Impact of Typhoid fever and its treatment in a Tertiary Level Hospital in Dhaka

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ID: 2005-3-70-024

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Dhaka

December 2009

Impact of Typhoid fever and its treatment in a Tertiary Level Hospital in Dhaka.

A Thesis paper submitted to the Department of Pharmacy, East West University in conformity with the requirements for 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, (ICH & SSFH) Dhaka.

This thesis paper is dedicated to

My parents.

Certificate

This is to certify that the thesis paper submitted to the Department of Pharmacy, East West University, Mohakhali, Dhaka in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (B.Pharm) was carried out by Nayiar Shahid Anika 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.

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Acknowledgement

First and foremost I would like to express my sincere thanks to **Farhana Rizwan**, Senior Lecturer and **Dr Sufia Islam**, Associate Professor for their invaluable guidance and support.

I am deeply indebted to **Farhana Rizwan**, for giving me the opportunity to participate in this research project when typhoid fever was a global burden in the modern world. Her pragmatic attitudes – always willing to listen, logically compromise and guiding me onto the right track during the research project – have been invaluable. Not only she has given me good scientific advice whenever needed, but also she gave me the chance to visit Institute of Child Health and Shishu Sasthya Foundation, Hospital.

My special thanks to **Professor Dr A.F.M Salim**; Department of Pediatrics, Institute of Child Health and Shishu Sasthya Foundation, Hospital; and **Dr Forhad Monjur**; Assistant Professor and Laboratory Medicine Specialist; for giving me their valuable time. Their encouragement and permission of collecting and analyzing patients' data helped me to go ahead with the study. I also thank **Mr Salauddin Ahmed**, librarian of Institute of Child health and Shishu Sasthya Foundation for helping me to collect and borrow the data from patient's record.

I express my special gratitude to **Professor Muniruddin Ahmed, PhD**; Pro-Vice Chancellor, **Professor Chowdhury Faiz Hossain**, Chairperson, East West University; for being my guardian in each and every sector.

I express my sincere gratitude to my caring parents for guiding me all through my life, including that for my research project.

I am gratefully acknowledged to my partners for their cordial support, help, enthusiastic cooperation and valuable hints.

Last but not the least; I would like to thank the almighty Allah, for being with me whenever I needed.

Abstract

Typhoid and paratyphoid fevers are caused by the bacteria *Salmonella typhi* and *Salmonella paratyphi* respectively. Typhoid fever is a major public health problem and one of the leading causes of febrile illness of children in developing countries. An estimated 600,000 deaths occur from typhoid fever annually throughout the world. Doctors are likely to suspect typhoid fever based on symptoms and medical history. But the diagnosis is usually confirmed by identifying S. typhi in a culture of the patient's blood or other body fluid or tissue and is placed on a special medium that encourages the growth of bacteria.

Typhoid fever is endemic in Bangladesh. Until the mid-1980s, Chloramphenicol, Ampicillin or Cotrimoxazole, were the standard treatments. Multi-drug resistance defined as resistance to these first-line agents used to treat typhoid has been endemic in most of South East Asia and the Indian Subcontinent for many years. However, in children, it poses a major therapeutic dilemma where the disorder is fast assuming epidemic proportions. Since then, Ciprofloxacine or third generation cephalosporins, Ceftriaxone have become the first-line treatment for typhoid fever. Infection with nalidixic acid-resistant *S.typhi* with decreased susceptibility to Ciprofloxacin has been reported from Vietnam, Tajikistan, the UK, India and Bangladesh since 1997. In the UK, the percentage of *S.enterica* serover Typhi strains showing decreased seuceptibility to Ciprofloxacin increased from 2.7% in 1995 to 21% in 1998. Hence, the routine disk diffusion test with Ciprofloxacin disk alone is unable to detect such cases. (Asna, S.M.Z.H., et.al). Currently, the recommendation for first-line therapy is Ceftriaxone but Ceftriaxone-resistant *Salmonella typhi* was detected in Bangladesh in 1999.

In this hospital-based study, the patients were treated with the following drugs: Amoxycillin, Cefixime, Ceftriaxone, Ciprofloxacin, Gentamicin, Levofloxacin and Ofloxacin; among which Ceftriaxone was found to be mostly used and effective despite its cost and problems in administration. The determination and evaluation of the impact of sensitivity of various antibiotics on clinical response in patients with typhoid fever was the main concern of the present study.

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CHAPTER 1

INTRODUCTION

1. INTRODUCTION

1.1. Definition of typhoid fever

Typhoid fever is defined as a continued fever occurring almost exclusively during the warm months and lasting from one to ten weeks. Typhoid and paratyphoid fevers are infections caused by bacteria that are transmitted from faeces to ingestion. The disease remains an important health problem in developing countries. In 2000, it was estimated that over 2.16 million episodes of typhoid occurred worldwide, resulting in 216 000 deaths, and that more than 90% of this morbidity and mortality occurred in Asia. Although improved water quality and sanitation constitute ultimate solutions to this problem, vaccination in high-risk areas is a potential control strategy recommended by WHO for short-to-intermediate term.
(Abu-Elyazeed, et al; 2008)

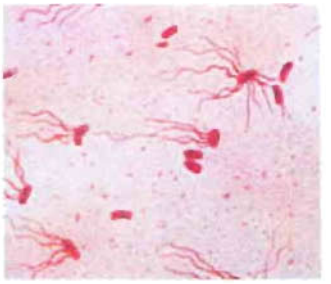
1.2. Causes

Typhoid and paratyphoid fevers are caused by the bacteria *Salmonella typhi* and *Salmonella paratyphi* respectively. Typhoid and paratyphoid germs are passed in the faeces and urine of infected people. People become infected after eating food or drinking beverages that have been handled by a person who is infected or by drinking water that has been contaminated by sewage containing the bacteria. Once the bacteria enter the person's body they multiply and spread from the intestines, into the bloodstream. In the blood vessel, typhoid germs are carried by white blood cells to the liver, spleen and bone marrow. Bacteria multiply in the next organ and this return to the blood vessel. When this occurs, the patient will experience symptoms of typhoid fever. Next the bacteria will enter the gall bladder ago lymph network usus. Here, the bacteria will breed more and more. Then, the bacteria will also penetrate intestinal wall and mixed with dirt. Well, apart from the examination of blood, fever, typhoid can also be ascertained by examination of dirt. (Green, et.al; Third edition)

1.2.1. Salmonella typhi

Salmonella enterica serovar Typhi is a member of the genus Salmonella in the family Enterobacteriaceae. The Salmonella genus contains two species, enterica and bongori. S. enterica is further divided into six subspecies (enterica, salamae, arizonae, diarizonae, houtenae and indica) containing 2443 serovars. Most of the salmonellae that cause disease,

with some important exceptions, are in the subspecies Salmonella enterica subspecies enterica. The agents that cause enteric fever are therefore Salmonella enterica subspecies enterica serovar Typhi (commonly referred to as S. enterica serovar *Typhi)* and *serovars Paratyphi A, B and C.* (Christopher M.P.; 2006)



(http://textbookofbacteriology.net/themicrobialworld/S.typhi.Fla.jpg)

Figure 1

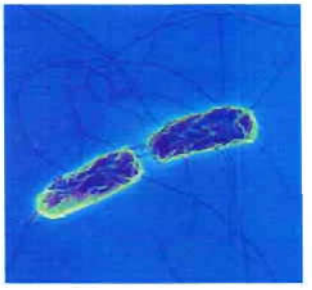


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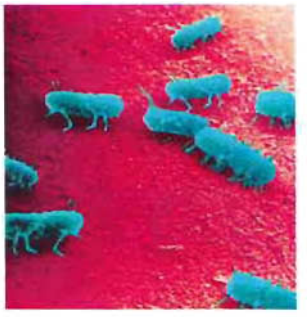
Figure 2



(http://www.marlerblog.com/salmonella_typhimurium_300.jpg)

Figure 3

Figure 1, 2 and 3 show strains of *Salmonella typhi* causing typhoid.

1.3. Historical background

Until the first quarter of the 19th century, typhoid fever was not recognised 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 is given to this disease. It was only in late 19th century that the disease was finally established as a distinct clinical entity. The term enteric fever was introduced in 1869 and now includes both typhoid fevers and paratyphoid fevers. (Singh, B.; 2001)

1.4. Transmission

The bacteria are derived from the faeces of a sufferer from the disease or from a carrier. The disease is spread by water or from contaminated food. Typhoid spread needs only a small number of organisms, and is therefore described as having high infectivity.

- Water supplies may be contaminated by human faeces through seepage of sewage into a reservoir, leakage from defective underground sewers or discharge of sewage into a river. Salmonella can live for about one week in sewage, or longer in water, which has been diluted, with sewage.
- Serious epidemics have also been traced to food. Milk can be contaminated by a carrier or from dirty equipment, which has been washed with contaminated water. Outbreaks of typhoid in England, such as Epping, 1931 (260 cases, 8 deaths) and Bournemouth, 1938 (718 cases, 70 deaths) were caused by infected milk supplies. Aberdeen had an outbreak in 1964 caused by contaminated corned beef.
- Shellfish, oysters and mussels are often responsible for transmitting typhoid, due to their filter method of feeding whereby pathogenic organisms are extracted from the surrounding water.

(Green; et.al; Third edition)

1.4.1. Mode of Transmission

This disease is transmitted by two means:

a) Fecal-oral route-

Typhoid and paratyphoid germs are passed in the faeces and urine of infected people. People become infected after eating food or drinking beverages that have been handled by a person who is infected or by drinking water that has been contaminated by sewage containing the

bacteria. Once the bacteria enter the person's body they multiply and spread from the intestines, into the bloodstream.

Faecal contamination thus includes:

(a) Food-or-water-borne material contaminated with faeces from infected person;

(b) Handling of contaminated objects;

(c) Vector, e.g. flies moving from human faeces to food.

b) Typhoid carriers-

Even after recovery from typhoid or paratyphoid, a small number of individuals (called carriers) continue to carry the bacteria. These people can be a source of infection for others. The transmission of typhoid and paratyphoid in less-industrialized countries may be due to contaminated food or water. In some countries, shellfish taken from sewage-contaminated beds is an important route of infection. Where water quality is high, and chlorinated water piped into the house is widely available, transmission is more likely to occur via food contaminated by carriers handling food.

(Ahmed; et al; 2005)

1.5. Distribution

Typhoid and paratyphoid fevers are common in less-industrialized countries, principally owing to the problem of unsafe drinking water, inadequate sewage disposal and flooding.

(WHO 2009)

1.6. Signs and Symptoms

- ✓ Severe headache
- ✓ Fever
- ✓ Loss of Appetite
- ✓ General discomfort, uneasiness, or ill feeling (malaise)
- ✓ Rash (rose spots) appearing on the lower chest and abdomen during the second week of the fever
- ✓ Abdominal pain
- ✓ Affects alimentary canal
- ✓ Constipation, then diarrhea
- ✓ Bloody stools

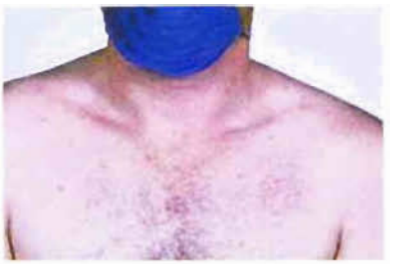
- ✓ Slow, sluggish, lethargic
- ✓ Fatigue
- ✓ Weakness
- ✓ Nosebleed
- ✓ Chills
- ✓ Delirium
- ✓ Confusion
- ✓ Agitation
- ✓ Fluctuating mood
- ✓ Difficulty paying attention (attention deficit)
- ✓ Hallucinations
- ✓ Ulceration and rupture of intestine

(Green, et.al; Third edition)

1.7. Clinical features

People infected with *S. typhi* usually have a fever (thus the term typhoid fever) -- sometimes up to 103-104 degrees F. The temperature rises in a stepladder fashion for 4 to 5 days. There is 'aise, with increasing headache, drowsiness and aching in the limbs. Constipation may be present, although in children diarrhea and vomiting may be prominent early in the illness. The pulse is often slower than would be expected from the height of the temperature; i.e. a relative bradycardia.

At the end of the first week, a rash may appear on the upper abdomen and on the back as sparse, slightly raised, rose-red spots, which fade on pressure. It is usually visible only on white skin. Cough and epistaxis occur. Around 7 to 10 day the spleen becomes palpable constipation is then succeeded by diarrhea and abdominal distention with tenderness. Severe diarrhea has been described in HIV patients with typhoid. Bronchitis and delirium may develop. By the end of the 2nd week the patient may be profoundly ill unless the disease is modified by antibiotic treatment. In the 3rd week toxemia increases and the patient may pass into coma and die. Such extreme cases are rare in countries with developed health services. Following recovery up to 5% of patients become chronic carries of *Salmonella typhi* and classically such patients have gallbladder disease. (Christopher M.P., et.al; 2006)



http://wpcontent.answers.com/wikipedia/commons/thumb/1/12/Salmonella_typhi_typhoid_fever_PHIL_2215_lores.jpg/190px-Salmonella_typhi_typhoid_fever_PHIL_2215_lores.jpg

Figure 4: *Patient with typhoid fever*

1.7.1. Summary of clinical features of typhoid fever

First week-

- Fever
- Headache
- Myalgia
- Relative bradycardia
- Constipation
- Diarrhea and vomiting in children.

End of first week-

- Rose spots on trunk
- Splenomegaly
- Cough
- Abdominal / distention
- Diarrhea

End of 2nd week-

- Delirium
- Complications

Coma and death (if untreated) (Crum; 2003)

1.8. Tests and Diagnosis

The lack of specific clinical signs complicates the diagnosis of typhoid fever, which must be distinguished from other endemic acute and sub acute febrile illnesses. These can include malaria, deep abscesses, tuberculosis, amoebic liver abscesses, encephalitis, influenza, dengue fever, infectious mononucleosis, infectious hepatitis, leptospirosis, endocarditis, brucellosis, typhus, visceral leishmaniasis, toxoplasmosis, lymphoproliferative disease and connective tissue diseases. A fever lasting more than one week without evident cause should be considered typhoid until proven otherwise and typhoid should always be considered when suspected malaria has not been confirmed or has not responded to antimalarial therapy. It is unusual for a patient hospitalized with typhoid fever to have no abdominal symptoms and normal bowel habit. In non-endemic countries, a travel history is crucial.

The haemoglobin, white cell and platelet count are usually within the normal range or reduced. Leucocytosis suggests either intestinal perforation or an incorrect diagnosis. Laboratory evidence of disseminated intravascular coagulation may be present but is very rarely of clinical significance. Liver transaminases are characteristically two to three times above normal. The urine may contain protein and leukocytes.

Blood cultures are the standard diagnostic method and can be positive in 60–80% of cases. In mild typhoid the number of bacteria may be as low as one colony-forming unit per ml of blood (Butler et al., 1978; Wain et al., 1998). The number of bacteria in the blood of children is higher than in adults and declines with increasing duration of illness. Recovery of th organism from blood cultures depends on several factors including the volume of blood cultured, the ratio of the volume of blood to the volume of culture broth in which it is inoculated (the ratio should be at least 1:8) and inclusion of anticomplementary substances in the medium (such as sodium polyethol sulfonate or bile). Culture of bone marrow is more sensitive regardless of the illness duration and is positive in 80–95% of patients despite prior antibiotic therapy. The higher sensitivity of bone marrow cultures compared to blood in part relates to the higher concentration of organisms in bone marrow.

(Christopher M.P.,et.al; 2006)

Serological tests for typhoid fever have been used since the late 19th century. Widal and Sicard in 1896 showed that the serum of patients with typhoid fever agglutinated typhoid bacilli. The Widal test, in which O and H agglutinins are demonstrated in serum, may be performed with appropriate antigens in tubes or on slides. Typically antibodies to the O and H antigens appear during the end of the first week of disease and peak at the end of the third week but there is much variability (Levine et al., 1978). The use of a single measurement of antibody titres is useful if the background levels of antibodies in the population are known. (Christopher M.P.,et.al; 2006).

1.8.1. Antibody and antigen testing

Doctor may recommend other tests to help diagnose typhoid fever, such as:

- *Enzyme-linked immunosorbent assay (ELISA):* This blood test looks for an antigen that's specific to typhoid bacteria. An antigen is any substance, such as a virus, bacterium, toxin or foreign protein that triggers an immune system response in body. An ELISA test can identify if the patient carry the disease, but not whether he/she have an active infection.

- *Fluorescent antibody test:* This test checks for antibodies to S. typhi. Antibodies are proteins produced by immune system in response to harmful substances (antigens). Each antibody is unique and defends our body against a single antigen.

(Crum; 2003)

1.8.2. Comparison of methods for the diagnosis of typhoid fever

The diagnosis is usually confirmed by culture of blood clot, or stool, together with the results of the Widal agglutination test. The usefulness of the Widal test has been questioned. In most cases only a single titre is obtained. Repeating the test may increase the number of positive results, but there is often neither an initial increase nor a rise in titres, even in culture positive typhoid fever. Furthermore, the results of the test are invalidated by a previous history of vaccination or typhoid fever. This study examines the relative contributions of each of these

four laboratory investigations to the diagnosis of typhoid fever over a five-year period. (Duthie and French; 1990)

Procedure

Results of Widal agglutination tests and *Salmonella typhi* cultures performed between April 1984 and December 1989 were obtained by retrospective analysis of laboratory records. There were very few paratyphoid infections, which were excluded from the study. Patients with a single positive Widal test with a previous history of typhoid fever or vaccination were also excluded. True positive, false positive and false negative Widal results were determined by reviewing patient records, culture results and notifiable disease returns.

Widal agglutination was performed using Wellcome reagents (Wellcome Diagnostics, Dartford) containing O and H antigens of *S typhi*. A dilution series of 1 in 50 to 1 in 400 of serum in 0.85% saline was made, and 0.3 ml of each dilution was added to 0.3 ml of antigen suspension. Positive and negative serum controls were included. The tubes were incubated in a 56° C water bath for 18 hours before reading. A titre of >1/100 to either antigen in a single serum specimen was taken to be indicative of typhoid fever. The laboratory participates in the external quality control programme of the Royal College of Pathologists of Australia and achieves consisitently good results for Widal tests.

After removal of serum for the Widal agglutination test the blood clot was placed in 10 ml of 0.5% bile salt broth (Oxoid, Basing stoke) for culture. After two days of incubation at 37° C the broth was subcultured to DCA and MacConkey agar plates (Oxoid). Negative cultures were terminally subcultured on day 6.

Blood cultures were made with the Bactec 460 radiometric system (Johnson Laboratories, Towson, Maryland), using the 6B aerobic and 7D anaerobic broth media. The blood: broth ratio was about 1:6. The cultures were examined daily for six days before being discarded. Stoold specimens were plated directly on DCA and MacConkey agar (Oxoid) and inoculated into Selenite F broth (Oxoid) for enrichment culture.
(Duthie and French; 1990)

Observation

There were 63 confirmed cases of typhoid fever during the study. In 54 the diagnosis was confirmed by culture: 45 of these were blood positive, 18 clots positive and 24 stools positive (table 1). In those patients in whom blood culture was performed, 45 of 49 (92%) yielded *S typhi*. The yield for blood clot culture was 18 of 44 (41%) and for stool culture 24 of 41 (59%). Of the 45 blood culture positive cases, 41 (90%) were diagnosed on the first culture performed. The modal time for the blood cultures to become positive was two days.

Over the same period 2258 assessable single Widal agglutination tests were performed. Sixty-eight were positive (0.03%), of which 23 were false positive. There were 13 culture positive cases of typhoid fever in which the Widal test was falsely negative. Widal test alone confirmed eleven cases. The results shown in the table below give a sensitivity for the Widal test of 78%, a specificity of 99%, a positive value of 66% and a negative predictive value of 99%.

There were 2189 blood clot cultures, of which 18-yielded *S typhi* (0.82%). In 42 patients both whole blood and blood clot cultures were performed. The blood culture was positive in 39 (93%), but the clot culture was positive in only 17 (40%). In three cases the clot culture was the only specimen, which yielded *S typhi,* but in only one of these was the Widal test negative. (Duthie and French; 1990)

The tables shown below summarize the results:

Table 1 Results of blood, stool, and clot culture and Widal agglutination in patients with bacteriologically confirmed typhoid fever

		Widal test								
		Positive			*Negative*			*Not done*		
		Stool culture								
Blood culture	*Clot culture*	+	−	*Not done*	+	−	*Not done*	+	−	*Not done*
−	−	6	2	1	2	1	1	1		
+	−	6	9	4	2		2		1	
+	ND		1	2	1			1	1	1
	+		1	1		1				
−	−				1					
ND	+			1						
ND	−				1					
ND	ND				1			2		

ND = Not done.

(Duthie and French; 1990)

Table 2: Results of single Widal agglutination titres

Clinical interpretation	Number (%)	
True positive results:	45	(2.0)
Culture positive typhoid fever	34	
Culture negative typhoid fever	11	
False positive results:	23	(1.0)
Fever, non-typhoid	20	
Salmonellosis	2	
Liver disease	1	
True negative results	2177	(97-0)
False negative results (culture)	13	(0.6)

(Duthie and French; 1990)

Table 3: Forty-two blood culture-blood clot culture pairs

Blood culture	*Blood clot culture*	*Number (%)*	
+	+	14	(33)
+	-	25	(60)
		3	(7)

(Duthie and French; 1990)

Interpretation

In this study an isolation rate of 92% was obtained, for blood culture with the Bactec 460 system using a blood:broth ratio of 1:6. This yield is comparable with those reported by other workers using 10% Oxgall. The Bactec 460 media contain liquoid whoch probably contributed to the good recovery rates. Some workers claim that bone marrow culture provides the highest yield of *S typhi* in the diagnosis of typhoid fever, but the detection rate of 84-92% is no better than this result for blood culture. The invasive nature of bone marrow culture precludes its use as a routine method.

These results suggest that modern blood culture techniques permit the bacteriological confirmation of typhoid fever in a high proportion of cases. Routine clot culture of specimens sent for the Widal test is not cost effective and the Widal test itself should be used more selectively. A single Widal test is not reliable for the diagnosis of typhoid fever because false positive and false negative results are common. In a patient strongly suspected to have typhoid fever it may be useful to perform the Widal test only if two blood cultures are negative.

(Duthie and French; 1990)

1.9. Epidemiology

Typhoid fever is estimated to cause 21 million illnesses and 200 000 deaths annually worldwide (Crump et al. 2004). The spread of multiple drug-resistant Salmonella enterica serotype Typhi (S. Typhi) has further compounded the burden of typhoid fever worldwide (Bhutta 1996; Rowe et al. 1997; Kabra et al. 2000). The disease is endemic to Central Asia, where countries are estimated to experience medium typhoid fever incidence (Crump et al. 2004). Unlike in low-incidence countries (Stroffolini et al. 1992; Olsen et al. 2001), there are likely to be multiple routes of typhoid fever transmission in endemic countries (Black et al. 1985; Luby et al. 1998; Luxemburger et al. 2001; Vollaard et al. 2004). As disease control efforts may differ considerably based on the principal modes of S. Typhi transmission, identification of risk factors for infection in endemic countries can guide the allocation of scarce resources for effective control programs. (Christopher M.P., et.al; 2006)

Over the past decade, S paratyphi A was shown to be an increasingly reprted cause of EF worldwide. An outbreak of EF caused by S paratyphi A has been reported from India and Nepal with a restricted number of clones. The incidence of EF appears to vary with age

groups and seasons. Paratyphoid fever has the highest incidence in teenagers and young adults in contrast to typhoid fever, which is more common in children. This is possibly due to a different mode of transmission between S typhi and S paratyphi A. (Christopher M.P., et.al; 2006)

1.10. Treatment

Physician is seen immediately if anyone thinks he has been exposed to typhoid fever. People who do not get treatment may continue to have fever for weeks or months, and may eventually die from complications. Treatment will probably include an antibiotic to treat the disease. Specific treatment for typhoid fever will be determined by physician based on patients:

- Age, overall health, and medical history
- Extent of the disease
- Tolerance for specific medications, procedures, or therapies
- Expectations for the course of the disease
- Opinion or preference

It is important to remember that the danger of typhoid fever does not end when symptoms disappear. The patient could still be carrying *S.Typhi* and the illness could return, or he could pass the disease to other people. People who have typhoid fever should:

- Take any prescribed antibiotics.
- Wash hands after using the bathroom.
- Have a series of stool cultures - to ensure that the S. Typhi bacteria are no longer present.

1.10.1. Antibiotic treatment

Intravenous fluids and electrolytes may be given. Appropriate antibiotics are given to kill the bacteria and antibiotic therapy is the only effective treatment for typhoid fever. There are increasing rates of antibiotic resistance throughout the world, so the choice of antibiotics should be a careful one.

(Livingstone, 19th edition)

1.10.2. Commonly prescribed antibiotics

In the United States, most doctors prescribe ciprofloxacin for no pregnant adults. Women who are pregnant and children most often receive Ceftriaxone (Rocephin) injections, because ciprofloxacin has been associated with problems in these groups. All of these drugs can cause side effects, and long-term use can lead to the development of antibiotic-resistant strains of bacteria.

Table 4: Antibiotic treatment of typhoid fever

Medicine	**Amount**	**Frequency/ Day**	**Route**
Ciprofloxacin	500mg	12 hourly (day)	Orally
Cotrimoxazole	500mg	12 hourly	Two tablets or IV equivalent
Cloramphenicol	500mg	6 hourly	Orally
Amoxicillin	750mg	6 hourly	Orally
Ceftriaxone	500mg	24 hourly	Parenterally

However an increasing number of salmonellae, including *Salmonella typhi* are now resistant to many antibiotics and some are only sensitive to Ciprofloxacin. The third generation Cephalosporin, Ceftriaxone and Cefotaxime are useful when the organism is resistance to Ciprofloxacin. Treatment should be continued for 14 days.

(Livingstone, 19th edition)

1.11. General information about the antibiotics used

Some general information like mechanism of action, pharmacokinetics, dose, contraindication and side effects of the antibiotics used to treat typhoid fever are as follows.

1.11.1. Chloramphenicol

Mechanism of action: Chloramphenicol inhibits bacterial protein synthesis by interfering with 'transfer' of the elongating peptide chain to the newly attached aminoacyl- tRNA at the ribosome-mRNA
complex. It specifically attaches to the 50S ribosome and thus may hinder the access of aminoacyl-tRNA to the acceptor site for amino acid incorporation. Probably by acting as a peptide analogue, it prevents formation of peptide bonds. (Tripathi, 5th edition)

Pharmacokinetics: It is rapidly and completely absorbed after oral ingestion. It is 50-60% bound to plasma proteins and are very widely distributed. Chloramphenicol is primarily conjugated with glucuronic acid in liver and little is excreted unchanged in urine.

Dose: In child it is 50-100 mg/kg daily in divided doses and in neonate it isunder two weeks 25 mg/kg daily (in 4 divided doses).

Contraindication: In pregnancy, breast-feeding and porphyria.

Side effects: Blood disorders including reversible and irreversible aplastic anaemia with reports of resulting leukaemia, peripheral neuritis, optic neuritis, headache, depression, urticaria, nocturnal haemoglobinuria reported, grey syndrome (abdominal distension, circulatory relapse) may follow excessive doses in neonates with immature hepatic metabolism. (British National Formulary, 2007)

1.11.2. Ampicillin

This is semi-synthetic extended spectrum penicillin called Aminopenicillin where benzyl group of Penicillin-G is replaced by chemically combining specific side chain such as amino group. The mechanism of action of all penicillins and cephalosporins are similar.

Mechanism of action: All beta-lactam antibiotics interfere with the synthesis of bacterial cell wall. The cell wall is a peptidoglycan structure where peptide chains crosslinks with sugars by transpeptidase enzyme. B-lactam inhibits the transpeptidases so that cross-linking does not take place and cell wall becomes irregular and not rigid. Since salt concentrations are greater

inside the cell than outside, water enters the cell by osmosis. As a result, the cell swells and lyses and the bacteria dies.

Pharmacokinetics: Ampicillin is not degraded by gastric acid; oral absorption is incomplete but adequate. Food interferes with absorption. It is partly excreted in bile and reabsorbe-enterohepatic circulation occurs. Plasma half-life is 1 hr. (Tripathi, 5th edition)

Dose: By mouth, 0.25-1g every 6 hours, at least 30 minutes before food; in children 1/2 of the adult dose. By intravenous infusion, 500 mg every 4-6 hours and in children 1/2 of the adult dose.

Contraindication: Penicillin hypersensitivity

Side effects: It shows irritative effects (nausea, vomiting) hypersensitivity reactions and antibiotic-associated colitis.
(Bangladesh National Formulary, 2006)

1.11.3. Ciprofloxacine

It is the most potent first generation fluroquinolones and all quinolones and fluroquinolones exhibit the same mechanism of action. For eg. Ofloxacin, Levofloxacin, Norfloxacin, etc.

Mechanism of action: It inhibit the enzyme bacterial gyrase, which nicks double stranded DNA, introduces negative supercoils and then reseals the nicked ends. This is necessary to prevent excessive positive supercoiling of the strands when they separate to permit replication or transcription. The DNA gyrase consists of two A and two B subunits; A subunit carries out nicking of DNA, B subunit introduces negative supercoils and then A subunit reseals the strand. FQ bind to A subunit with high affinity and interfere with its strand cutting and resealing function.

Pharmacokinetics: Ciprofloxacin is rapidly absorbed orally, but food delays absorption, and first pass metabolism occurs. Plasma protein binding is 20-35 % and elimination half-life is 3-5 hrs. (Tripahi, 5th edition)

Dose: It is not recommended in child but where benefit outweighs risk, by mouth 10-30 mg/kg daily in two divided doses.

Contraindication: It is contraindicated in pregnant and lactating mothers. It causes arthropathy in the weight bearing joints of immature animals. Short course in child may be justified only in special circumstances.

Side effects: It results irritative effects, dizziness, sleep disorders, photosensitivity, tendon inflammation, arthralgia, myalgia. (Bangladesh National Formulary, 2006)

1.11.4. Gentamicin

It is a class of aminoglycoside antibiotic and works in the same way as other aminoglycosides like Streptomycin, Kanamycin, Netilmicin, Neomycin, etc.

Mechanism of action: Transport of aminoglycoside into bacteria is a multi-step process through the bacterial cell wall and cytoplasmic membrane. Once inside the cell, Gentamicin binds to both 30S and 50S ribosomes as well as 30S-50S interface. It freeze initiation of protein synthesis by preventingpolysome formation. The ribosome has to identify the mRNA codon and binding of aminoglycoside to this juncture causes distortion of mRNA codon recognition resulting in misreading of the code. Wrong amino acids with tRNA incorporation cause toxic or unrequired protein synthesis.

Pharmacokinetics: It is highly ionized, neither absorbed nor destroyed in the g.i.t. Absorbtion frm injection site in muscles is rapid. Gentamicin is not metabolized and excreted unchanged in urine with plasma half-life of 2-4 hrs. (Tripahi, 5th edition)

Dose: In children from 2 weeks-12 years, 2 mg/kg every 8 hours and in neonate upto 2 weeks, 3 mg/kg evry 12 hours.

Contraindication: Myasthenia gravis.

Side effects: Vestibular and auditory damage, Nephrotoxicity, rarely hypomagnesaemia on prolonged therapy, stomatitis and irritative effects.

(British National Formulary, 2007)

1.11.5. Cotrimoxazole

The fixed dose combination of trimethoprim and sulfamethoxazole is called cotrimoxazole.

Mechanism of action: Sulfonamide inhibits folate synthetase which helps in the conversion of PABA to DHFA. Trimethoprim is a diaminopyrimidine related to the antimalarial drug pyrimethamine which selectively inhibits bacterial dihydrofolate reductase (DHFRase), which converts DHFA to THFA. Thus Cotrimoxazole causes sequential block of folate metabolism which is required for the bacteria.

Pharmacokinetics: Both Sulphamethoxazole and Trimethoprim have same half-life of 10 hr. Since trimethoprim has a larger volume of distribution iand lower plasma concentration, it enters many tissues and the two are given in a dose ratio pf 5:1. Trimethoprim is more rapidly absorbed than sulphamethoxazole and it is 40% plasma protein bound, while the sulfer drug is 65% bound. Trimethoprim is partly metabolized in liver and excreted in urine. (Tripathi, 5th edition)

Dose: By mouth: in children every 12 hours, 6 weeks-5 months, 120 mg; 6 months-5 years, 240 mg; 6-12 years, 480 mg. By intravenous infusion: in children 36 mg/kg daily in two divided doses increased to 54 mg/kg daily in severe infections.

Contraindications: Porphyria, not given during pregnancy.

Side effects: Irritative effects, megaloblastic anaemia, blood dyscrasias, neonatal haemolysis and methemoglobinemia, patients with renal disease develop uremia, among AIDS patients it results rash, bone marrow hypoplasia. With diuretics produce thrombocytopenia. (British National Formulary, 2007)

1.11.6. Cephalosporins

These are group of semisynthetic antibiotics chemically related to penicillins. They are divided into 4 generations.

First generation: Cefalexin, Cefradine

Second generation: Cefuroxime, Cefroxime axetil

Third generation: oral- Cefixime parenteral- Cefotaxime, Ceftriaxone, Ceftazidime

Fourth generation: Cefepime.

Mechanism of action: All cephalosporins are bactericidal and have the same mechanism of action as penicillin,i.e. inhibition of bacterial cell wall synthesis.

Pharmacokinetics: Until recently, only some first generation cephalosporins were absorbed appreciably after oral administration, but this has changed with the availability of cefuroxime axetil (2nd generation) and cefixime (3rd generation). Depending on the drug, absorption may be delayed, unaltered, or increased if administered with food. There are reported species variations in the oral bioavailability of some cephalosporins that are detailed under each individual drug's monograph. So except the first generation others are administered intramusculary or intravenously.

Cephalosporins are widely distributed to most tissues and fluids, including bone, pleural fluid, pericardial fluid and synovial fluid. Higher levels are found in inflamed than in normal bone. Very high levels are found in the urine, but they penetrate poorly into prostatic tissue and aqueous humor. Bile levels can reach therapeutic concentrations with several of the agents as long as biliary obstruction is not present. With the exception of cefuroxime, no first or second generation cephalosporin enters the CSF (even with inflamed meninges) in therapeutically effective levels. Therapeutic concentrations of cefotaxime, moxalactam, cefuroxime, ceftizoxime, ceftazidime and ceftriaxone can be found in the CSF after parenteral dosing in patients with inflamed meninges. Cephalosporins cross the placenta and fetal serum concentrations can be 10% or more of those found in maternal serum. Cephalosporins enter milk in low concentrations. Protein binding of the drugs is widely variable and species specific. Cephalosporins tend to bind to equine and canine plasma proteins less so then to human plasma proteins.

Cephalosporins and their metabolites (if any) are excreted by the kidneys, via tubular secretion and/or glomerular filtration. Some cephalosporins (*e.g.,* cefotaxime, cefazolin, and cephapirin) are partially metabolized by the liver to deacetyl compounds that may have some antibacterial activity. Since this antibiotic is excreted primarily by the kidney dosage should be altered in patients with renal insufficiency. Probenecid slows the tubular secretion of most cephalosporins. Some are excreted in the bile like cefoperazone and cefpiramide.
(Hardman and Limbird; International edition)

Contraindications/Precautions/Reproductive Safety: Cephalosporins are contraindicated in patients who have a history of hypersensitivity to them. Because there may be cross-reactivity, use cephalosporins cautiously in patients who are documented hypersensitive to other beta-lactam antibiotics (*e.g.,* penicillins, cefamycins, carbapenems).

Oral systemic antibiotics should not be administered in patients with septicemia, shock or other grave illnesses as absorption of the medication from the GI tract may be significantly delayed or diminished. Parenteral routes (preferably IV) should be used for these cases.

Cephalosporins have been shown to cross the placenta and safe use of them during pregnancy have not been firmly established, but neither have there been any documented teratogenic problems associated with these drugs. However, use only when the potential benefits outweigh the risks.

Dose: Ceftriaxone is given to infant and child as 20-50 mg/kg daily as a single dose; up to 80 mg/kg daily in severe infections; doses of over 50 mg/kg by intravenous infusion only. In neonates, by intravenous infusion over 60 minutes, 20-50 mg/kg daily as a single dose.

Side effects: Irritative effects, allergic reactions, nervousness, reversible transient hepatitis, cholestatic jaundice, disturbances in liver enzymes, blood disorders including thrombocytopenia, leucopenia, aplastic aemia and agranulocytosis also reported.
(Bangladesh National Formulary; 2006)

1.12. Case studies

1.12.1. Comparative study of Chloramphenicol, Cotrimoxazole, Amoxycillin and Cephalosporins in typhoid fever:

Ever since the introduction of Chloramphenicol in 1948, it has remained the drug of choice in the treatment of typhoid fever. However, the time for defervescence has been noted to be gradually lengthening and the dose to be escalating. It is not a bactericidal drug and has no effort in the treatment of carriers. Aside from this, it carries a risk for development of marrow aplasia. (Mathur and Subhodaya; 1996)

Another drug, cotrimoxazole has been reported to be equally effective as chloramphenicol in the treatment of typhoid fever. Amoxycillin (a-amino-p-hydroxyl-benzyl penicillin) is a semi-synthetic penicillin that differs structurally from ampicillin by the presence of a p-hydroxyl group. It acts as a bactericidal agent.

Table 5 below presents the clinical response as judged by time for symptoms to subside, time for defervescence and the improvement in toxemia and "well being".

Table 5: Results

	Chloramphenicol	**Cotrimoxazole**	**Amoxycillin**
Time for symptoms to subside	7	6	6
Time for temperature to return to normal	6	6	7
Improvement in toxemia and '"well being"	4	4	3

(Mathur and Subhodaya; 1996)

Clinical and temperature responses are quite the same with the amoxicillin and cotrimoxazole groups although improvement in toxemia and well-being occurred much faster with the amoxicillin cases. In the chloramphenicol group, the rate of defervescence is a little longer than the two groups. There were no relapses or carriers, in the amoxicillin and cotrimoxazole treated group patients whereas there were two relapses and six convalescent carriers in the chloramphenicol group.

Two patients under chloramphenicol had a recurrence of symptoms after initial response with *S.typhi* in blood. There were six patients receiving chloramphenicol who exhibited positive stool cultures even after the end of the two weeks therapy. These are considered as carriers and re-treatment with amoxycillin for another two weeks gave excellent results.

The hemoglobin values were more affected on those under chloramphenicol medication. Increased transaminases values were observed on all cases with jaundice on admission, returning to normal however with treatment. (Mathur and Subhodaya; 1996)

It is concluded that amoxycillin is comparable to cotrimoxazole and better than chloramphenicol in the treatment of typhoid fever. In a developing country such as for economic reason, it is believed that amoxycillin should be reserved for the treatment of more serious cases or those with severe complications. (Mathur and Subhodaya; 1996)

1.12.2. Clinical efficacy of the antibiotics

The phenomenon of chloramphenicol resistance in enteric fever is not entirely new but the emergence of *S. typhi* strains resistant to multiple drugs has posed serious problems in the management. Two hundred and ten cases of typhoid fever were studied between January 1990 to September 1991. Ciprofloxacin was successfully used as first line during MDRST cases. No serious side effects were noted. While quinolones have been used mostly in adults with good efficacy, its toxicity its profile especially in view of it not being recommended in children below 12 years, has been an area of concern for its wider use. An (Adverse Drug Reaction) ADR monitoring survey in India has further shown that musculoskeletal side effects were reported in 8.6% patients on Ciprofloxacin, and arthropathy and CNS symptoms have been reported in pediatric patients given Pefloxacin.

This situation has led doctors to use the second and third generation of cephalosporins the latter having been widely used as parenteral preparations. Cefotaxime, Ceftriaxone, Cefoperazone and Cefuroxime have all been used with considerable success, with efficacy rates reported around 80-90%. The disadvantage of these drugs in young children is that they must be given intravenously for 10-14 days.

Cefuroxime axetil has a longer half-life and can be administered in a twice-daily dosage schedule. The results of this study with Cefuroxime axetil administered in doses of 250 mg b.d. have also been very encouraging in enteric fever, with the mean time for defervescence of temperature being 3.4 days. Various other studies have shown that cefotaxime may take on an average 10 days and Ceftriaxone and Ciproflaxacin about 4 days for defervescence of temperature. Results with Cephalosporins in enteric fever have reported failure rates with

Cefamandole-35%, Cefotaxime-12%, Ceftriaxone-4%, Cefaperazone-3% and Cefuroxime-0%. It has been postulated that their individual Beta lactamase stability and biliary concentration may be contributory factors for these differences.
(Lal, N.M, et.al; 1996)

1.12.3. Nalidixic Acid-Resistant Salmonella enterica Serovar Typhi with Decreased Susceptibility to Ciprofloxacin Caused Treatment Failure

Typhoid fever is endemic in Bangladesh. Until the mid-1980s, ampicillin, chloramphenicol, or cotrimoxazole was the standard treatment for typhoid fever. Since then, ciprofloxacin or third generation cephalosporins (namely, ceftriaxone) have become the first line of treatment for typhoid fever. In 1999, ceftriaxone-resistant *Salmonella typhi* was detected in Bangladesh. Here two cases of typhoid fever are described that were unresponsive to treatment with ciprofloxacin. (Asna, et.al; 2003)

A 25-year-old man was admitted to Chittagong Medical College Hospital (a teaching hospital in the southern part of Bangladesh) with a high fever. Blood culture yielded growth of *Salmonella enterica* serovar Typhi. Antibiotic susceptibility testing was performed by Kirby-Bauer disk diffusion technique with disks from Oxoid, Ltd., Hampshire, UK. The strain was found to be susceptible to ciprofloxacin (5 mg disk) and ceftriaxone (30 mg disk), but resistant to nalidixic acid (30 mg), ampicillin (10 mg), chloramphenicol (30 mg), and co-trimoxazole (25 mg). The patient was treated with ciprofloxacin (1 g daily) for 14 days without improvement. The patient was then given intravenous ceftriaxone (2 g daily), and remission of fever occurred on the third day. (Asna, et.al; 2003)

Subsequent to this case, another patient with typhoid fever (a 20-year-old male), who was admitted to the same hospital, likewise did not respond to treatment with ciprofloxacin. *S. enterica* serovar Typhi was isolated from his blood. The isolate was found by the disk diffusion test to be susceptible to ciprofloxacin (5 mg) and ceftriaxone (30 mg), but resistant to nalidixic acid (30 mg). Moreover, the isolate was also resistant to ampicillin, chloramphenicol, and co-trimoxazole. The patient responded to treatment with intravenous ceftriaxone. (Asna, et.al; 2003)

The antibiotic therapy for typhoid fever in Bangladesh is based on the antibiogram of the isolated organism. In both cases above, the isolated organisms were resistant to first-line antibiotics. Later, the minimum inhibitory concentrations (MIC) of ciprofloxacin and of nalidixic acid of the isolates of *S. enterica* serovar Typhi from the two patients mentioned above were determined by agar dilution method. The MICs of ciprofloxacin were between 0.4-0.8 mg/L. No plasmid was found in either strain. The *gyrA* mutations mediating fluoroquinolone resistance were not analyzed. Although the MIC range of both strains was below the breakpoint for ciprofloxacin recommended by the National Committee for Clinical Laboratory Standards (4 mg/L), the treatment with ciprofloxacin failed because these patients were infected with strains of *S. entrica* serovar Typhi that had decreased susceptibility to ciprofloxacin (MIC: □0.25 mg/L). This decreased susceptibility could not be detected by the disk diffusion method; both strains were found to be fully susceptible to the 5 mg ciprofloxacin (zone of inhibition: >21 mm) disk. However, both strains were found resistant to the 30 mg nalidixic acid disk. Therefore, nalidixic acid resistance determined by the disk diffusion method could be an indication of decreased susceptibility to ciprofloxacin. (Asna, et.al; 2003)

Since 1997, infection with nalidixic acid-resistant *S. typhi (S. enterica* serovar Typhi) with decreased susceptibility to ciprofloxacin has been reported from Vietnam, Tajikistan, the UK, and India. In the UK, the percentage of *S. enterica* serovar Typhi strains showing decreased susceptibility to ciprofloxacin increased from 2.7% in 1995 to 21% in 1998. Treatment failure with ciprofloxacin occurred in such cases. The majority of these strains were imported from India and Pakistan. These two cases have demonstrated that strains of *S. eneterica* serovar Typhi with decreased susceptibility to ciprofloxacin are present in Bangladesh. The routine disk diffusion test with ciprofloxacin disk alone is unable to detect such cases. It is recommended that laboratories should also test all *S. enterica* serovar Typhi strains with a nalidixic acid disk to detect resistant strains as treatment failure might occur in cases of typhoid fever infection with strains of *S. enterica* serovar Typhi that are apparently ciprofloxacin-susceptible but nalidixic acid-resistant. (Asna, et.al; 2003)

1.12.4. Case report of response to Ceftriaxone

A previously healthy 29-year-old man from Bangladesh, but living in Italy since 1999, travelled back home in January 2006 and returned to Italy mid-March 2006. Three weeks later, he presented to the emergency room of a hospital complaining of persistence of alternating diarrhea and constipation during the previous 2 weeks and of the sudden occurrence of high-grade fever (>39°C), headache, and fatigue. On admission, he presented with fever, modest dehydration, and bradycardia (heart rate 53 bpm). His total leukocyte count was normal; malarial parasites were not detected on examination of thin and thick smears of peripheral blood. C-reactive protein (CRP) was 11.9 mg/dL (range 0 – 0.5). Routine chest X-rays showed areas of fibrosis at the lower part of the left lung. Abdominal sonography showed mild splenomegaly. Liver tests showed increase in aspartate transaminase (AST) (323 UI/L; range 0 – 40), alanine transaminase (ALT) (367 UI/L; range 0 – 40), gamma-glut amyl transferase (GGT) (436 UI/L; range 0 – 50), alkaline phosphatase (ALKP) (1,917 UI/L; range 95 – 275), total bilirubin (2.4 mg/dL; range 0.2 – 1.2), and lactate dehydrogenase (LDH) (1,307 UI/L; range 145 – 460). Serological and viral markers of acute viral hepatitis were negative (markers for hepatitis C virus, including hepatitis C virus RNA, hepatitis A virus, hepatitis B virus, hepatitis E virus, cytomegalovirus, and Epstein – Barr virus). Urinalysis showed the presence of red blood cells, white blood cells, and urobilinogen. Serum ions were lower than normal: Na 130 mEq/L (range 135 – 150) and K 3 mEq/L (range 3.5 – 5). No sign of immune suppression was present. The patient — weighing 58 kg — was treated initially with doxycycline, but when culture results became available, he was switched to a first-choice drug for MDR *S typhi* , ie, ceftriaxone (CEF) 2 g given intravenously once daily. (Cassola, et.al; 2008)

Blood (three samples) and stool cultures yielded the growth of *S typhi* . The isolate was found to be MDR (resistant to chloramphenicol, ampicillin, and cotrimoxazole) and also resistant to gentamicin, ciprofloxacin, levofloxacin, cefoxitin, and cefazolin, but it was susceptible to cefotaxime and Ceftriaxone CEF [minimum inhibitory concentration (MIC) ≤ 4 _ g/mL] and tetracycline (MIC ≤ 2 _ g/mL). The patient remained highly febrile (≥ 39°C) for 6 days from starting CEF and febrile (<39°C, but >37°C) for an additional 6 days. Notwithstanding persistent high-grade fever, after starting CEF, the patient was feeling better, and it was observed that, a rapid and progressive improvement of liver enzymes, serum ions, and CRP. For this reason, the patient continued CEF despite the persisting fever. In addition, blood and

stool cultures were tested, respectively, after 7 and 17 days of CEF and were negative. (Cassola, et.al; 2008)

The patient left the hospital after 20 days, well and fully recovered. To conclude, the spreading resistance of *S.typhi* strains more and more limits ciprofloxacin use. If MDR strains resistant both to ciprofloxacin and to CEF start to circulate frequently, there might be serious difficulties in finding relatively cheap and easy-to-use antibiotics to treat this " once " easily treatable infectious disease. (Cassola, et.al; 2008)

The general sensitivity patterns of cases that cultured positive for *S. typhi* are depicted in *Table 6.*

Drug	Tested	% Sensitive
Chloramphenicol	81	28
Sulphamethoxazole	77	36
Trimethoprim	75	35
Ampicillin	76	20
Amoxycillin	65	20
Ciprofloxacin	79	94
Cefuroxime	82	97

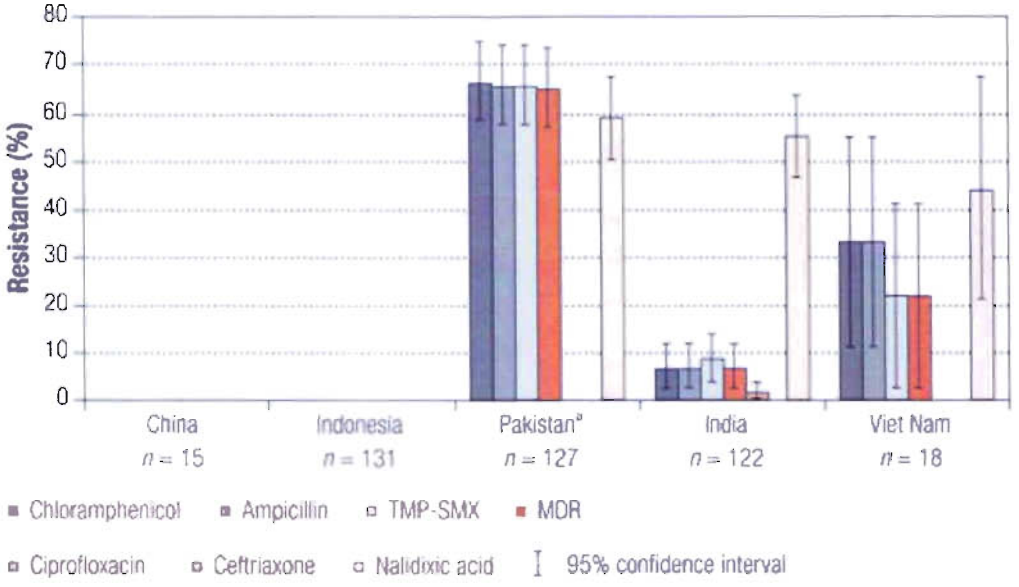
Table 6: *Antimicrobial Sensitivity Pattern in Culture Positive cases*
(Lal, N.M., et.al; 1996)

1.13. Antibiotics resistance

1.13.1 Problems with antibiotic resistance

In the past, the drug of choice was chloramphenicol. Doctors no longer commonly use it, however, because of severe side effects, a high relapse rate and widespread bacterial resistance. In fact, the existence of antibiotic-resistant bacteria is a growing problem in the treatment of typhoid, especially in the developing world. In recent years, S. typhi also has proved resistant to trimethoprim-sulfamethoxazole and ampicillin. (Cassola, et.al; 2008)

During the past 20 years, *Salmonella enterica* serovar typhi strains resistant to many first-line drugs emerged. In particular, strains resistant to chloramphenicol, ampicillin, and cotrimoxazole — defined as multidrug resistant (MDR) — have been reported. In addition, strains of *Salmonella typhi* resistant to quinolones (including ciprofloxacin) started to be reported about 15 years ago and are now frequent in the Indian subcontinent. Nevertheless, this resistance pattern has a global relevance and it is not limited to Asia. In fact, resistant strains can be locally acquired and carried by travellers to other countries both by persons in the incubation period and by asymptomatic carriers. (Cassola, et.al; 2008)



http://www.who.int/bulletin/volumes/86/4/06-039818-F3.jpg

***Figure 5**: Percentage distribution of resistance of antibiotics used against typhoid fever*

1.13.2. Effect of resistance on treatment

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, 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. (Bhutta,Z.A; 2006)

Appropriate antibiotic treatment (the right drug, dose, and duration) is critical to curing typhoid with minimal complications.18 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.17 The emergence of multidrug resistant typhoid 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.19 In recent years, however, the emergence of resistance to quinolones has placed tremendous pressure on public health systems in developing countries as treatment options are limited. (Bhutta,Z.A; 2006)

Despite appropriate treatment, some 2-4% of infected children relapse after initial clinical response to treatment.17 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,Z.A; 2006)

In summary, many challenges remain for the effective control and management of typhoid in endemic countries. Although these include establishing rapid clinical diagnosis and confirmation, the fact that both S typhi and S paratyphi are rapidly becoming resistant to commonly used antibiotics is of great concern. Addressing this issue would require a host of measures, including adequate investments in safe water and sanitation services, community education, control over antimicrobial prescribing and over the counter sales, and large scale vaccination strategies. (Bhutta,Z.A; 2006)

1.13.3. Resistance Overcome of antibiotics

According to an International Task Force studying antibiotic resistance, although antibiotics are said to have saved and improved millions of lives than any other class of medicine, their use has set in motion the biggest intervention in population genetics. The effects of that intervention are seen in the distributions of antibiotic resistance genes

throughout the world's bacterial populations. This change although not seen apparently has had a very profpund effect on human health as the antibiotics themselves. (Ahmed, 2006)

Some bacteria are naturally resistant to certain antibiotics, but usually resistance is acquired. Bacteria can become resistant to an antibiotic that was previously effective.Resistant mosly develops after long time treatment with antibiotics that kill a wide range of bacteria. The antibiotics should be used only when prescribed or advised by the physician. There are three basic principles to help ensure that indicated antibiotic treatment would be effective. (Ahmed, 2006)

1) The dosage of an antibiotic is a very important factor for antibiotic effectiveness and safety. If the dosage is not correct or adequate, it will not be effective against the infection and bacteria are more likely to develop resistance. (Ahmed, 2006)

2) Full course of antibiotic should be taken for the full amount of time prescribed by the doctor. Very often, it is observed that the patients stop taking medicine when they began to feel better with a misconception that the illness has been cured. The fact is, even after the symptoms disappear, the bacteria may still be present in small quantities and subsequently the infection may return if the antibiotic use is stopped. The discontinuance of the prescribed dose may also cause resistant. (Ahmed, 2006)

3) Antibiotic should not be saved or reused. All of the antibiotics should be taken and none of them should be left over. In any case, if it happens, then the antibiotics should not be used to treat any other infectious diseases. Because, different types of antibiotics are used for different infections. (Ahmed, 2006)

1.14. Vaccination treatment

Although improved water quality and sanitation constitute ultimate solutions to this problem, vaccination in high-risk areas is a potential control strategy recommended by WHO for the short-to-intermediate term. Two safe and efficacious typhoid vaccines, the injectable Vi polysaccharide and the oral Ty21a, have been licensed; and new, improved candidate vaccines are currently being tested. However, typhoid vaccination has not been implemented

as a routine public health measure in most typhoid-endemic countries despite the low price of the vaccine (Vi polysaccharide costs of treating the disease. (Abu-Elyazeed, et.al; 2008)

There are currently two vaccines available in the United States against *S. typhi*. One is an injectable vaccine made from the capsule that surrounds the bacteria's cells. This vaccine given in a single dose covers immunity for about two years in children as young as two years. Another booster dose is needed after two years period of time. The other is an oral vaccine consisting of live but weakened *S. typhi* and comes as a set of four capsules. This oral vaccine must be taken one capsule every other day for four days; each one should be taken about 1 hour before meal. The other is an oral vaccine capsule should be in the refrigerator until taken. This vaccine works only down to age six years, and must be boosted every five years. (Abu-Elyazeed, et.al; 2008)

1.15. Supportive therapy

Other treatment steps aimed at managing symptoms include:

- Drinking fluids. This helps prevent the dehydration that results from a prolonged fever and diarrhea. If you're severely dehydrated, you may need to receive fluids through a vein in your arm (intravenously).
- Eating a healthy diet. Nonbulky, high-calorie meals can help replace the nutrients you lose when you're sick.

1.16. Prevalence of Salmonella typhi and paratyphi infection in children: a hospital based study.

The purpose of this study was to find out the prevalence and antibiotic sensitivity pattern of Salmonella typhi and paratyphi isolated from children presenting with fever at Kanti Children's Hospital in Kathmandu, Nepal. A total of 9,856 blood samples collected for culture during one year period (April 2007 to March 2008) were included in the study. Out of total, 235 (2.0%) were positive for S. typhi and paratyphi A. Of the total positive, 195 (83.0%) were S. typhi and 40 (17.0%) were S. paratyphi A. The growth positive rate in two genders (M: 53.2% and F: 46.8%) was not significant ($P > 0.05$). Over two-third of cases were clustered in the age-group of 1-10 years. The occurrence of infections was common in summer months (rainy season). S. typhi was found to be most sensitive to cefotaxime

(100.0%) followed by ceftriaxone (98.9%), ofloxacin (93.5%), cotrimoxazole (93.5%) and chloramphenicol (93.2%) and was least sensitive to amoxyccilin (66.7%) followed by ciprofloxacin (86.6%). S. paratyphi also was found to be most sensitive to cefotaxime (100.0%), followed by ceftriaxone (97.4%), cotrimoxazole (97.1%) and chloramphenicol (92.5%) and was least sensitive to amoxycillin (15.0%) followed by ciprofloxacin (51.3%) and ofloxacin (70.3%). (Prajapati, et.al; 2008)

1.17. Risk factors

Typhoid fever remains a serious threat in the developing world, where it affects more than 12 million people annually. The disease is endemic in India, Southeast Asia, Africa, South America and in many other areas.Worldwide, children are at greatest risk of getting the disease, although they generally have milder symptoms than adults do.

- If we live in a country where typhoid fever is rare, we are at increased risk if we:
- Work in or travel to areas where typhoid fever is endemic
- Have close contact with someone who is infected or has recently been infected with typhoid fever
- Have an immune system weakened by medications such as corticosteroids or diseases such as HIV/AIDS
- Drink water contaminated by sewage that contains S. typhi

1.18. Complications

1.18.1. Intestinal bleeding or perforation

The most serious complication of typhoid fever — intestinal bleeding or perforation — may develop in the third week of illness. About 5 percent of people with typhoid fever experience this complication.Intestinal bleeding is often marked by a sudden drop in blood pressure and shock, followed by the appearance of blood in your stool.A perforated intestine occurs when your small intestine or large bowel develops a hole, causing intestinal contents to leak into your abdominal cavity and triggering signs and symptoms such as severe abdominal pain, nausea, vomiting and bloodstream infection (sepsis). This life-threatening emergency requires immediate medical care. (Azad,A.K., 1985)

1.18.2. Effect of Intestinal perforation

In Bangladesh, clinical records of 323 patients with typhoid fevere were reviewed t study the incidence, fatality, and optimal therapy of the complication of intestinal perforation. Fifteen patients (4.6%) developed intestinal perforation. Case-fatality rates were six of nine patients treated medically and one of four patients treated surgically for whom the postoperative courses were known. A literature review of 57,864 cases of typhoid fever in developing countries in the antibiotic era revealed that perforation developed in 2.5% of patients, a percentage that was similar to the incidence of 2.8% reported in the preantibiotic era. The median of case-fatality rates in these reports was 43% and the proportion of all reported typhoid deaths attributable to perforation was 25%. The case-fatality rates for patients with perforation were 70% for 410 patients managed medically and 26% for 1,835 patients managed surgically. These results indicate that intestinal perforation persist as a major cause of death in cases of typhoid fever in developing countries in the antibiotic era and that surgical treatment with use of antibiotic therapy is optimal for this complication.
(Azad,A.K., 1985)

1.19. Prognosis

The prognosis in typhoid fever should be always very guarded. Besides being a very severe disorder, intestinal perforation may happen in the mildest cases, and where, from the absence of well-marked symptoms, it has been difficult to make out a diagnosis, and during convalescence, as well as in the course of severe attacks. When it occurs, the patient complains first of a feeling of unusual warmth in the abdomen, followed by sharp pain, heightened by pressure—the weight of bedclothes, poultices, and fomentations, being intolerable—which quickly extends over the whole abdomen. This is soon followed by nausea, and instant and obstinate vomiting of greenish matter,hiccup, a pale, shrunken, anxious face, a rapid, small pulse, tympany, constipation, retention of urine, and cold, clammy sweat over the whole body. Shortly before death all the violent symptoms usually cease.

The younger the subject, the better the chances of recovery. After forty, typhoid fever is a very fatal disorder. It is more fatal when it attacks robust than feeble persons. With respect to the prognostic value of particular symptoms, it may be said that parotitis is a very unfavorable symptom. Deafness, when limited to one ear, should make a guarded prognosis.

Early somnolence is a very unfavorable symptom, as well as the persistent declaration of the patient that he is quite well. Great rapidity of pulse, with feebleness or extinction of the first sound of the heart, or intermittence of the beats, or a persistently quick, small, and contracted pulse, are met with in fatal cases. Early active delirium is a bad symptom. Few pregnant women attacked with typhoid fever, who aborts in the course of the disease, recover.
(Aitken and Clymer; Volume 1)

1.20. Pathophysiology

Humans are the only natural host and reservoir of infection for *S.enterica* serover Typhi. The infectious dose in volunteers varies between 10^3-10^9 organisms. Vi negative strains of *S.enterica* serover Typhi are less infectious and less virulent than Vi positive strains. *S.enterica* serovar Typhi must survive the gastric acid barrier en route to the small intestine. Achlorhydria, due to ageing, previous gastrectomy, treatment with H_2 receptor antagonists, proton-pump inhibitors, large amounts of antacids or *Helicobacter pylori* infection increase susceptibility to typhoid fever. In the small intestine, the bacteria adhere to mucosal cells and then invade, translocate to the intestinal lymphoid follicles and the draining mesenteric lymph nodes and some pass on to the reticuloendothelial cells of the liver and spleen. Salmonellae are able to survive and multiply within the mononuclear phagocytic cells of the lymphoid follicles, liver and spleen. After 1 7-to-14-day incubation period, the onset of a sustained secondary bacteraemia results in clinical disease.

The bacteraemia of typhoid fever persists for several weeks if antibiotic therapy is not given. In this phase the organism disseminates widely to the liver, spleen, bone marrow, gall bladder and the Peyer's patches of the terminal ileum. (Christopher M.P.,et.al; 2006)

1.21. Circumstances under which Death may ensue in Cases of Typhoid Fever

1. By poisoning of the blood generally, as indicated by many symptoms which typhoid fever has in common with typhus fever, cholera, small-pox, dysentery, scarlet fever, diphtheria, ichorrhasrnia. The intensity of the fever (measured by the thermometer) is generally great in those cases, and the fatal event occurs either at a very early period of the fever, associated with cerebral congestion, or it may occur later, when it may be supposed that the danger is past. This is sometimes termed the secondary poisoning of the blood (septicaemia), and is

most likely due to the ulcerated intestines, with the bowel perhaps on the verge of perforation. The pulse becomes rapid and small; cold, clammy sweats appear; and the body begins, even in life, to exhale a putrid odor. In cases where the blood is so gravely implicated, gas has been observed to become developed during life, and has been detected in the veins at the root of the neck for some minutes before death.

2. By implication of excretory organs at an early period—for example, the kidney, as denoted by albuminuria, or by bloody urine—conditions which tend to aggravate the blood poisoning.

3. By congestions of important organs—for example, the lungs and the brain, in consequence of poisoned blood; and which congestions are still further brought about by the circulation in the bloodvessels of putrid juices, or of the substance of fibrinous debris of clots in a granular condition having formed as plugs in the varicose veins surrounding the sloughs and ulcers of the intestines.

4. By hemorrhage from the bowels during the separation of the gland-sloughs.

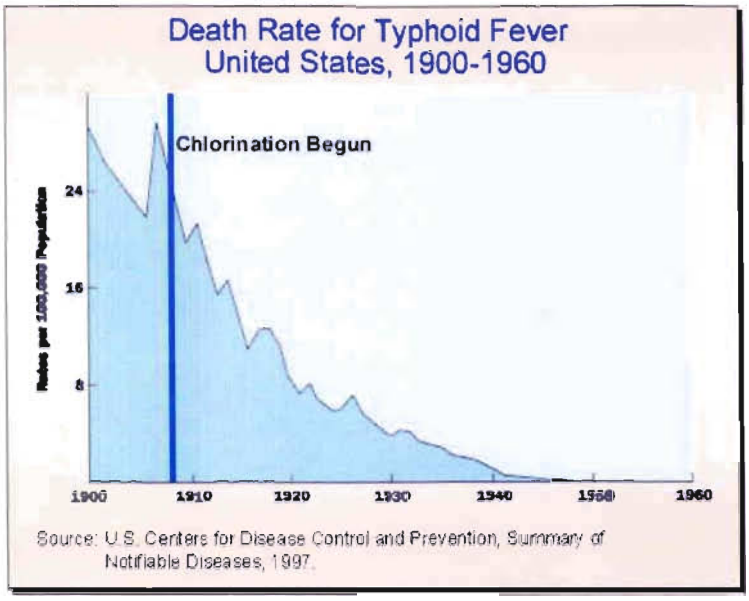
5. By exhaustion from profuse diarrhoea in cases where the catarrh of the mucous membrane has been excessive.

6. By peritonitis, with or without perforation of the intestines. There are two periods in the course of the fever when perforation is apt to take place. The first period is during the separation of the sloughs, about the end of the second and throughout the third week. The second period is during protracted convalescence, with atrophy of the intestine already described, and when the ulcers are in a weak atonic state, the result of intense protracted fever and profuse catarrh".

7. By peritonitis subsequent on suppuration of the large mesen- teric glands, and rupture of their "inclosing capsul; or from the bursting of softened new growth from the spleen into the peritoneum; or from ulceration of the gallbladder. The average mortality among cases of typhoid fever appears to be about 1 in b\ to 1 in 6. It is considerably less in autumn than in spring; and is least of all in winter. It tends to be greater among males than females; and the average age of fatal cases appears to be about 23.5. The mortality increases to a small extent as life advances. The disease in certain places seems never to be absent, and is invariably

most prevalent during autumn, at the time that diarrhoea is most common; and it has been observed to be especially prevalent in seasons remarkable for their high temperature.

(Aitken.W; Volume1)



http://upload.wikimedia.org/wikipedia/en/a/a8/Typhoid_stats.png

Figure 6: *Death rate of typhoid in USA, 1990-1960*

1.22. Preventions and Controls

In many developing nations, the public health goals that can help prevent and control typhoid — safe drinking water, improved sanitation and adequate medical care — may be difficult to achieve. For that reason, some experts believe that vaccinating high-risk populations is the best way to control typhoid fever.

Two vaccines are currently in use — one is injected in a single dose, and the other is given orally over a period of days. Neither is 100 percent effective, and both require repeat vaccinations. Immunization is not always completely effective and at-risk travellers should drink only boiled or bottled water and should eat well-cooked food. Experimentation with an oral live attenuated typhoid vaccine is now underway and appears promising.

Adequate water treatment, waste disposal, and protection of food supply from contamination are important public health measures. Carriers of typhoid must not be allowed to work as food handlers.

If travelling to an area where typhoid fever is endemic, we should consider being vaccinated. But because the vaccine will not provide complete protection, we should assure to follow these guidelines as well:

- Washing hands: Frequent hand washing is the best way to control infection. Hands should be washed thoroughly with hot, soapy water, especially before eating or preparing food and after using the bathroom. An alcohol-based hand sanitizer should be carried on for times when water isn't available.
- Untreated water is avoided: Contaminated drinking water is a particular problem in areas where typhoid is endemic. For that reason, only bottled water or canned or bottled carbonated beverages, should be used. Carbonated bottled water is safer than uncarbonated bottled water. The outside of all bottles and cans are wiped before opening. Drinks should be asked without ice. Bottled water has to be used to brush teeth, and in the shower water shall not be swallowed.
- Raw fruits and vegetables are avoided. Fruits and vegetables that can't be peeled is avoided, especially lettuce. To be absolutely safe, we may want to avoid raw foods entirely.
- Hot foods are chosen: Food that's stored or served at room temperature is avoided. Steaming hot foods are best. And although there's no guarantee that meals served at the finest restaurants are safe, it's best to avoid food from street vendors — it's more likely to be contaminated.

(Bhutta,Z.A; 2006)

1.23. Ways to prevent infecting others

- If recovering from typhoid, these measures can help keep others safe:
- Washing hands often- This is the single most important thing done to keep from spreading the infection to others. Use plenty of hot, soapy water and scrub thoroughly for at least 30 seconds, especially before eating and after using the toilet.

- Household items cleaned daily: Clean toilets, door handles, telephone receivers and water taps at least once a day with a household cleaner and paper towels or disposable cloths.
- Handling food avoided: Avoid preparing food for others until doctor says you're no longer contagious. If you work in the food service industry or a health care facility, you won't be allowed to return to work until tests show that you're no longer shedding typhoid bacteria.
- Personal items are kept separate: Set aside towels, bed linen and utensils for own use and wash them frequently in hot, soapy water. Heavily soiled items can be soaked first in disinfectant.

Typhoid is slowly disappearing from the United States because of the prevalence of preventive measures; the number of cases dropped from 5,595 in 1942 to about 400 in 2005, and most of these cases were acquired when people traveled to other countries. Compulsory inspection of milk and water supplies, and the pasteurization of milk in particular, have greatly reduced the incidence of the typhoid bacilli.

Another important factor in the control of typhoid fever is typhoid inoculation of persons exposed to the disease, such as hospital employees and travelers to areas with poor sanitary facilities.

(Bhutta,Z.A; 2006)

1.24. General principles for the management of typhoid

- Rapid diagnosis and institution of appropriate antibiotic treatment
- Adequate rest, hydration, and correction of fluid-electrolyte imbalance
- Antipyretic therapy as required (such as paracetamol 120-750 mg taken orally every 4-6 hours)
- Adequate nutrition: a soft, easily digestible diet should be continued unless the patient has abdominal distension or ileus
- Close attention to hand washing and limitation of close contact with susceptible individuals during acute phase of infection

- Regular follow-up and monitoring for complications and clinical relapse (this may include confirmation of stool clearance in non-endemic areas or in high risk groups such as food handlers)

(Bhutta,Z.A; 2006)

CHAPTER 2

AIM & SIGNIFICANCE

2.1. AIM OF THE STUDY

Typhoid is a systemic infection caused by *Salmonella enterica* serotype Typhi *(S.typhi)*. It can be treated with various types of antibiotics but the common antimicrobials are becoming resistant.

Main Objectives:

The main purpose of the survey was to assess the following:

- Impact of typhoid fever and its treatment with types of drugs used
- Comparison of clinical efficacy and sensitivity pattern of the antibiotics
- Comparison of resistance of the antibiotics

Secondary Objectives:

Secondary objectives include the following:

- Impact of some environmental factors like age, weight, symptoms, etc.
- Impact of the clinical pattern of typhoid fever on the clinical outcome
- Revised estimate of the global burden of typhoid fever, an accurate understanding of which is necessary to guide public heath decisions for disease control and prevention efforts. (Crump, et.al; 2004)

2.2. SIGNIFICANCE OF THE STUDY

Typhoid fever is an acute systemic infection caused by the bacterium *Salmonella enterica* serover Typhi. Typhoid and paratyphoid fevers are collectively referred to as enteric fevers. Typhoid is transmitted by the fecal-oral route via contaminated food and water and is therefore common where sanitary conditions are inadequate and access to clean water is limited.

Typhoid fever presents some interesting and mostly unexplained epidemiological features. It is an endemic health problem throughout Africa and Asia and persists in the Middle East, a few southern and eastern European countries and central and South America. Some hospital and community-based studies have found a significant incidence of typhoid in pre-school children. In endemic areas, peaks of transmission occur in dry weathers or at the onset of rains.

Prevalence of typhoid fever in Bangladesh is increasing day by day and pre-schooled and school aged children are mostly affected than adults. Risk factors of this disease include eating food and prepared outside the home, drinking contaminated water and eating vegetables that have been grown with human waste as fertilizer. Thus, the major mode of spread is contamination with human feces. Hence the epidemiology of the disease involves person-to-person spread.

The lack of specific clinical signs complicates the diagnosis of typhoid fever, which must be distinguished from other endemic acute and subacute febrile illnesses. Therefore, proper and careful diagnosis of typhoid fever should be an important part of the study. Efforts to develop effective treatments against these diseases became important steps of the study. However, this study shows evidence of resistance of some effective drugs and preventive measures to overcome the resistance of mostly used antibiotics.

In most endemic areas, approximately 90% of enteric fever is typhoid. Although typhoid fever was common in the United States and Europe in the 19th century, it is now encountered mostly throughout the developing world. In the last fifteen years, the emergence of resistance to the antibiotics used for treatment has led to large epidemics, and complicated the management of this serious disease.

Prevention of enteric diseases comprises basic sanitary and hygiene measures including purifying water supplies, improving water delivery and sewage control, supplying hand washing facilities, latrines, boiling water and supervising food handlers. Most of the time, however, it is difficult to apply these recommendations properly, and the problems are compounded by the emergence of drug-resistant strains of *Salmonella typhi*.

The percentage of the sensitivity and resistant pattern to some antibiotics was an interesting knowledge that could draw conclusion about the previously used antibiotics, whether they were effective anymore or became resistant in the body and through this the antibiotic that was most effective could be determined. From this piece of information, antibiotics that already show efficacy against typhoid fever now and the drugs that can show efficacy in future can be discovered with further research work.

CHAPTER 3

MATERIALS & METHODS

3. MATERIALS & METHODS

3.1.a. Place of study

The survey was carried out in Institute of Child Health and Shishu Sasthya Foundation Hospital, Dhaka.

3.1.b. Duration of study

Four members carried out the study over a consecutive period of one and a half year from A January 2008 to May 2009.

3.2. Background

The study was divided into two portions. One include the I) Tests and the other is the II) Procedure of collecting information.

At first a *list* of drugs (antibiotics) used in the treatment of typhoid fever was made and the information included in it is as follows:

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

The drugs found were: Chloramphenicol, Amoxicillin, Trimethoprim and Sulfamethoxazole,Ciprofloxacin, Cefotaxime, Azithromycin, Ceftriaxone, Cefoperazone, Ofloxacin, Levofloxacin, Dexamethasone,

Secondly, a *project protocol* was prepared based on the disease and the following information.

- Project title
- Background information
- Introduction
- What is typhoid fever?
- How does it spread?
- Clinical features of Typhoid fever
- Summary of clinical features
- Paratyphoid fever
- Complications
- Summary of complications
- Investigations
- Treatment
- 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

3.3. 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.

3.4. 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. Jan 2007

3.5. Tests

A study of different tests was done in the hospital during the survey. The types of blood tests used include:

1) Haematological test: In this test the total count and the differential count of neutrophil was made to check if the patient is infected.
2) Serological (widal) test: This antigen/antibody test was done to check if the patient is infected by the bacteria *Salmonella typhae*. The widal range was 1:40; 1:80; 1.160.
3) Culture and microbiological test: This is the confirmatory test done for the diagnosis of typhoid.

3.6. Data collection procedure

The four members of the team were instructed in a very well manner about the data collection procedure and were set separately in different areas with taking the respective responsibilities in the surveyed health facilities. The steps can be presented in a flow diagram as shown below.

Protocol writing and approval

↓

Case report form development

↓

Selecting Population and study site

↓

Data collection → Quantitative and qualitative

↓

Data summarization in a chart

↓

Data analysis statistically

↓

Thesis writing

Figure 6: *Flow chart of study procedure*

3.7. Sensitivity pattern

Sensitivity pattern of *Salmonella typhae* to different antibiotics was collected from hospital files that had the following information:

Table 7

Sl. No	Hospital ID	Lab ID	Name	Age	Sex	Organism	Sensitivity

With this information, a sensitivity pattern sheet was prepared from which it could be understood whether the micro-organism *Salmonella typhae* was sensitive, resistant or intermediate (moderate) to the antibiotics. The following information was entered into the sensitivity pattern sheet. A sample is shown below and sheets are made like this for fifty patients.

Table 8

Name of drugs	Bishwoy 15939	Atia 15963	Simran 16231	Siam 17212	Sachho 17300
Ceftazidime			S		S
Netilmicin				S	
Ceftriaxone			S	S	S
Ciprofloxacin			S	S	S
Nitrofuratoin					
Imipenem				S	
Azithromycin			R		
Cephradine					
Nalidixic Acid			R	R	
Cotrimoxazole					S
Coxacillin					
Aztreonam					
Amikacin					
Carbenicillin					
Cephalexin				M	
Ampicillin			R	S	S
Gentamicin				S	
Penicillin					
Doxycycline					
Chloramphenicol			R	S	S
Amoxicillin					
Oxacillin					
Erythromycin					
Sulphamethoxazole/Trimethoprim					
Doxycycline Hydrochloride					
Sulphamethoxazole			R		
Cefotaxime				S	

3.8. Summary of data

Preparing a chart summarized the information collected from data collection sheet. The following parameters were considered for fifty patients in the chart.

- Name and ID
- Age
- Weight
- Sex
- Fever (Days)
- Abdominal pain (Days)
- Vomitting (Days)
- Diarrhoea (Days)
- Constipation (Days)
- Cough/Respiratory distress (Days)
- Maximum temperature reached (Degree Celsius)
- Others
- Drugs received before admission
- Treatment given
- Culture and sensitivity pattern
- Widal test
- Day at which temperature became afebrile
- Day at which discharged

From here the information about day at which temperature became afebrile and date of discharge were taken from "Temperature, pulse and respiration chart" of the patient's history book in the hospital.

3.9. Statistical Analysis

These datas were represented statistically in tables, bar charts, histograms, piecharts and normal distribution curve to present the results and analysis to draw a conclusion

CHAPTER 4

CASE REPORT FORM

4. CASE REPORT FORM

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 5

RESULTS & ANALYSIS

5. RESULTS AND ANALYSIS

5.1. A graph of age versus frequency

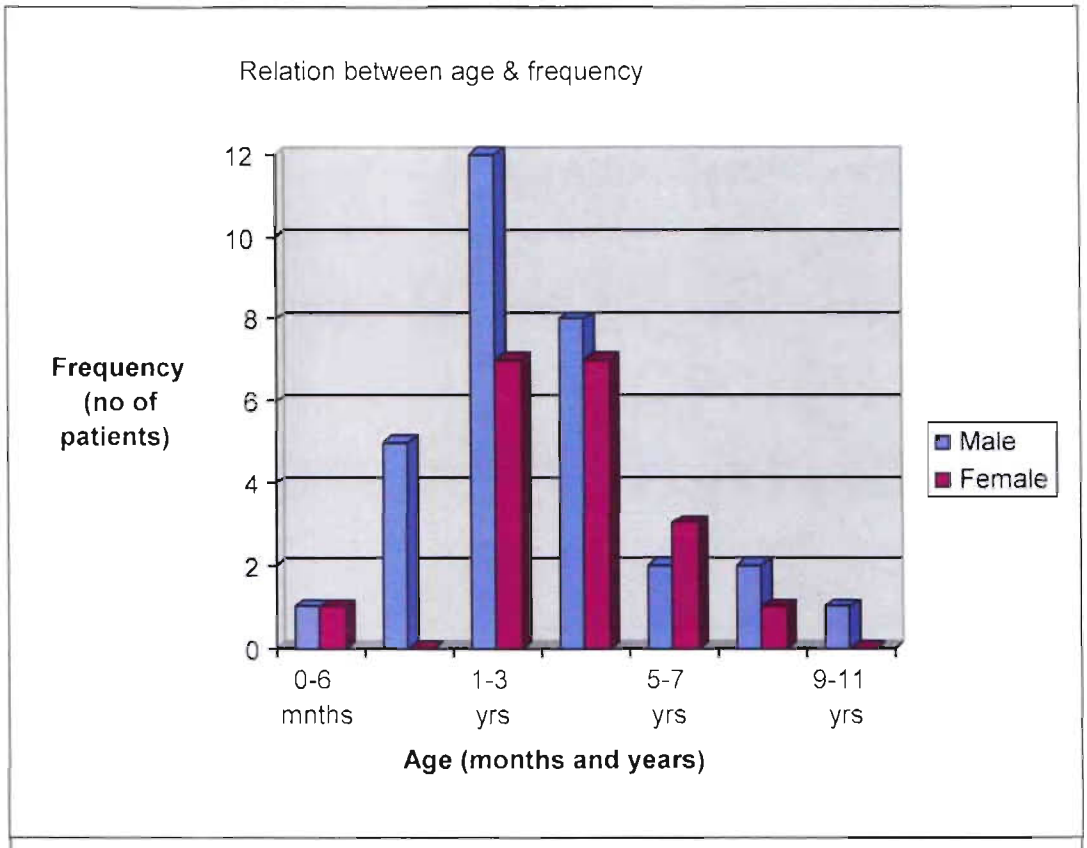


Figure 1: A graph of age against frequency

Figure 1 shows that the age that is mostly affected by typhoid using bar chart method. Typhoid fever occurs mostly in patients with age range 1-3 years. It can be calculated that the mean age of 42 patients who suffered from typhoid is 4.01 years.

5.2. A graph of weight versus frequency

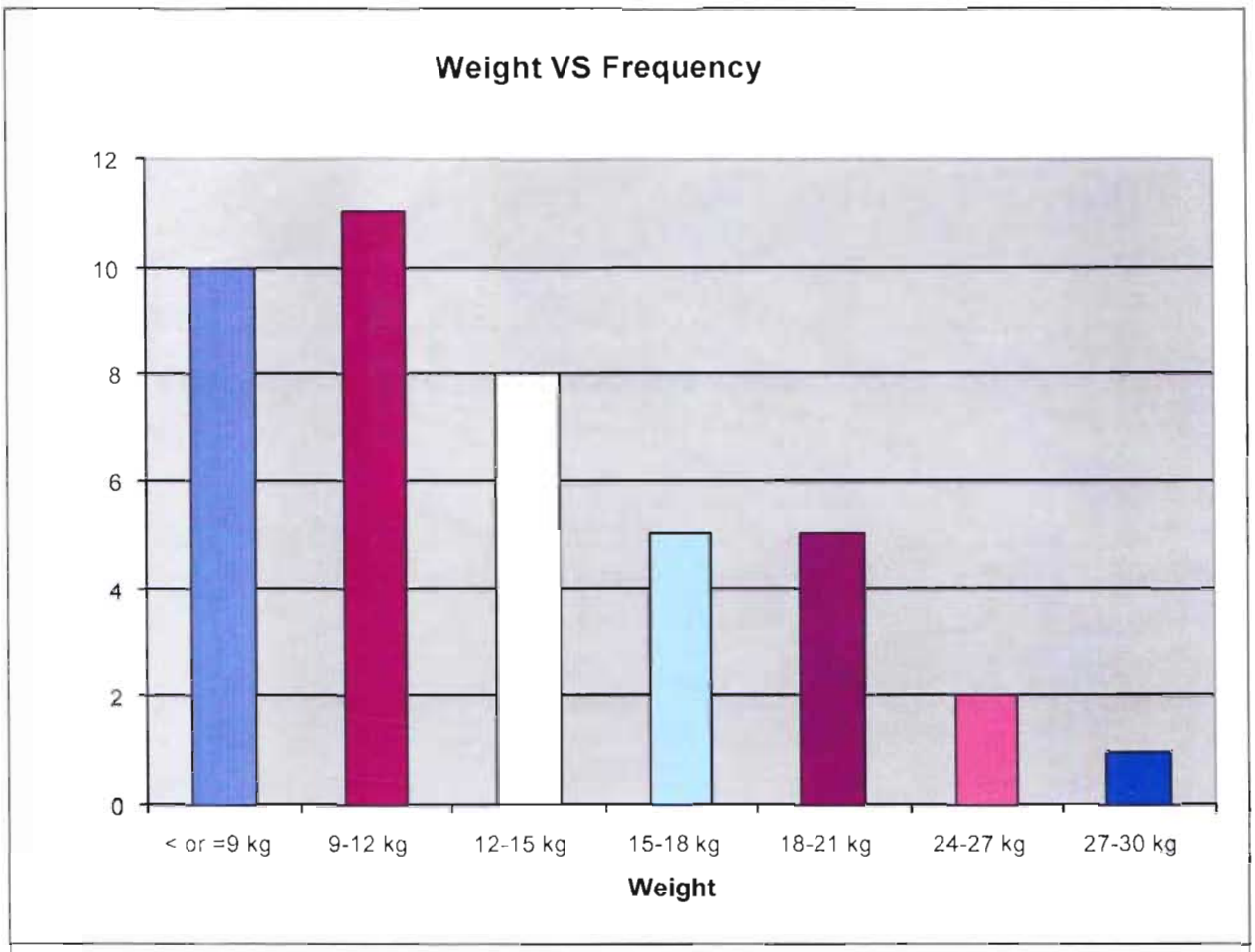


Figure 2: A graph of weight against frequency

Figure 2 shows that the weights of the typhoid patients admitted to the hospital. It can be seen that usually 9-12 kg weighed patients are mostly affected. The mean weight was found to be 13.41 kg.

5.3. Percentage distribution of typhoid

Table 9

	Male	*Female*
Total number	31	19
Percentage	31/50x100=62%	19/50x100=38%

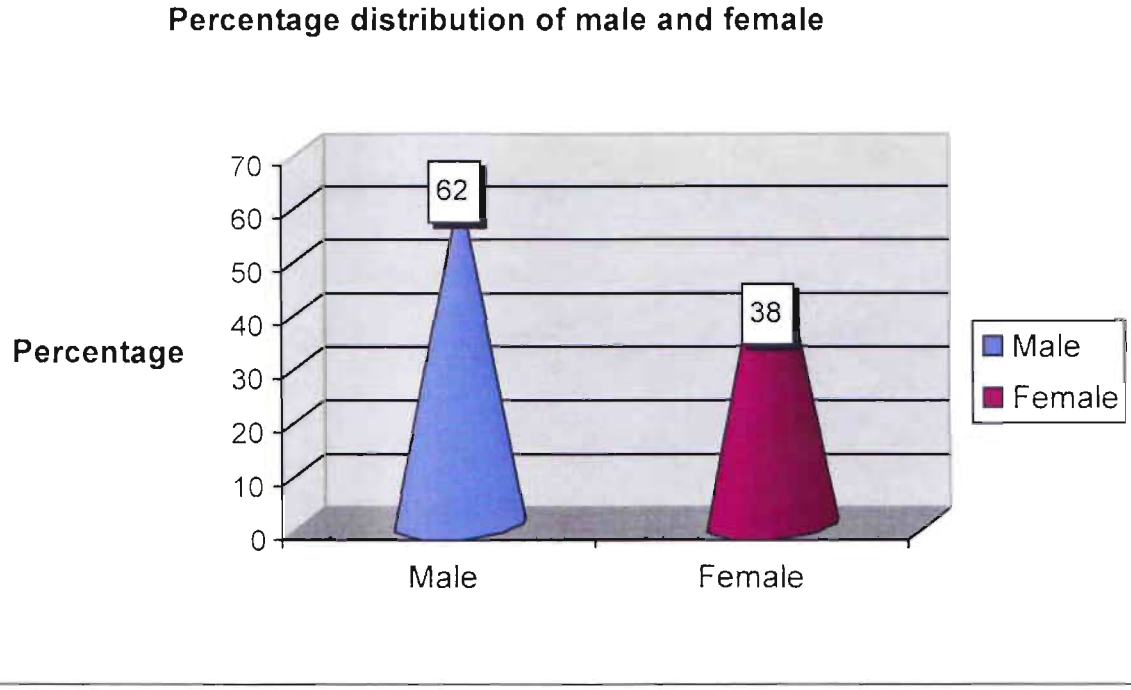


Figure 3: Distribution of typhoid fever between male and female

Figure 3 shows the percentage distribution of typhoid between male and female. Males are more prone to typhoid than female since 62% of male are affected by typhoid while only 19% female are affected. Table 4 states the value of total number of male and female affected by typhoid fever out of fifty patients.

5.4.1. Frequency distribution of symptoms

Table 10

Symptoms	Abdominal pain	Cough	Diarrhoeae	Vomitting	Others
Frequency	10	7	31	21	39

The table shows the frequency of signs and symptoms of typhoid fever seen in the indoor and outdoor patients (in total 50) of "National Child Health and Institute". The most common is diarrhoea.

5.4.2. Percentage distribution of symptoms

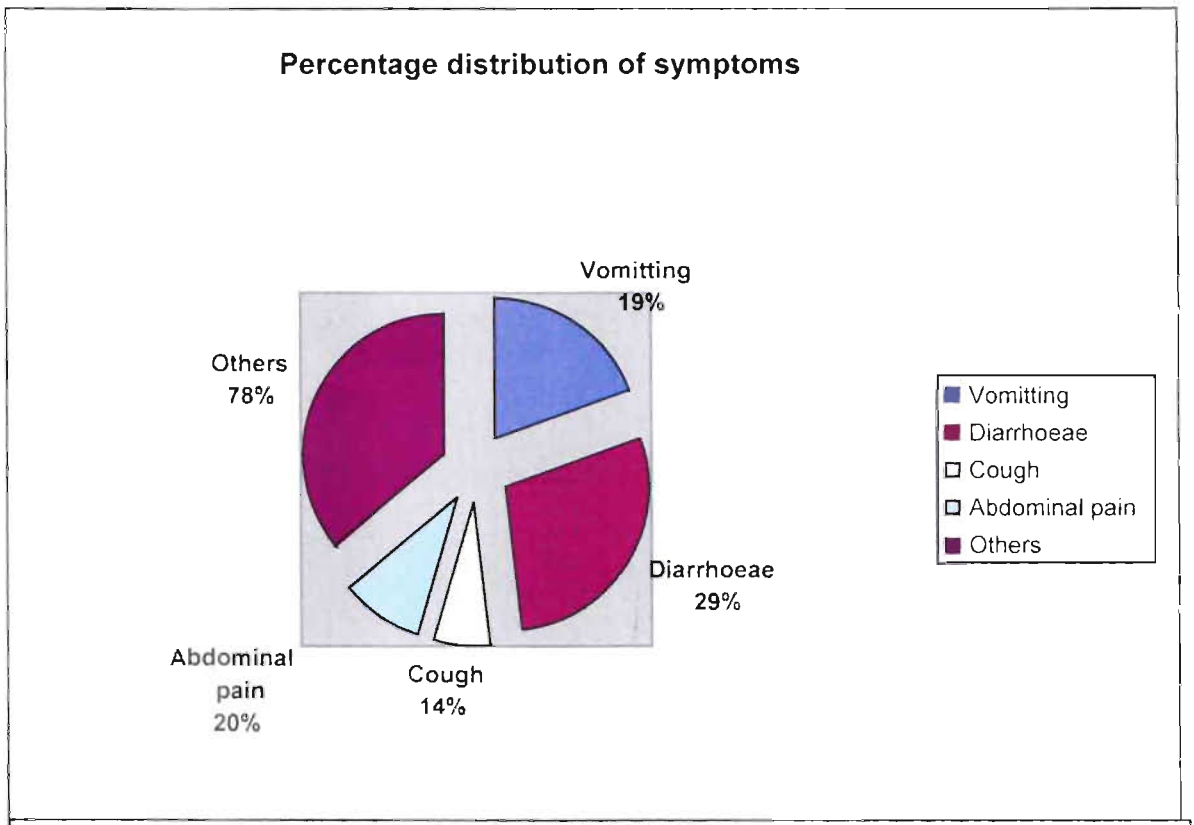


Figure 4: Distribution of the major symptoms of typhoid fever among 50 patients

From **Figure 4** it can be seen that 20% of the patients suffer from abdominal pain, 14% have cough. 29% suffer from diarrhoeae. 19% had vomiting and 78% had other symptoms.

5.5.1. Frequency distribution of other symptoms

Table 11

Symptoms	Anemea	Coated tongue	Convulsion	Dehydration	Loss of appetite
Frequency	1	10	9	4	8

In the table the numbers of patients showing other symptoms are given.

5.5.2. Percentage distribution of other symptoms

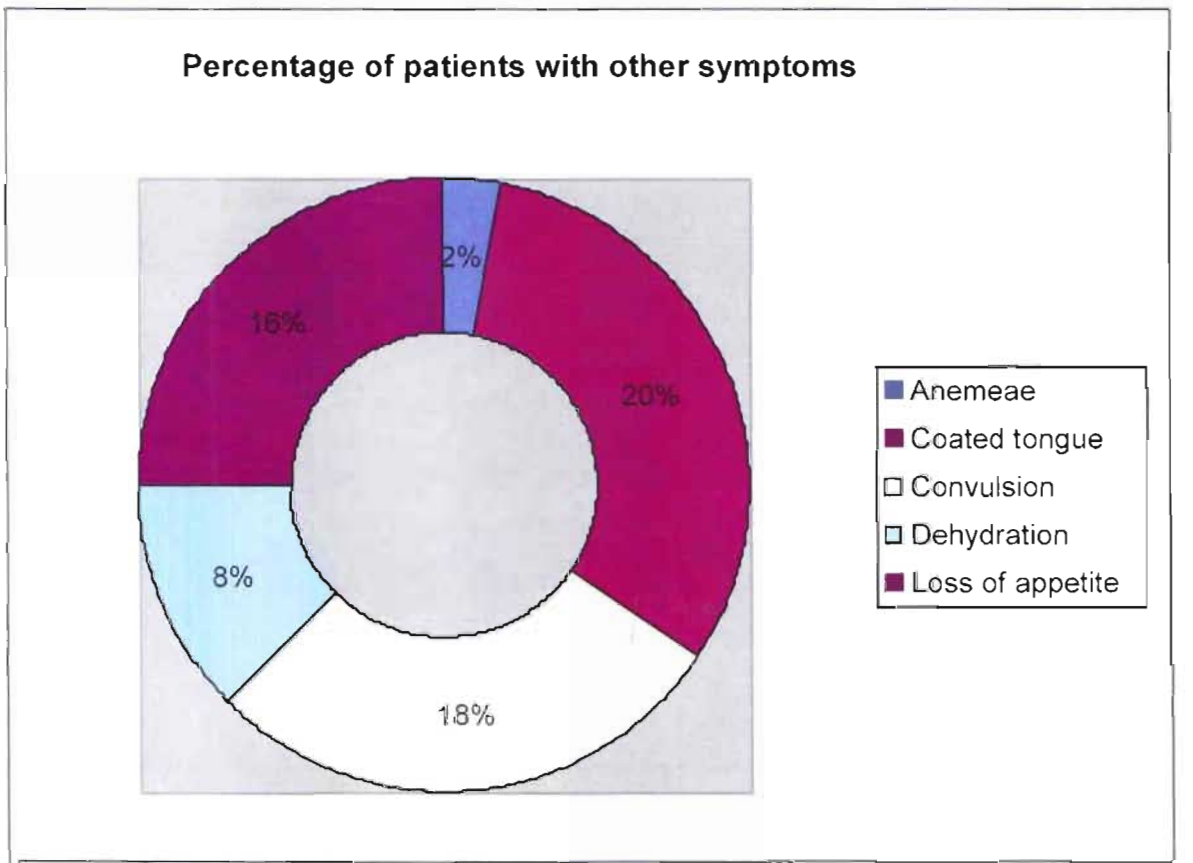


Figure 5: Percentage distribution of other symptoms among the patients

Figure 5 shows other symptoms of typhoid where 2% had anemia, 20% with coated tongue, 18% had convulsion, 8% showed dehydration and 16% had loss of appetite.

5.6. Duration of fever against frequency

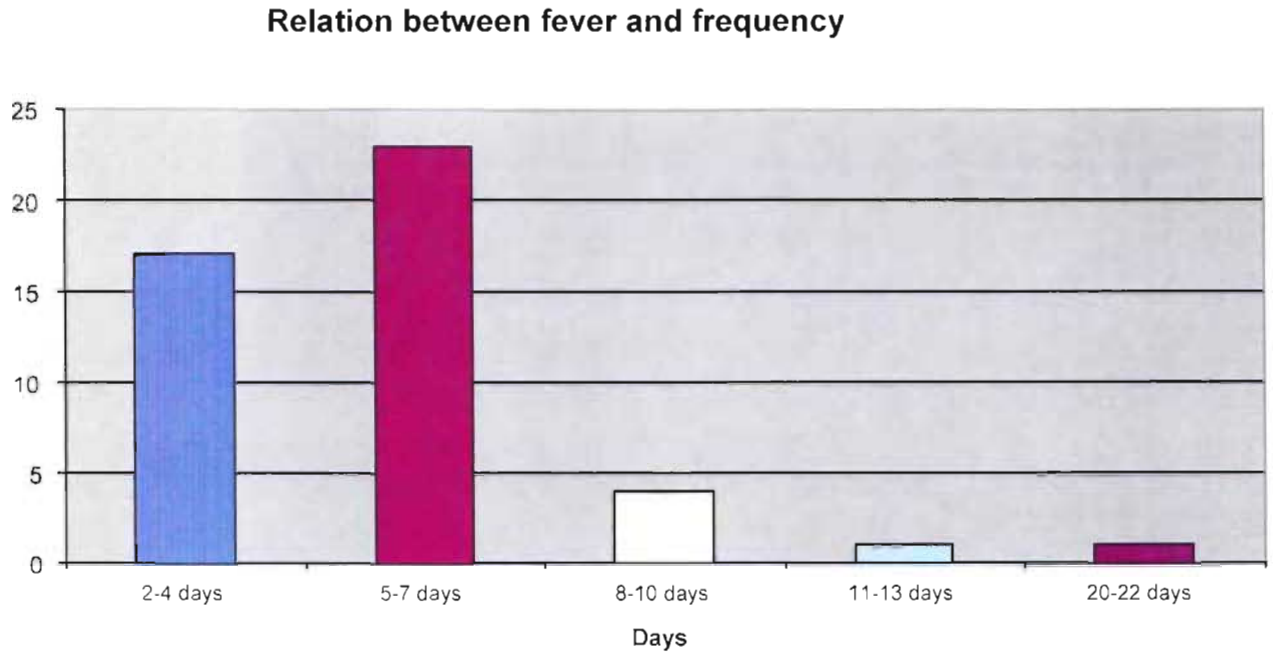


Figure 6: A graph of number of days fever lasted and frequency

Figure 6 shows the number of days fever lasted for different patients. It can be seen that the fever lasted for 5-7 days in most cases. In some cases it took 8-10 days and in few cases even more that.

5.7. A graph of maximum temperature versus frequency

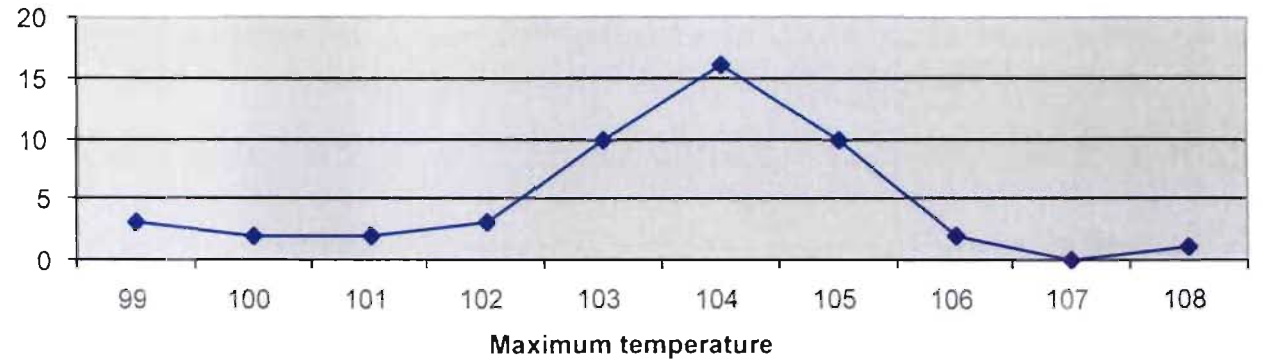


Figure 7: A curve of temperature reached by number of patients.

Figure 7 shows the temperatures reached by the number of patients. The maximum temperature reached by 16 patients was 104°. It follows normal distribution curve where with increasing number of patients' temperature increases at first but later the number of patients' decreases with increasing temperature.

5.8. Relation between afebrile and patient frequency

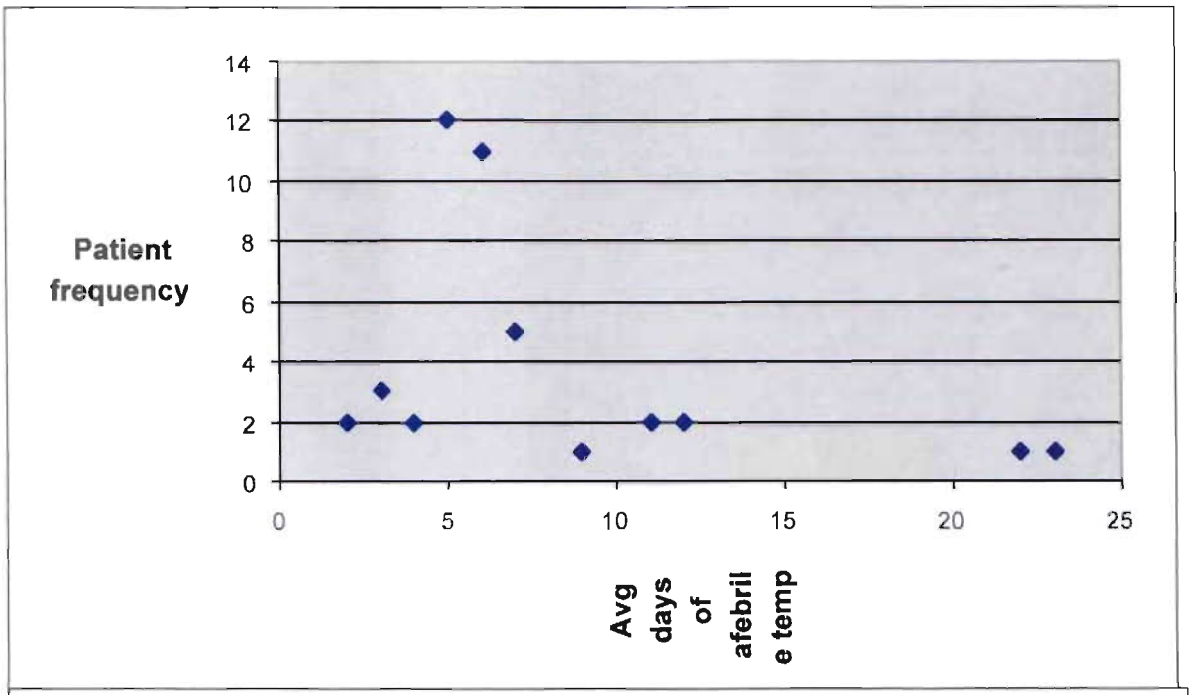


Figure 8: A graph of average day of patient becoming afebrile and frequency

Figure 8 illustrates the average day at which patient became afebrile. It shows the greatest number of patients became afebrile on the 5th day (average).

5.9. A bar graph of drugs used before admission against frequency of patients

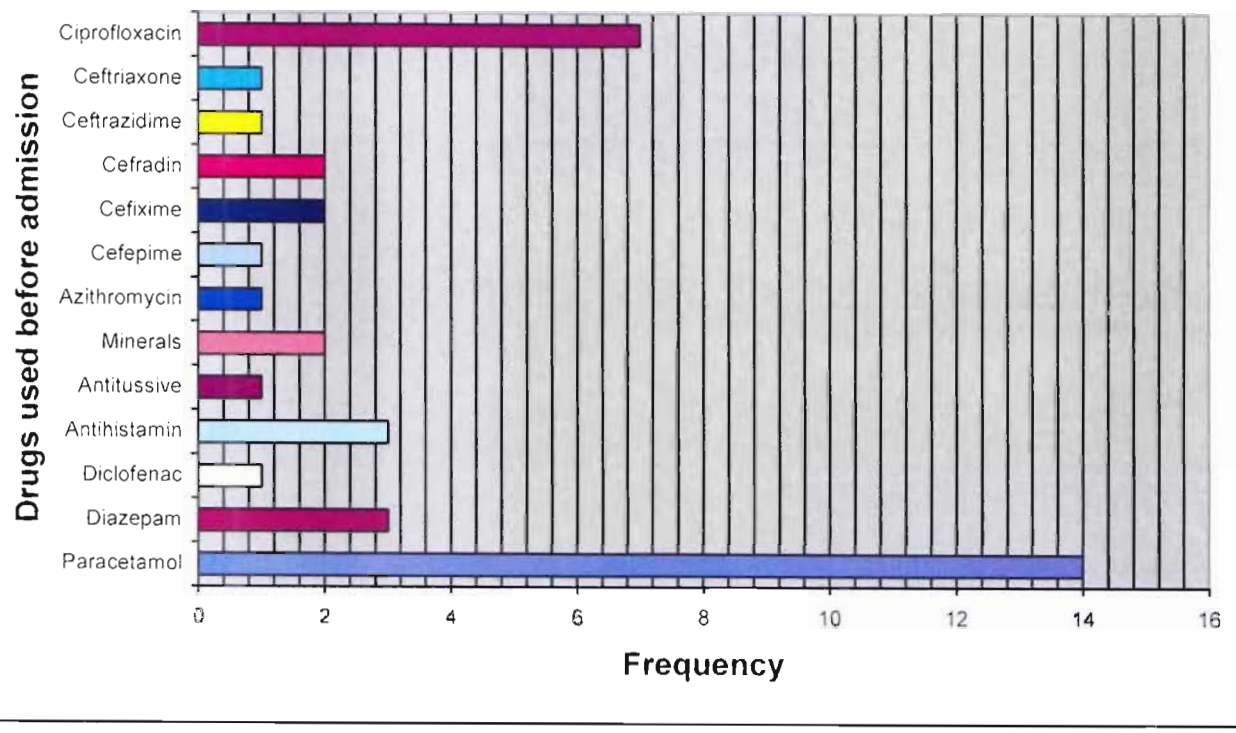


Figure 9: A graph of drugs used by the patients before admission against the number of patients.

Figure 9 shows the number of patients treated with different medicines before they got admitted to the hospital. It is observed that most of them took paracetamol and then ciprofloxacine.

5.10.1. Frequency of patients receiving and not receiving medicine

Table 12

Patients receiving drug before admission	33
Patients not receiving drugs before admission	17

The table above gives the actual numbers of patients receving and not receiving medication before admitted to the hospital.

5.10.2. Percentage of patients treated with medicine before admission

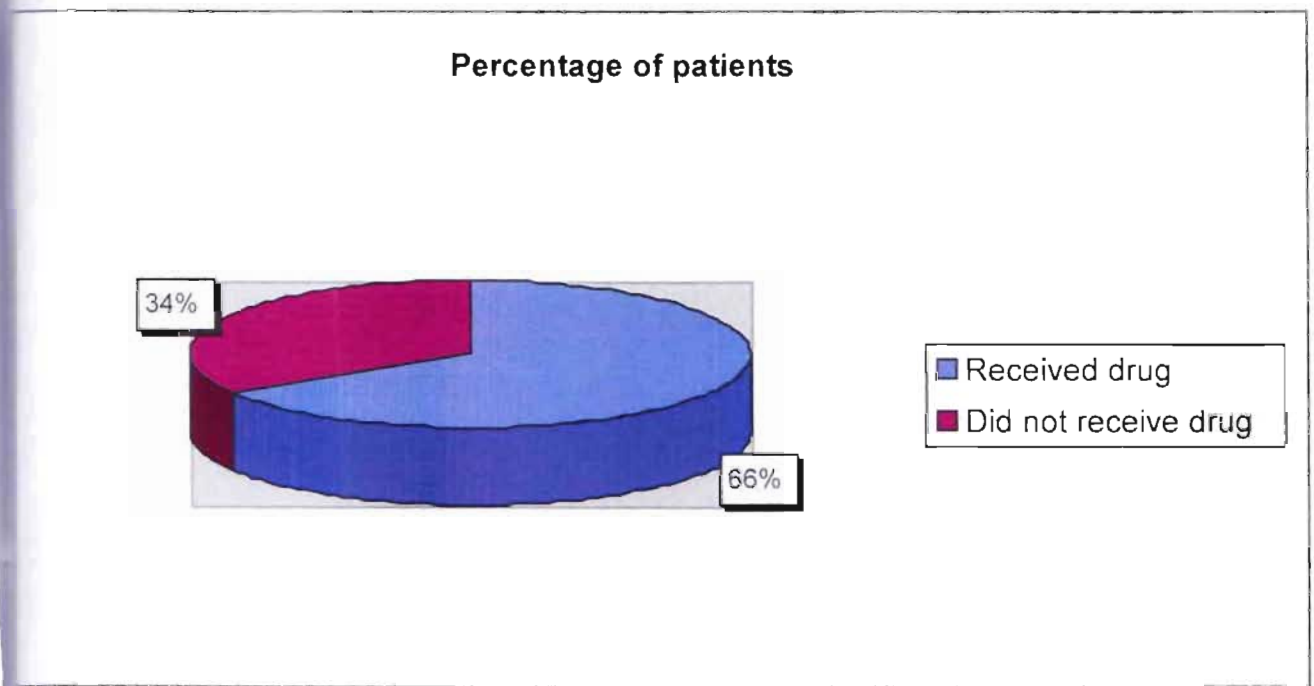


Figure 10: A peichart showing percentage of patients who received drug and percentage of patients who did not receive medication.

Figure 10 shows the percentage of patients receiving and not receiving drugs before admission. 66% of the patients received drug whereas 34% did not. From the data summarization chart. a table can be drawn like this to show the number of patients.

5.11. Relationship between drugs used and day at which afebrile reached

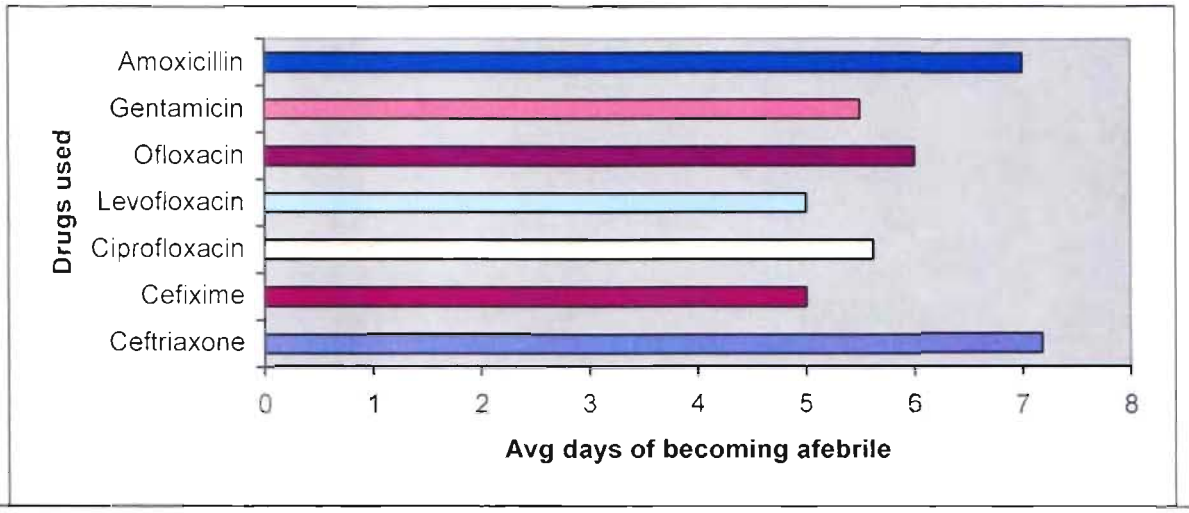


Figure 11: A graphical view of average days it took for patients to become afebrile and drugs responsible for this.

5.12.1. Frequency distribution of antibiotic used in the hospital

Table 13

Drugs used	***Number of patients treated with antibiotics***
Ceftriaxone	34
Cefixime	2
Cefpodoxime proxetil	1
Ciprofloxacin	14
Levofloxacin	1
Ofloxacin	1
Gentamicin	6
Amoxicllin	1
Ampicillin	1

This table shows the actual number of patients taking different types of antibiotics in the hospital. It can be seen that 34 out of 50 patients have been treated with Ceftriaxone. The second mostly used antibiotic is Ciprofloxacin since 14 patients have been treated with it. The least used drugs in the hospital are Ampicillin, Amoxicillin, Levofloxacin, Ofloxacin and Cefpodoxime proxetil.

5.12.2. Percentage distribution of antibiotics used in the hospital

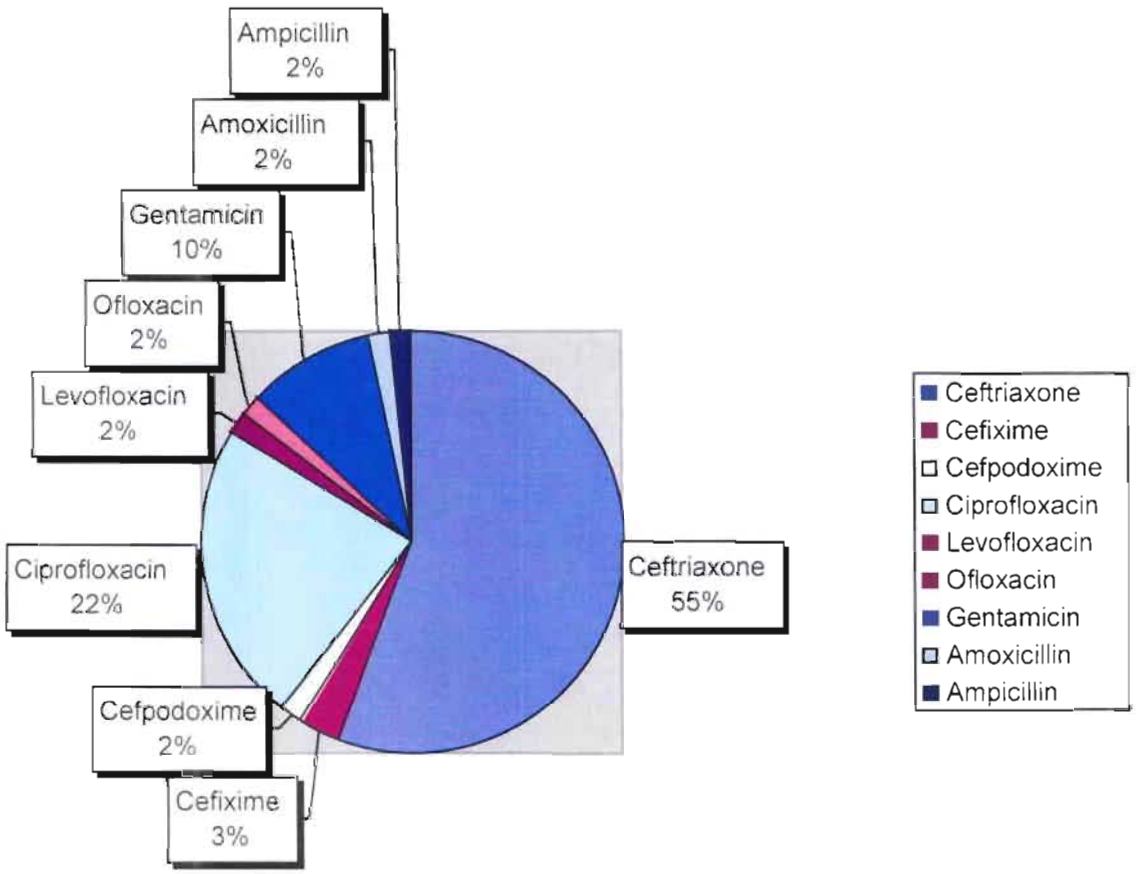


Figure 12: This piechart gives the percentage of patients treated with various antibiotics

Figure 12 illustrates the percentage of patients treated with antibiotics. Ceftriaxone and ciprofloxacin are the mostly used drugs in the hospital.

5.13. Sensitivity pattern of various antibiotics

Table 14

Name of drugs	*Sensitive*	*Resistant*	*Moderate*
Ceftazidime	27	4	1
Cefotaxime	19	3	2
Gentamicin	17	6	1
Cotrimoxazole	13	8	0
Sulphamethoxazole & Trimethoprim	2	3	1
Sulphamethoxazole	3	3	0

The number of patients showing sensitivity pattern to the various antibiotics are shown in the table above among which the third generation Ceftazidime was found to be the most sensitive.

5.13.a. Percentage distribution of sensitivity pattern

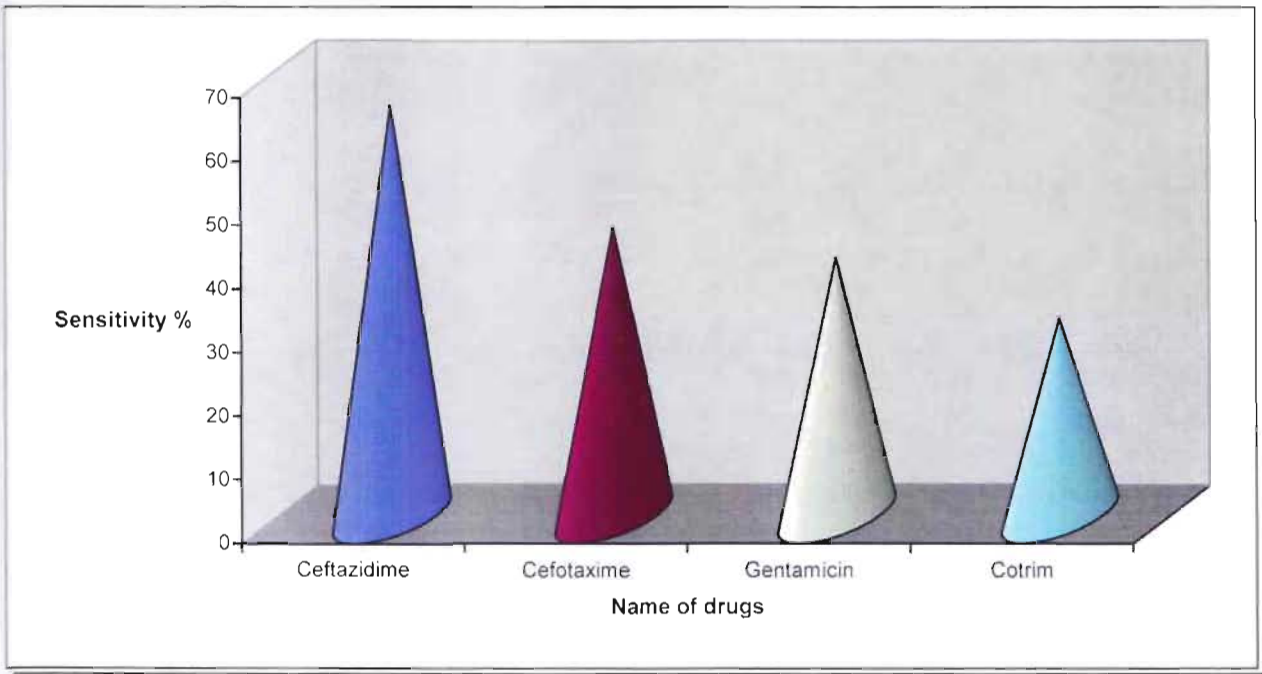


Figure 13 (a): A graph of percentage sensitivity against the four antibiotics. Ceftazidime is the most effective among them.

5.13.b. Percentage distribution of resistance pattern

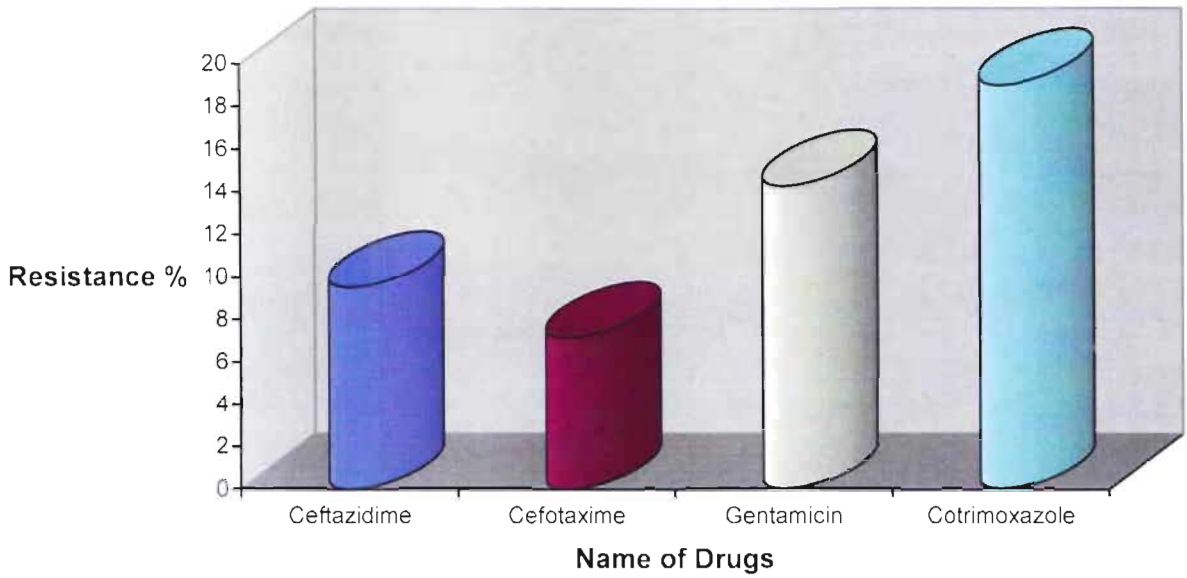


Figure 13 (b): A graph of percentage resistance to the four antibiotics. Cotrimoxazole is the most resistant among them.

5.13.c. Percentage distribution of moderate pattern

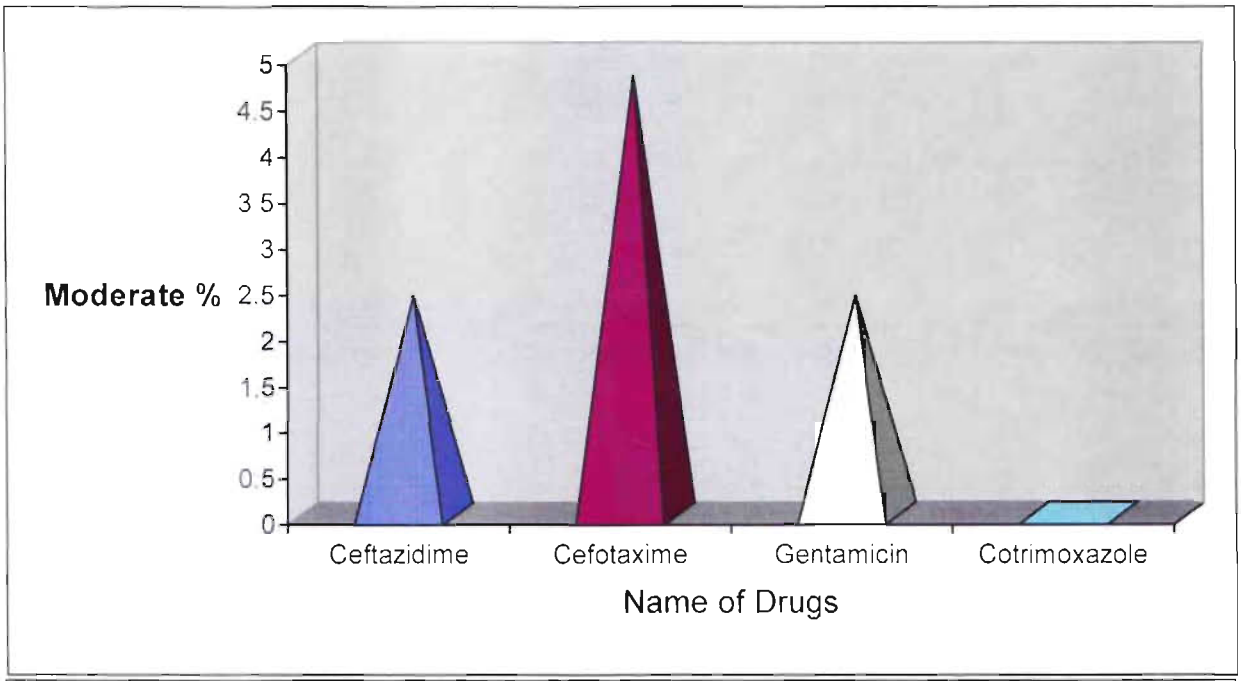


Figure 13 (c): A graph of percentage moderate or intermediate response against the four antibiotics. Cefotaxime is the most moderate antibioitic among them or it gives most intermediate response.

Figure 13 a,b,c shows that all antibiotics are not sensitive and some developed resistance. It can be seen that the most sensitive antibiotic among the four are Ceftazidime, the most moderate is Cefotaxime and the most resistant is Cotrimoxazole. Thus Ceftazidime is the most effective among the four antibiotics compared here.

5.14.a. Sensitivity pattern of Ceftazidime

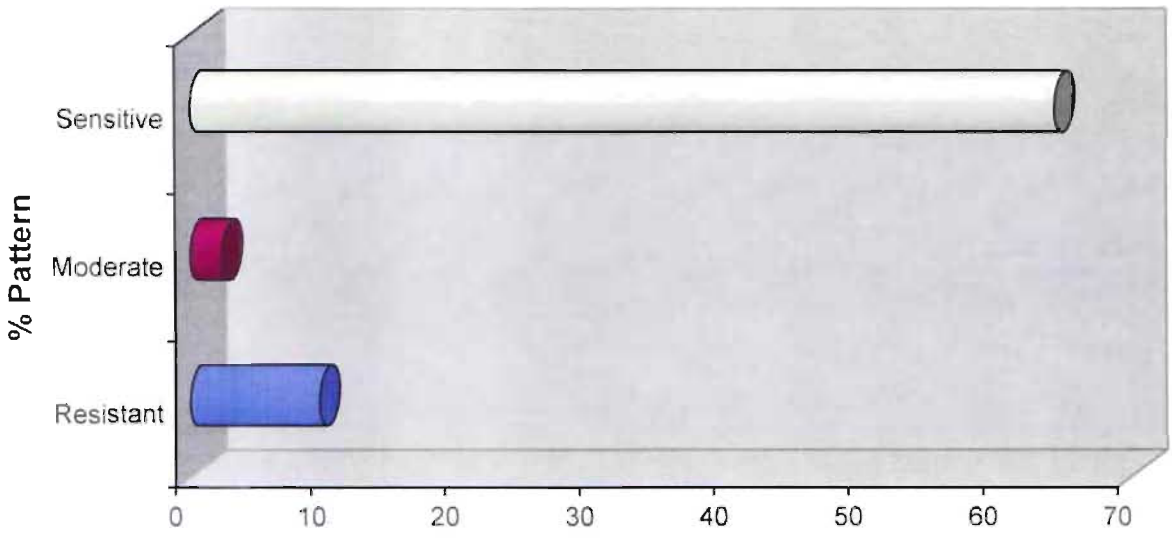


Figure 14 (a): A bar graph showing the sensitivity patterns of Ceftazidime, the most sensitive antibioitic among the four.

5.14.b. Sensitivity pattern of Cefotaxime

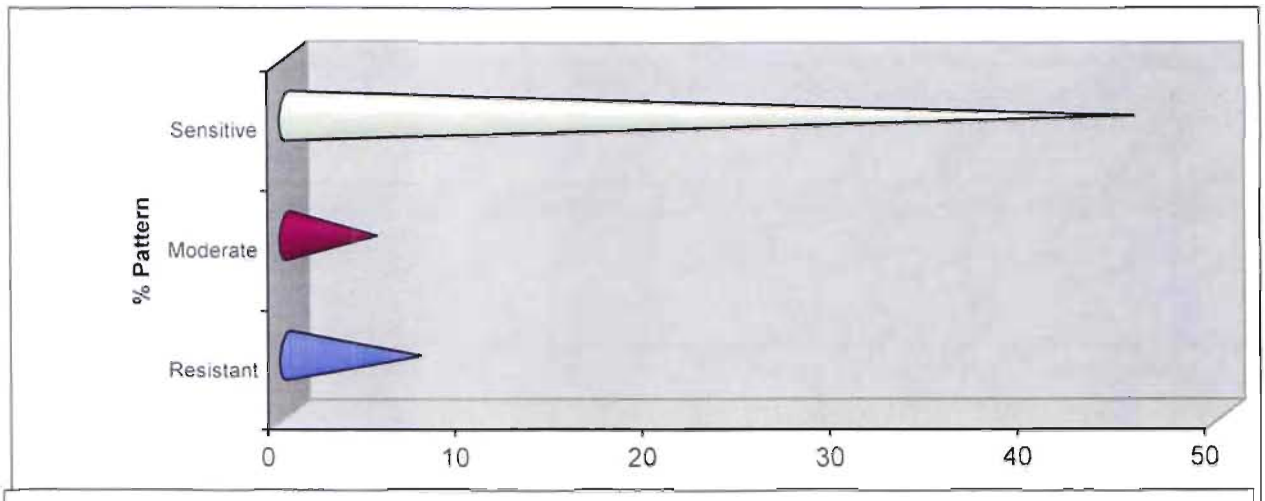


Figure 14 (b): A bar chart showing the sensitivity patterns of the second sensitive antibiotic, Cefotaxime.

5.14.c. Sensitivity pattern of Gentamicin

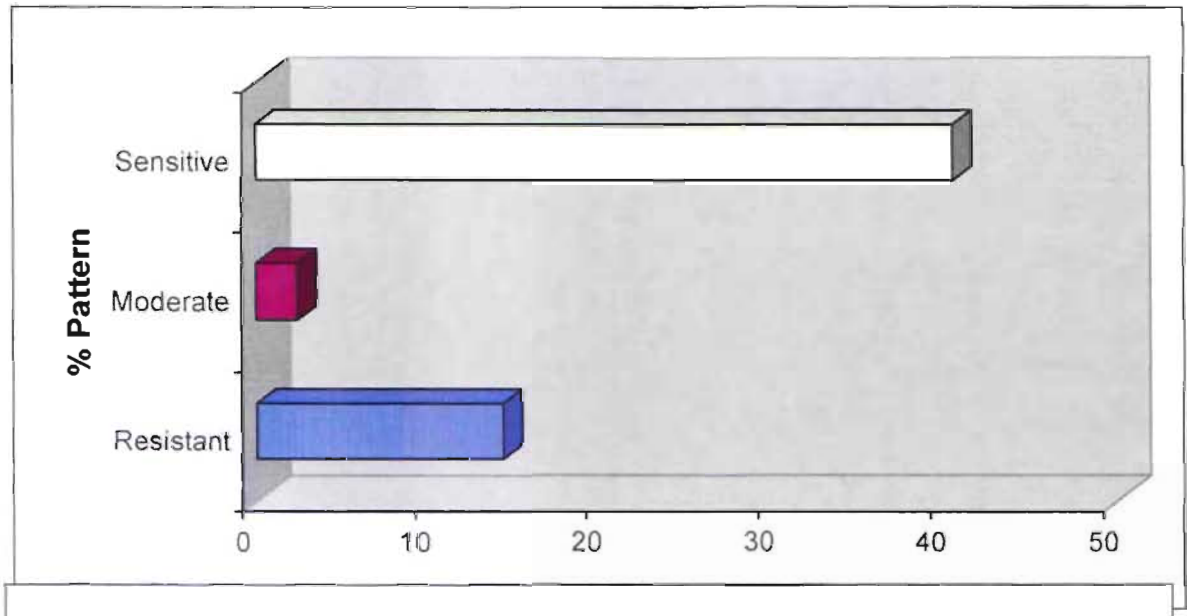


Figure 14 (c): A bar graph illustrating the sensitivity patterns of the aminoglycoside, Gentamicin. It is the second resistant drug among the four.

5.14.d. Sensitivity pattern of Cotrimoxazole

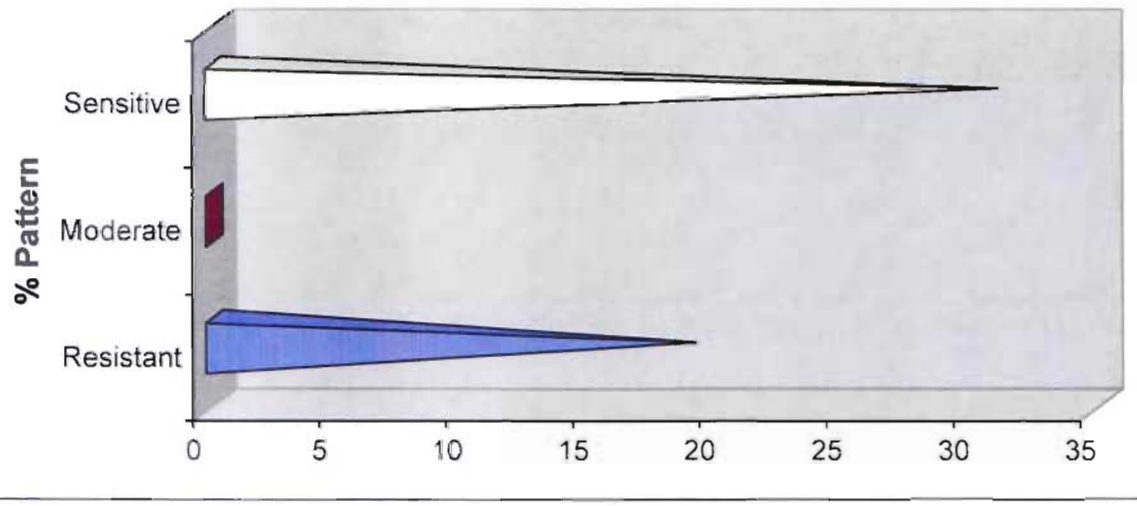


Figure 14 (d): A bar diagram showing the sensitivity pattern of sulpher drug, Cotrimoxazole that seemed to be the most resistant antibiotic here.

Figure 14 shows the sensitivity, resistance and moderate responses of *Salmonella typhi* to each antibiotic in 42 patients. Different antibiotics give different patterns. Ceftazidime seems to be the most effective while cotrimoxazole seems to be the least effective that is the bacteria is most resistant to this drug.

5.15. Percentage distribution of sensitivity pattern of the sulpher drugs

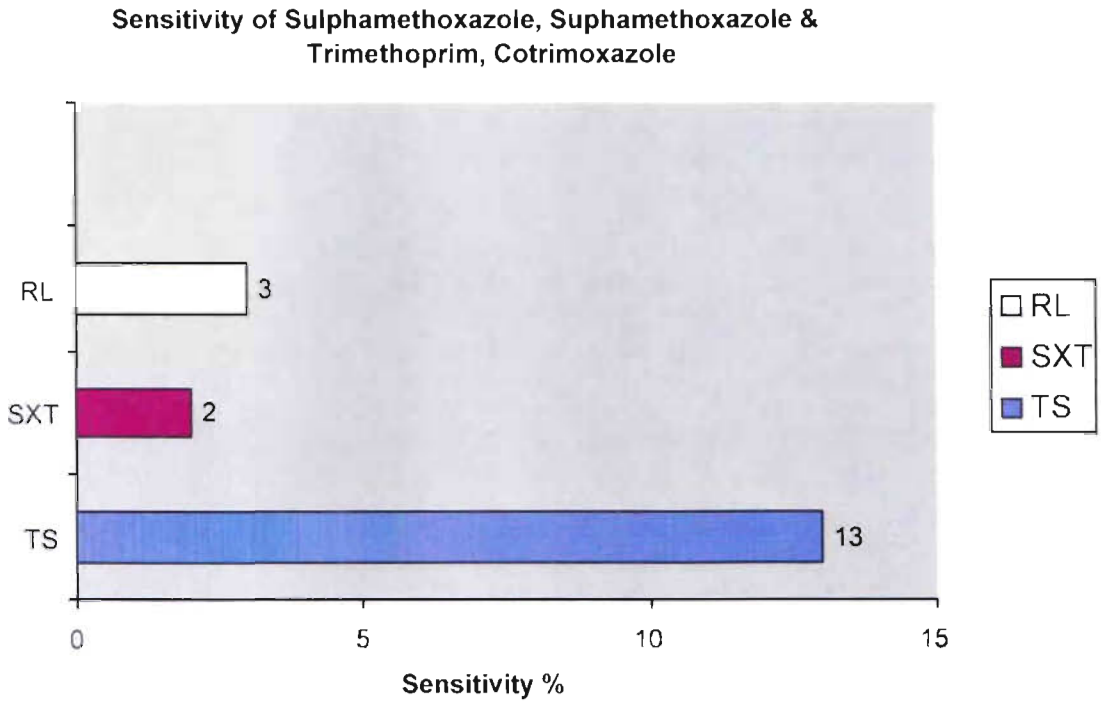


Figure 15: A bar graph showing percentage sensitivity of the sulpher drugs. Cotrimoxazole is the most sensitive here.

Figure 15 compares the sensitivity pattern among the sulpher drugs: Sulphamethoxazole (RL), Suphamethoxazole /Trimethoprim (SXT), and Cotrimoxazole (TS). The combination form (Cotrimoxazole) appeared to be the most sensitive while Sulphamethoxazole taken with Trimethoprim alone seems to be the most resistant.

CHAPTER 6
DISCUSSION

6. DISCUSSION

Typhoid fever was reportedly rare in infancy and early childhood. Only 29 cases in patients under the age of 10 in a total of 214 typhoid admissions to the Ibadan Teaching Hospital Huckstep reported from East Africa a series of 240 cases of which 56 were in children aged between 2 and 15, and only six of these were less than 5. (Mulligan; December 1971). This report contrast markedly with our study of typhoid fever in 50 patients in the hospital, "Instiitute of Child Health and Shishu Sasthya Foundation, Dhaka", where it was found that the age range that was mostly affected was 1-3 years and their weight range was 9-12 kg. Also male children were more prone to typhoid than female children. Our results are consistent with the geographical patterns of typhoid cited in a recent review. Our data also indicate that preschool aged children were more vulnerable to the disease than school aged children. Whereas, in the study of typhoid fever in five Asian countries, the incidence of typhoid fever in pre-school children aged 2-5 years was of the same order of magnitude as that of school children aged 5-15 years. These findings were consistent with earlier work. (Abu-Elyazeed, Acosta, Agtini, Albert, Ali, Baiqing, Bhattacharya, Bhutta, Canh, Clemens, Danovaro-Holiday, Farrar, Galindo, Ochiai, Page, Pang, Seidlein, Shin, Wain; April 2008).

The presentation of typhoid fever in children aged over 5 closely resembles that in older patients. Younger children and infants have more non-specific symptoms. Fever; with or without convulsions, diarrhoea and vomiting, dehydration and anaemia are all common paediatric problems anywhere in the world, and especially in the tropics. Many children with malaria or an infectious disease present with clinical features resemble those of typhoid fever. (Mulligan; December 1971). In addition to this, since dengue cannot be tested before 5 days, there is a chance of misdiagnosing dengue as typhoid fever since symptoms are similar. Thus, diagnosis is very important to identify the disease or else wrong treatment can lead to adverse effect of the antibiotics. In this survey, main symptom 'diarrhoeae' was shown by 29% of the 50 patients and among other symptoms, patients usually suffered from convulsion (20%).

In the article clinical and laboratory presentation of typhoid fever, Mayer and Tarpley reported that, among 75 children, the usual symptoms were fever and abdominal pain with a mean duration of 10.5 days and the eman age was 11.4 years. (Hosoglu, Katar, Ozbek, Tas,

Yalcin, Yaramis, Yildrim; 2001). In our study, the fever lasted for maximum 21 days and minimum 2 days, though in case of most patients it lasted for around 6 days and the mean age of patients was 4.101 years. The maximum temperature reached by greatest number of patients was 105°. Also, most children were treated with Paracetamol and Ciprofloxacin before they got admitted to the hospital and 34% of the patients had not taken any drug before their admission. All these factors about patients, age, weight, symptoms and maximum temperature reached, mostly taken medication and medical history, are all important concerns for the doctors to prescribe the antibiotic.

Besides, sensitivity patterns of various types of antibiotics were taken into considerations. Though multiple resistant *S.typhi* isolates have been reported in many parts of the world, it was not as yet a problem for Turkish isolates. In a study, Phuong et al. reported that, 85% of isolates of *S.typhi* were resistant to Chloramphenicol, Sulphamethoxazole and Tetracycline. In another study, Akan et al. found no resistance to the antibiotics studied except Tetracycline in their isolates of *S.typhi.* Of the 67 blood culture isolates in the clinical study, the percentages of antimicrobial resistance rate were as follows: Ampicillin (17%), Trimethoprim-Sulphamethoxazole (5%), Ceftriaxone (4%), Sulbactam-Ampicillin (6%). There was no resistant to Quinolones and Chloramphenicol. (Hosoglu, Katar, Ozbek, Tas, Yalcin, Yaramis, Yildrim; 2001). In our study, among the following drugs, (Cefotaxime; Ceftazidime, Cotrimoxazole; Gentamicin; Sulphamethoxazole alone; and Sulphamethoxazole with Trimethoprim), the antibiotic that was most sensitive to the *Salmonella typhi* was Ceftazidime – the third generation cephalosporin, showing percentage value of 64.49%. The second most resistant antibiotic was another third generation cephalosporin, Cefotaxime. The antibiotic that was the most resistant was found to be Cotrimoxazole, showing percentage value of 19.05%. An aminoglycoside, Gentamicin was the next resistant antibiotic. It was found that Cotrimoxazole, being a combination of Sulphamethoxazole and Trimethoprim gave much higher sensitive percentage value compared to the two other forms: Sulphamethoxazole alone or Sulphamethoxazole with Trimethoprim individually. This is probably because; the combination form gives synergistic effect.

Since 1989, outbreaks caused by strains of *S.typhi* resistant to chloramphenicol, ampicillin and trimethoprim and with additional resistance to streptomycin, sulfonamides and tetracycline have been reported in many developing countries including Bangladesh. Such

strains have been termed multi-drug resistant (MDR). (Rowe, Threlfall, Ward; 1997). After that, ciprofloxacine or third generation cephalosporins (namely ceftriaxone) have become the first line of treatment for typhoid fever. Since 1997, two cases have demonstrated that strains of the microorganism with decreased susceptibility to Ciprofloxacin were present in Bangladesh. (Asna, Haq, Rahman). In a case study, response to Ceftriaxone was delayed and such a situation raised the question whether *Salmonella typhi* had reduced susceptibility to Ceftriaxone though treatment duration was much shorter. (Cassola, Feasi, MD, Mori, Pontali and Usiglio; 2008).

In contrast to this, in our study, although most patients had taken Paracetamol and Ciprofloxacin and other drugs before their admission to the hospital, there they were treated with the following drugs: Amoxycillin, Cefixime, Ceftriaxone, Ciprofloxacin, Gentamicin, Levofloxacin and Ofloxacin and the average days of afebrile temperature reached was highest in case of Ceftriaxone and Amoxicillin. Despite these, only 1 patient was treated with Amoxicillin, 6 with Gentamicin, 14 with Ciprofloxacin and 34 with Ceftriaxone. This shows defervescence of temperature (fall of temperature below 98.4°F for atleast 48 hours without antipiretic) does not always mean that a patient is clinically cured (fall of temperature along with improvement of well being and physical conditions and improved appetite).

Multi-drug resistant (MDR) typhoid in children poses a major therapeutic dilemma in developing countries where the disorder is fast assuming epidemic proportions. The resistance of *Salmonella typhi* to commonly administered antibiotics is usually plasmid mediated and spreads rapidly. The journey of treating this infectious disease started from Chloramphenicol, Cotrimoxazole and Ampicillin but the high prevalence of MDR in our subcontinent resulted in dependence on fluoroquinolones (Ciprofloxacin) and parenteral third generation cephalosporins for the treatment of typhoid fever in this region. Although antibiotics are the most effective in treating typhoid fever they are expensive, difficult to administer in case of children and besides, the safety of Ciprofloxacin has yet to be established. *(Shakur; 2007)*

CHAPTER 7

CONCLUSION

7. CONCLUSION

Typhoid fever is a major public health problem and one of the leading causes of febrile illness of children in developing countries like Bangladesh. It is defined as temperature >101°F for more than 5 days with symptoms like anaemia, convulsion, vomiting, diarrhoeae, abdominal pain, coated tongue, etc. (Shakur).

Typhoid and paratyphoid are caused by the bacteria Salmonella typhi and Salmonella paratyphi respectively. Paratyphoid is very similar to typhoid, but is usually milder in its symptoms. The bacteria are derived from the faeces of a sufferer from the disease or from a carrier. The disease is spread by water or contaminated food. Typhoid spread needs only a small number of organisms, and is therefore described as having high infectivity. After being swallowed the strains migrate to the lymph glands where they multiply during a ten-day incubation period and then spread into the bloodstream.

Usually children of the age 1-3 years are more prone to the disease than infants or young children. Since other infectious diseases like malaria, dengue, etc have common symptoms of high fever followed by diarrhoeae and vomitting like typhoid, sometimes those diseases are treated as typhoid, thereby leading side effects of the antibiotics used. Suspicion is of paramount importance in the diagnosis of typhoid, and when there is an epidemic greater care should be taken to exclude it in young child who is febrile. Thus, proper diagnosis of typhoid fever or any other diseases is very much important to avoid wrong treatment.

In the sensitivity pattern, out of five antibiotics, the third generation cephalosporin-Ceftazidime was found to be the most sensitive to the microbial strain. The two most important preventive measures of typhoid are proper sewage treatment and purification of water supplies. Contamination of food can be reduced by personal hygiene, hygienic measures in the food trade and in the home, and control of flies, which can transfer faecal material to food. (Green, Soper, Stout, Taylor; Third edition)

Typhoid fever is endemic in Bangladesh. Until the mid 1980s, Ampicillin, Chloramphenicol, Cotrimoxazole, Azithromycin, Gentamicin were the standard treatment of the infectious disease. However in 1990s, resistance to these antibiotics have become

common and referred as multi-drug resistant typhoid. Since then, ciprofloxacine and third generation cephalosporins (namely ceftriaxone) have become the first line of treatment for typhoid fever. Recent study showed delayed response of Ceftriaxone and decreased susceptibility to Ciprofloxacine. MDR enteric fever continues to be a worldwide health problem and the emergence of isolates showing resistance to Ciprofloxacine and Ceftriaxone is a cause of concern for physicians in developing countries. The aminoglycosides, Gentamicin and Amikacin has been found to be cost-effective therapy against MDR typhoid fever. (Mandal, Pal; 2009). Also, Cefpodoxime Proxetil, Cefixime, Ceftazidime can be used for the treatment of typhoid fever. Since resistnce to antibiotics has become a global problem with a major and devastating impact on health care in both developed and developing countries proper use of antibiotics is recommended. Although two vaccines have been licensed, this treatment of vaccination has not been implemented in most typhoid endemic countries despite of low price. Hence, development and implementation of new vaccines should be started to target the sufferers.

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