chemotherapy, 3*(5), 382-383.
23. Guidelines for drinking water quality. (3rd ed). Vol 1. 2004. WHO Geneva 2004.

24. Ikeda, F., Ikemoto, A., Matsumoto, K., Matsumoto, Y., Tawara, S. & Wakai, Y., 2001. Mechanism of therapeutic effectiveness of cefixime against typhoid fever. *Antimicrobial Agents and Chemotherapy, 45*(9), 2450–2454.

25. Incidence of typhoid fever, Dhaka, 2001. *Health and Science Bulletin, 1*(3).

26. International Medical Guide for Ships. (2nd ed). 1988. WHO Geneva 1988.

27. Ray, K., 2002. Typhoid Fever (1st ed.). New York: The Rosen Publishing Group, Inc.

28. Singh, B., 2001. Symposium: Typhoid fever. *Journal, Indian Academy of Clinical Medicine, 2*(1 and 2), 11-12.

EXTERNAL LINKS

1. http://www.biosci.utexas.edu/ib/ScienceUnderStars/index.html
2. http://www.richardstupart.com/2009/07/01/things-you-can-die-from-between-cape-town-and-cairo/
3. www.pathguy.com/lectures/infect.htm