Typhoid fever and its treatment with sensitivity patterns of various antibiotics

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Certificate

This is to certify that the thesis submitted to the Department of Pharmacy, East West University, Mohakhali, Dhaka in partial fulfillment of the requirements for the degree of bachelor of Pharmacy was carried out by Abdul Maruf Asif Aziz, ID: 2005-3-70-009, 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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Dedication - This thesis paper is dedicated to my parents and my sister

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Abstract

With an estimated 16–33 million cases of annually resulting in 500,000 to 600,000 deaths in endemic areas, the World Health Organization identifies typhoid as a serious public health problem. Its incidence is highest in children and young adults between 5 and 19 years old.

Typhoid fever, also known as *Salmonella Typhi* or typhoid, is an illness. Commonly worldwide, it is transmitted by the ingestion of food or water contaminated with faeces from an infected person. The bacterium grows best at 37 °C/99 °F – human body temperature. Typhoid fever is characterized by a sustained fever as high as 40 °C (104 °F), profuse sweating, gastroenteritis, dehydration and nonbloody diarrhea.

Diagnosis is made by any blood, bone marrow or stool cultures and with the Widal test (demonstration of salmonella antibodies against antigens O-somatic and H-flagella).

Where resistance is common, the treatment of choice is a fluoroquinolone such as ciprofloxacin otherwise, a third-generation cephalosporin such as ceftriaxone or cefotaxime is the first choice. Cefixime is a suitable oral alternative.

Typhoid fever in most cases is not fatal. Antibiotics, such as ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, amoxicillin and ciprofloxacin, have been commonly used to treat typhoid fever in developed countries. Prompt treatment of the disease with antibiotics reduces the case-fatality rate to approximately 1%.

When untreated, typhoid fever persists for three weeks to a month. Death occurs in between 10% and 30% of untreated cases. Though in some case-fatality rates may be as high as 47%.

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Chapter – 1

Introduction

1.1 Background Information on typhoid

Typhoid fever is an acute illness associated with fever caused by the Salmonellae Typhi bacteria. The bacterium is deposited in water or food by a human carrier, and is then spread to other people in the area (Kotton C. MedilinePlus, 2007).

Typhoid Fever is contracted by the ingestion of the bacteria in contaminated food or water. Patients with acute illness can contaminate the surrounding water supply through the stool, which contains a high concentration of bacteria. The bacteria multiply in the gallbladder, bile ducts, or liver and passes into the bowel. The bacteria can survive for weeks in water or dried sewage. These chronic carriers may have no symptoms and can be the source of new outbreaks of typhoid fever for many years (Kotton C, 2007).

After the ingestion of contaminated food or water, the Salmonella bacteria invade the small intestine and enters the blood stream temporarily. It is carried by white blood cells in the liver, spleen, and bone marrow. The bacteria then multiplies in the cells of these organs. Patients develop symptoms including fever, when the organism reenters the blood stream. Bacteria invade the gallbladder, biliary system, and the lymphatic tissue of the bowel. Here, they multiply in high numbers. The incubation period is usually 1-2 weeks and duration of the illness is about 4-6 weeks. The bacteria can be identified for diagnosis in cultures from the stool tested in the laboratory (Kotton C, 2007).

Typhoid fever is a life-threatening illness caused by the bacterium *Salmonella typhi*. In the United States about 400 cases occur each year, and 75% of these are acquired while traveling internationally. Typhoid fever is still common in the developing world, where it affects about 21.5 million persons each year. Typhoid fever can be prevented and can usually be treated with antibiotics.

Typhoid fever is a potentially life-threatening illness that is caused by the bacteria Salmonella typhi (S. typhi). Persons with typhoid fever carry the bacteria in their bloodstream and intestinal tract and can spread the infection directly to other people by contaminating food or water.

Typhoid Fever is an acute illness associated with fever caused by the *Salmonellae* Typhi bacteria. The bacterium is deposited in water or food by a human carrier, and is then spread to other people in the area. The incidence of the illness in the United States has markedly decreased since the early 1900's. This improvement is the result of improved environmental sanitation. Mexico and South America are the most common areas for U.S. citizens to contract typhoid fever. India, Pakistan, Bangladesh and Egypt are also known high risk areas for developing this disease.

In developing countries typhoid and paratyphoid fevers, which are transmitted by the faecal-oral route, are important causes of fever. The enteric fevers are caused by infection with *Salmonella typhi* and *Salmonella paratyphi* A and B. High levels of transmission continue in India, sub-Saharan Africa and Latin America. The bacilli may live in the gall bladder of carriers for months or years after clinical recovery and pass intermittently in the stool and less commonly in the urine. The incubation period of typhoid fever is about 10-14 days. After a few days of bacterium, the bacilli localize mainly in the lymphoid tissue of the small intestine. The typical lesion is in the Peyer's patches and follicles (Cooke FJ, Wain J, Threlfall 2006), (The Eclectic Journal of Medicine)

1.2 Spread of typhoid

Anyone can get typhoid fever if they drink water or eat food contaminated with the S. typhi bacteria. Travelers visiting developing countries are at greatest risk for getting typhoid fever. Typhoid fever is still common in the developing world, where it affects about 12.5 million persons each year. Only about 400 cases occur each year in the United States.

Typhoid Fever is contracted by the ingestion of the bacteria in contaminated food or water. Patients with acute illness can contaminate the surrounding water supply through the stool, which contains a high concentration of the bacteria. Contamination of the water supply can, in turn, taint the food supply. Also, about 3-5% of patients become carriers of the bacteria after the acute illness. Some patients suffer a very mild illness that goes unrecognized. These patients can become long- term carriers of the bacteria. The bacteria multiply in the gallbladder, bile ducts, or liver and passes into the bowel. The bacteria can survive for weeks in water or dried sewage.

These chronic carriers may have no symptoms and can be the source of new outbreaks of typhoid fever for many years (Cooke FJ, Wain J, Threlfall 2006).

Immunization is not routinely recommended for household and close contacts of active cases. Immunization is recommended for household and close contacts of typhoid fever carriers. Two vaccines are currently available: Ty21a (oral vaccine) and ViCPS (parenteral vaccine). We can further consult with DHMH for recommendations regarding use of the appropriate vaccine (Crump JA, Luby SP, Mintz ED. Bull World Health Organ. 2004).

1.3 Education

Educated household members and employees in group settings (e.g., food handlers, daycare staff and personnel in long-term care facilities) to do the following:

- Thorough hand washing with soap and running water before food preparation and eating, after using the bathroom, handling soiled diapers, bed linen, commodes, etc., and personal hygiene in general.
- Use scrupulous cleanliness in food preparation and handling of food, especially salads and other cold-serve foods.
- Make sure to properly refrigerate and store of food (Crump JA, WHO, 2004).

1.4 The cause of spreading

The causing bacteria grow only in the digestive systems and bloodstreams of humans. People who are infected with S. typhi can shed the bacteria in their stools, and people who are not infected can pick up S. enterica typhi from the stools of infected people or from eating or drinking food or liquids that have been contaminated with the stools of infected people. After ingesting S. typhi, the bacteria begin to multiply in the body (Schoenstadt, 2006).

Actual contact and ingestion of stools is very rare. Eating or drinking something contaminated with an infected person's stools is not rare at all. Outbreaks of typhoid fever are occasionally seen

developed areas with clean water supplies and good sewage systems, but are quite common in developing countries where the water used for drinking and washing is not clean and all too often comes in contact with sewage (Crump JA, Mintz ED. Bull World Health Organ. 2004).

We can get typhoid fever by eating or drinking contaminated food or water. Food or water can be contaminated by a food handler with S. typhi, or may be contaminated if sewage accidentally gets into the food or water. Some infected persons may not show any symptoms of typhoid fever but can shed the S. typhi bacteria in their feces for many years. These persons are called typhoid fever "carriers". *S typhi* is only found in humans. Typhoid Fever is contracted by the ingestion of the bacteria in contaminated food or water. Patients with acute illness can contaminate the surrounding water supply through the stool, which contains a high concentration of the bacteria. Contamination of the water supply can, in turn, taint the food supply. Also, about 3-5% of patients become carriers of the bacteria after the acute illness. Some patients suffer a very mild illness that goes unrecognized. These patients can become long- term carriers of the bacteria. The bacterium multiply in the gallbladder, bile ducts, or liver and passes into the bowel. The bacteria can survive for weeks in water or dried sewage. These chronic carriers may have no symptoms and can be the source of new outbreaks of typhoid fever for many years (Crump JA, Mintz ED. Bull World Health Organ. 2004).

1.5 The cause of the disease by the bacterium

After the ingestion of contaminated food or water, the Salmonella bacteria invade the small intestine and enter the blood stream temporarily. It is carried by white blood cells in the liver, spleen, and bone marrow. The bacteria then multiply in the cells of these organs and reenter the blood stream. Patients develop symptoms, including fever, when the organism reenters the blood stream. Bacteria invade the gallbladder, biliary system, and the lymphatic tissue of the bowel. Here, they multiply in high numbers. The bacteria passes into the intestinal tract and can be identified for diagnosis in cultures from the stool tested in the laboratory (Schoenstadt, MD, 2006).

1.6 Treatment and prognosis

Typhoid Fever is treated with antibiotics which kill the *Salmonella* bacteria. Prior to the use of antibiotics, the fatality rate was 10%. Death occurred from overwhelming infection, pneumonia, intestinal bleeding, or intestinal perforation. With antibiotics and supportive care, mortality has been reduced to 1-2%.

Several antibiotics are effective for the treatment of typhoid fever. Chloramphenicol was the original drug of choice for many years. Because of rare serious side effects, Chloramphenicol has been replaced by other effective antibiotics. If relapses occur, patients are retreated with antibiotics.

The carrier state, which occurs in 3-5% of those infected, can be treated with prolonged antibiotics. Often, removal of the gallbladder, the site of chronic infection, will cure the carrier state.

(Arnold L. Lentnek, MD, Division of Infectious Disease, Kennestone Hospital, Marietta, GA.)

1.7 Symptoms after exposure

Symptoms usually occur within 1-2 weeks after exposure to the bacteria, but can occur from 3 days - 3 months after exposure.

Persons with typhoid fever usually have a sustained fever as high as 103 to 104 degrees Fahrenheit (39 to 40 degrees Centigrade).

Chest congestion develops in many patients and abdominal pain and discomfort are common. The fever becomes constant. Improvement occurs in the third and fourth week in those without complications. About 10% of patients have recurrent symptoms (relapse) after feeling better for one to two weeks. Relapses are actually more common in individuals treated with antibiotics (Fery J Rebecca, Encyclopedia of Medicine, 2008)

1.5 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, Bangladesh, 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.

The risk factors include:

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

Drinking water contaminated by sewage that contains S. typhi. (Black RE, et al. *Arch Intern Med*, 1991).

S typhi are able to survive a stomach pH as low as 1.5. Antacids, histamine-2 receptor antagonists (H2 blockers), proton pump inhibitors, gastrectomy, and achlorhydria decrease stomach acidity and facilitate *S typhi* infection.

HIV/AIDS is clearly associated with an increased risk of nontyphoidal *Salmonella* infection; however, the data and opinions in the literature as to whether this is true for *S typhi* infection are conflicting. If an association exists, it is probably minor.

Other risk factors for clinical *S typhi* infection include various genetic polymorphisms. These risk factors often also predispose to other intracellular pathogens. For instance, *PARK2* and *PACGR* code for a protein aggregate that is essential for breaking down the bacterial signaling molecules that dampen the macrophage response. Polymorphisms in their shared regulatory region are found disproportionately in persons infected with *Mycobacterium leprae* and *S typhi*.

On the other hand, protective host mutations also exist. The fimbriae of *S typhi* bind in vitro to cystic fibrosis transmembrane conductance receptor (CFTR), which is expressed on the gut

membrane. Two to 5% of white persons are heterozygous for the CFTR mutation F508 del, which is associated with a decreased susceptibility to typhoid fever, as well as to cholera and tuberculosis. The homozygous F508 del mutation in CFTR is associated with cystic fibrosis. Thus, typhoid fever may contribute to evolutionary pressure that maintains a steady occurrence of cystic fibrosis, just as malaria maintains sickle cell disease in Africa.

Environmental and behavioral risk factors that are independently associated with typhoid fever include eating food from street vendors, living in the same household with someone who has new case of typhoid fever, washing the hands inadequately, sharing food from the same plate, drinking unpurified water, and living in a household that does not have a toilet. As the middle class in south Asia grows, some hospitals there are seeing a large number of typhoid fever cases among relatively well-off university students who live in group households with poor hygiene. American clinicians should keep this in mind, as members of this cohort often come to the United States for higher degrees. (Black RE, et al. *Arch Intern Med.* 1991).

1.9 Clinical features of Typhoid Fever

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 malaise, 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. (Crum NF. Aug 2003).

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 toxaemia increases and the patient may pass into coma and die. Such extreme

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. (Manfredi R, *Infez Med.* 1999)

1.10 Summary of clinically 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 NF. Aug 2003).

1.11 Paratyphoid fever

The course tends to be shorter and milder than that of typhoid fever and the onset is often more abrupt with acute enteritis. The rash may be more abundant and the intestinal complications less frequent. There are three species of Salmonellae that cause paratyphoid: Salmonella paratyphi A, S paratyphi B and S. paratyphi C .They are transmitted by means of contaminated water or food. The paratyphoid bears similarities with typhoid fever, but its course is more benign (Harman, Robin J Pharm press: 2002).

1.12 Pathophysiology of Typhoid Fever

The pathophysiology of typhoid fever is complex and occurs through several stages. Once, the bacteria (Salmonella typhi), survives the acidity of the stomach, it reaches the intestine and invades the Payer's patches of the intestinal wall.Payer's patches are the clusters of cell primarily composed of Macrophages are specialised cells that are essential to kill the bacteria. (Steinberg EB, *Clin Infect Dis*. 2004).

Salmonella Typhi is unaffected by these macrophages but, start survive within the macrophage itself. So, during this asymptomatic incubation period of 7-14 days, the bacteria spread throughout the reticuloendothelial system of liver, spleen, gallbladder, and bone marrow (Steinberg EB, *Clin Infect Dis*. 2004).

The first week of symptomatic period is characterised by progressive elevation of temperature. In the second week, the victim may experience abdominal pain, spleen enlargement and notice Rose spots on his skin. All pathogenic *Salmonella* species are engulfed by phagocytic cells, which then pass them through the mucosa and present them to the macrophages in the lamina propria. Non typhoidal salmonellae are phagocytized throughout the distal ilium and colon. With toll-like receptor (TLR)–5 and TLR-4/MD2/CD-14 complex, macrophages recognize pathogen-associated molecular patterns (PAMPs) such as flagella and lipopolysaccharides. Macrophages and intestinal epithelial cells then attract T cells and neutrophils with interleukin 8 (IL-8), causing inflammation

and suppressing the infection. (Steinberg EB, *Clin Infect Dis*. 2004).

In contrast to the non typhoidal salmonellae, *S typhi* enters the host's system primarily through the distal ilium. *S typhi* has specialized fimbriae that adhere to the epithelium over clusters of lymphoid tissue in the ilium (Peyer patches), the main relay point for macrophages traveling from the gut into the lymphatic system. *S typhi* has a Vi capsular antigen that masks PAMPs, avoiding neutrophil-based inflammation. The bacteria then induce their host macrophages to attract more macrophages.

It co-opts the macrophages' cellular machinery for their own reproduction as it is carried through the mesenteric lymph nodes to the thoracic duct and the lymphatics and then through to the reticuloendothelial tissues of the liver, spleen, bone marrow, and lymph nodes. Once there, the *S typhi* bacteria pause and continue to multiply until some critical density is reached. Afterward, the bacteria induce macrophage apoptosis, breaking out into the bloodstream to invade the rest of the body.

The gallbladder is then infected via either bacteremia or direct extension of *S typhi* –infected bile. The result is that the organism re-enters the gastrointestinal tract in the bile and reinfects Peyer patches. Bacteria that do not reinfect the host are typically shed in the stool and are then available to infect other hosts (Steinberg EB, *Clin Infect Dis*. 2004).

1.13 Complications

Hemorrhage form or a perforation of the ulcerated Peyer's patches may occur at the end of the 2nd week or during the 3rd week of the illness. A drop in temperature to normal or subnormal levels may occur in those with intestinal hemorrhage. This can be falsely reassuring as it occurs even before there is clinical evidence of bleeding such as melaema. Additional complications may involve almost any viscous or system because of the septicaemia presents during the first week; these include cholecytitis, pneumonia, myocarditis, arthritis, osteomyetitis and meningitis. Bone and joint infection is seen, especially in children with sickle-cell disease.

Summary of complications of typhoid fever:

- Bowel irritation and dehydration
- Perforation
- Hemorrhage
- Septicaemic foci-
- Bone and joint infection
- Meningitis
- Cholecytitis
- Toxic phenomena-
- Myocarditis
- Nephritis

(Manfredi R, *Infez Med.* 1999)

1.14 Treatment

Typhoid fever is treated with antibiotics. A person will usually recover in 2-3 days with prompt antibiotic treatment. People that do not get prompt medical treatment may continue to have a

ver for weeks or months, and as many as 20% may die from complications of the infection.

you are being treated for typhoid fever, it is important to do the following:

- Take the prescribed antibiotics for as long as the doctor has asked you to take them.
- Wash your hands carefully with soap and water after using the bathroom
- Do not prepare or serve food to other people.
- Have your doctor collect follow-up stool samples to ensure that no S. typhi bacteria remain in the body.

the first week the diagnosis may be difficult because in this invasive stage with bacterium the mptoms are those of a generalized infection without localizing features. A white blood count y be helpful as there is typically a leucopenia blood culture is the most important diagnostic thod in a suspected. The faeces will contain the organism more frequently during the 2nd and weeks. The widal reaction detects antibodies to the causative organism. However, it is not are ble diagnostic test and should be interpreted with caution, particularly in typhoid-vaccinated dent. (Cooke FJ, Wain J, Threlfall EJ 2006).

14.1 Table 1 Antibiotic treatment of typhoid fever (Cooke FJ, Wain J, Threlfall EJ 2006)

dicine	Amount	Frequency/ Day	Route
rofloxacin	500mg	12 hourly (day)	Orally
trimoxazole	500mg	12 hourly	Two tablets or IV equivalent
ramphenicol	500mg	6 hourly	Orally
oxicillin	750mg	6 hourly	Orally
triaxone	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.

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. (Acharya IL, *N Engl J Med*. Oc(Acharya IL, *N Engl J Med*.1987.)

An intervention study was carried out in Paediatric wards for a period of one year from January 2003 to December 2003 to determine the efficacy and safety of Azithromycin in the treatment of uncomplicated childhood typhoid fever. It was found that once daily administration of oral azithromycin for seven days in the treatment of uncomplicated typhoid fever was effective and reasonably safe.

In a study on Laboratory-based surveillance of Salmonella serotype Typhi infections in the United States: antimicrobial resistance on the rise showed that ciprofloxacin and ceftriaxone are appropriate empirical therapy for suspected typhoid fever. The resistance may be anticipated. Continued monitoring of antimicrobial resistance among Salmonella Typhi strains will help determine vaccination and treatment policies.

1.14.2 Table 2: Different types of antibiotics used in typhoid fever

(Acosta C et al,2003; Cunha BA, 2008; Carcelen A,1989; Frenck RW, 2000)

Drug name	Dose	Contradictions	Interactions	Precautions
1.Chloramphe-nicol	Adult Dose:500 mg PO/IV q4h until defervescence, then q6h for a total course of 14 d Pediatric Dose 50-75 mg/kg/d PO/IV divided q6h	Documented hypersensitivity	Concurrently with barbiturates, chloramphenicol serum levels may decrease while barbiturate levels may increase, causing toxicity; manifestations of hypoglycemia may occur with sulfonylureas;	Use only for indicated infections or as prophylaxis for bacterial infections; serious and fatal blood dyscrasias (eg, aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) can occur;
2.Amoxicillin	Adult Dose 1 g PO q8h Pediatric Dose 20-50 mg/kg/d PO divided q8h for 14 d	Documented hypersensitivity	Reduces the efficacy of oral contraceptives	Adjust dose in renal impairment; may enhance chance of candidiasis

Trimethoprim and sulfamethoxazol	Adult Dose 6.5-10 mg/kg/d PO bid/tid; can be given IV if necessary; 160 mg TMP/800 mg SMZ PO q12h for 10-14 d Pediatric Dose <2 months: Do not administer >2 months: 15-20 mg/kg/d PO, tid/qid for 14 d	Documented hypersensitivity ; megaloblastic anemia due to folate deficiency	May increase PT when used with warfarin (perform coagulation tests and adjust dose accordingly); coadministration with dapsone may increase blood levels of both drugs;	Adjust dose in severe renal impairment; associated with severe colitis.

Azithromycin	Adult Dose 1 g PO once Day 1: 500 mg PO Days 2-5: 250 mg PO qd Pediatric Dose <6 months: Not established >6 months Day 1: 10 mg/kg PO once; not to exceed 500 mg/d	Documented hypersensitivity; hepatic impairment; administration with pimozide	May increase toxicity of theophylline, warfarin, and digoxin; effects are reduced with coadministration of aluminum and/or magnesium antacids; nephrotoxicity may occur when coadministered with cyclosporine	Site reactions can occur with IV route; bacterial or fungal overgrowth may result with prolonged antibiotic use; may increase hepatic enzymes and cholestatic jaundice;

3.Ceftriaxone (Rocephin)	Adult Dose 1-2 g IV q12h Pediatric Dose >7 days: 25-50 mg/kg/d IV/IM; not to exceed 125 mg/d Infants and children: 50-75 mg/kg/d IV/IM divided q12h; not to exceed 2 g/d	Documented hypersensitivity	Probenecid may increase levels; coadministration with ethacrynic acid, furosemide, and aminoglycosides may increase nephrotoxicity	Adjust dose in renal impairment; caution predelivery and in breastfeeding; pseudobiliary lithiasis; non–*Clostridium difficile* diarrhea

Cefoperazone Cefobid	Adult Dose 2-4 g/d IV/IM divided bid; not to exceed 12 g/d Pediatric Dose Not established; 100-150 mg/kg/d IV/IM divided q8-12h; not to exceed 12 g/d (suggested)	Documented hypersensitivity	Probenecid may increase levels; coadministration with furosemide and aminoglycosides may increase nephrotoxicity	Adjust dose in severe renal impairment; has been associated with severe colitis.

Ofloxacin	Adult Dose 200-400 mg PO q12h Pediatric Dose <18 years: Not recommended >18 years: Administer as in adults	Documented hypersensitivity	Antacids, iron salts, and zinc salts may reduce serum levels; administer antacids 2-4 h before or after taking fluoroquinolones	In prolonged therapy, perform periodic evaluations of organ system functions (eg, renal, hepatic, hematopoietic); superinfections may occur with prolonged or repeated antibiotic therapy

Dexamethasone	Adult Dose 3 mg/kg PO/IM/IV initially, followed by 8 doses of 1 mg/kg q6 Pediatric Dose Not established	Documented hypersensitivity ; active bacterial or fungal infection		Increases risk of multiple complications, including severe infections; monitor adrenal insufficiency when tapering drug; abrupt discontinuation of glucocorticoids may cause adrenal crisis;

Levofloxacin	Adult Dose 500 mg PO qd for 7-14 d Pediatric Dose <18 years: Not recommended >18 years: Administer as in adults	Documented hypersensitivity	Antacids, iron salts, and zinc salts may reduce serum levels; administer antacids 2-4 h before or after taking fluoroquinolones ; cimetidine may interfere with metabolism of fluoroquinolones ; reduces therapeutic effects of phenytoin; probenecid may increase serum concentrations;	In prolonged therapy, perform periodic evaluations of organ system functions (eg, renal, hepatic, hematopoietic) ; adjust dose in renal function impairment; superinfections may occur with prolonged or repeated antibiotic therapy.

1.15 Management

Pyrexia may persist for up to five days after the start of specific therapy. The chronic carrier should be treated for four weeks with Ciprofloxacin. Cholecystectomy may be necessary in some cases. When Salmonella typhi is resistant to several different antibiotics, then a patient with a multiple-resistant strain may need two or more different antibiotics at the same time. 10-15% of patients relapses after antibiotic treatment, and may need to be retreated with different antibiotics.

(Fery J Rebecca, 2008)

1.16 Preventive measures

The following steps are performed to protect if someone travel to an area where the disease is common:

1. Get vaccinated against typhoid fever. Both injectable and oral vaccines are available. Visit a doctor or travel clinic to discuss your vaccination options. Vaccines are not 100% effective, so it is important to take the additional measures listed to prevent typhoid fever.

2. Use careful selection of food and drink while you are in a developing country. This will also help protect you from other illnesses such as cholera, dysentery and hepatitis A.

3. Only use clean water. Buy it bottled or make sure it has been brought to a rolling boil for at least one minute before you drink it. Bottled carbonated water is safer than noncarbonated water.

4. Ask for drinks without ice unless the ice is made from bottled or boiled water.

5. Only eat foods that have been thoroughly cooked.

6. Avoid raw vegetables and fruits that cannot be peeled.

7. When you eat raw fruits or vegetables that can be peeled, wash your hands with soap, then peel them yourself. Do not eat the peelings.

8. Avoid foods and beverages from street vendors. Many travelers get sick from food bought from street vendors.

(Fdy. *Epidemiol.* 2008) ;(Fery J Rebecca, 2008)

1.17 Precaution

1. Even if your symptoms go away without treatment, you may still be carrying the *S. typhi* bacteria, and your illness could return and be passed to other people.

2. If you work at a job where you handle food or care for small children, you should not go back to work until a doctor has determined that you no longer carry any *S.typhi* bacteria.

3. Even if you are vaccinated, you should carefully select your food and drink, especially when visiting areas where typhoid fever is common.

(*Wkly. Epidemiol.*2008).

Typhoid Fever at a glance:

- Typhoid Fever is caused by salmonella typhi bacteria.
- Typhoid Fever is contracted by the ingestion of contaminated food or water.
- Diagnosis of typhoid fever is made when the Salmonella bacteria is detected with a stool culture.
- Typhoid Fever is treated with antibiotics.
- Typhoid Fever symptoms are poor appetite, headaches, generalized aches and pains, fever, and lethargy.
- 3-5% of patients become carriers of the bacteria after the acute illness.

(*Wkly. Epidemiol.* 2008)

1.18 Prevalence of Typhoid Fever

Community-based surveillance for typhoid fever in Kamalapur during 2001 found that 49 (5.5%) blood cultures grew Salmonella Typhi. S. Typhi isolations represented 75% of all positive blood cultures; 53% were in children <5 years of age. The overall incidence of typhoid fever was 3.9 cases per 1,000 populations per year; in children <5 years of age, the rate was 18.7 per 1,000 children per year. Children <5 years of age had an 8.9-fold increased likelihood of infection

when compared with all others. Less than 50% of isolates were susceptible to ampicillin, trimoxazole or chloramphenicol. All isolates were susceptible to ciprofloxacin and 98% were susceptible to ceftriaxone. The findings of this report indicate a high burden of disease in this urban population. Age-specific infection rates suggest that vaccination would be most beneficial in the first year of life.

Typhoid fever is both a water-borne and food-borne gastrointestinal infection, with an estimated global prevalence between 16 million and 33 million cases per year, with 700,000 deaths (1, 2). To determine disease incidence within a high-risk population, and to estimate age-specific incidence rates, a 10-month prospective community-based study among an urban poor population in Dhaka was conducted by ICDDR, B.

These are the first community-based epidemiological data on typhoid disease burden from Bangladesh, and they indicate a high burden of disease in this urban population. The greatest incidence of infection was in children <5 years of age. The findings are similar to those of a recent community-based study of typhoid incidence from India. This is in Clinical Pathology Laboratory, ICDDR, B. 2003).

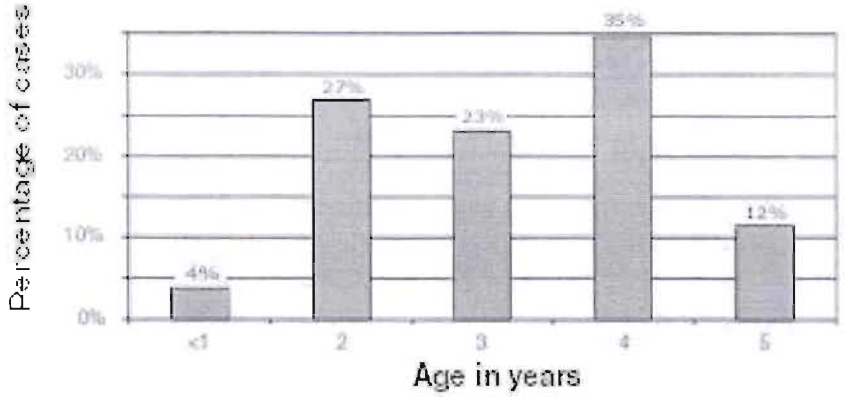
Age-specific infection rates suggest that vaccination would be most beneficial in the first year of life, before infection rates become high during the second and subsequent years of early childhood. For optimal impact contrast with hospital-based studies which have suggested peak incidence in children 5 to 15 years of age (Clinical Pathology Laboratory, ICDDR, B 2003).

A laboratory-based study from Dhaka also showed that 54.5% of S. Typhi isolates were from children <5 years of age. Further study will be required to determine whether dissimilar clinical presentations, healthcare seeking behaviors, or clinical management are responsible for differences observed with hospital-based studies (in Bangladesh and in similar settings, new typhoid vaccines will need to be efficacious and practical for administration to infants.

Surveillance also detected high rates of resistance of S. Typhi to commonly used antimicrobial drugs. It is an important finding that all patients fully recovered, despite some being treated with drugs to which there was in vitro resistance. Systematic evaluation of the impact of in vitro resistance on clinical outcome would be helpful to define the optimal treatment regimen for

uncomplicated (non-hospitalized) typhoid fever in Bangladesh (Clinical Pathology Laboratory, ICDDR, B 2003).

Figure 1: Age distribution of typhoid cases for patients <5 years of age, Kamalapur 2001



1.19 Resistance pattern

Widespread use of fluoroquinolones has resulted in emergence of *Salmonella typhi* strains with decreased susceptibility to fluoroquinolones. These strains are identifiable by their nalidixic acid-resistance. We studied the impact of infection with nalidixic acid-resistant *S. typhi* (NARST) on clinical outcomes in patients with bacteriologically-confirmed typhoid fever.

Clinical and laboratory features, fever clearance time and complications were prospectively studied in patients with blood culture-proven typhoid fever, treated at a tertiary care hospital in north India, during the period from November 2001 to October 2003. Susceptibility to amoxicillin, co-trimoxazole, chloramphenicol, ciprofloxacin and ceftriaxone were tested by disc diffusion method. Minimum inhibitory concentrations (MIC) of ciprofloxacin and ceftriaxone were determined by E-test method.

Typhoid fever is one of the most common febrile illnesses encountered by the physicians in Bangladesh. Diagnosis is not difficult but has lately become a challenge due to changed clinical

ern of the disease, lack of adequate facilities for blood, stool, urine culture, excessive reliance nonspecific Widal test and non availability of any reliable rapid diagnostic tests. Further, the scriminate and injudicious use of antibiotics for treating fever in undiagnosed febrile illnesses y has created problems to the physicians to reach to a diagnosis later on. This has also led to emergence of high level resistance to many of the commonly used antibiotics in our country. floxacin is often used empirically for treating the disease though there is already a high level stance. In this case the organism is in-vitro sensitive to ciprofloxacin but resistant to nalidixic d. Third generation cephalosporins (ceftriaxone and cefixime) are still the effective drugs for ing typhoid fever. The drug needs to be used in proper dose and duration to prevent ergence of resistance. Azithromycin though advocated by many as an alternative to floxacin in resistant cases, has recently lost its credibility due to emergence of resistance. We ld not rely on Widal test in diagnosing typhoid fever. In a suspected case, the patient should be prescribed any antibiotic without sending blood sample for culture sensitivity.

ump JA, *Bull World Health Organ.* 2004)

20 Mechanisms of antibiotic resistance

genes for antibiotic resistance in *S typhi* and *S paratyphi* are acquired from *Escherichia coli* other gram-negative bacteria via plasmids. The plasmids contain cassettes of resistance genes are incorporated into a region of the *Salmonella* genome called an integron. Some plasmids y multiple cassettes and immediately confer resistance to multiple classes of antibiotics. This ains the sudden appearance of MDR strains of *S typhi* and *S paratyphi;* often without mediate strains that have less-extensive resistance (Capoor MR, *J Med Microbiol.* 2007).

initial strains of antibiotic-resistant *S typhi* and *S paratyphi* carried chloramphenicol ltransferase type I, which encodes an enzyme that inactivates chloramphenicol via lation. MDR strains may carry dihydrofolate reductase type VII, which confers resistance to thoprim. The use of nalidixic acid as an in vitro stand-in for fluoroquinolones is unreliable. tions in *gyr* A are the most common form of fluoroquinolone resistance.

hoid fever caused by NARST infection is associated with poor clinical outcomes, probably

due to delay in initiating appropriate antibiotic therapy. Fluoroquinolone breakpoints for *S. typhi* need to be redefined and fluoroquinolones should no longer be used as first-line therapy, if the prevalence of NARST is high.

Typhoid fever is a common illness in developing countries like India and is a potential threat to developed nations, in an era of increasing air travel and global operations. In the absence of appropriate chemotherapy, typhoid fever was often a fatal illness and introduction of effective antibiotic therapy in 1950s led to a sharp decline in the rates of complications and mortality due to typhoid fever. However, in early 1990s multidrug-resistant strains of *Salmonella enterica* serotype *typhi* (MDR-ST) that were resistant to all the three first-line drugs then in use, namely chloramphenicol, amoxicillin and co-trimoxazole emerged, and sooner MDR-ST became endemic in many areas of Asia, including India. This change in pattern of susceptibility was reflected even in places far away, such as the United Kingdom and the United States of America. Fluoroquinolones are very effective against MDR-ST, achieving fever clearance in less than four days with cure rates exceeding 96%, and are currently the first-line drug for the treatment of typhoid fever.

However, towards the end of the last decade, it was observed that fever took longer time than before to clear, and at times surprisingly failed to respond to ciprofloxacin therapy. These isolates had comparatively higher minimal inhibitory concentrations (MIC) of fluoroquinolones, although they were susceptible to fluoroquinolones by conventional disc diffusion testing and recommended MIC breakpoints. Nevertheless, such strains of *S. typhi* are resistant to nalidixic acid and it was noted that clinical response to fluoroquinolones in patients infected with nalidixic acid-resistant *S. typhi* (NARST) was inferior to the response in those infected with nalidixic acid-sensitive *S. typhi* (NASST) strain. However, it is not clear whether fluoroquinolones can still be used as first-line drug for the treatment of typhoid fever, and if used whether this has any adverse impact on clinical outcomes other than treatment failure such as development of complications and morbidity assessed in terms of total duration of illness. In this scenario, the present study was undertaken to evaluate the impact of infection with NARST on clinical outcomes in patients with typhoid fever. (Capoor MR, *J Med Microbiol*.2007)

2.1 Awareness

Sanitation and hygiene are the critical measures that can be taken to prevent typhoid. Typhoid does not affect animals and therefore transmission is only from human to human. Typhoid can only spread in environments where human feces or urine are able to come into contact with food or drinking water. Careful food preparation and washing of hands are therefore crucial to preventing typhoid. (*Wkly. Epidemiol.* 2008).

There are two vaccines currently recommended by the World Health Organization for the prevention of typhoid: these are the live, oral vaccine (sold as *Vivotif Berna*) and the injectable Typhoid polysaccharide vaccine (sold as *Typhim Vi* by Sanofi Pasteur and *Typherix* by GlaxoSmithKline). Both are between 50 to 80% protective and are recommended for travelers to areas where typhoid is endemic. There exists an older killed whole-cell vaccine that is still used in countries where the newer preparations are not available, but this vaccine is no longer recommended for use, because it has a higher rate of side effects (mainly pain and inflammation at the site of the injection). (*Wkly. Epidemiol.* 2008).

2.2 Natural Home Remedies for Typhoid Fever

- Complete bed rest is essential.
- Patient should be kept on a liquid diet of orange, barley juice and milk. Orange juice especially hastens recovery as it increases energy, promotes body resistance and increases urinary output. Administer warm water enema regularly.
- Apply cold compress to head if temperature rises above 103 degree Fahrenheit. Or wrap the body and legs twice with a sheet wrung in cold water and then cover it with a warm material. The pack should be kept for an hour and renewed after every 3 hours. Hot water bottles may be applied to the sides of the body and feet.
- Fresh fruits and easily digestible foods can be given after temperature comes down to normal.

- Plain water or unsweetened lemon water can be used for drinking

(Breakey WR, *Br Med J.* Aug 06)

23 Control

Exclusion from work and social activities should be considered for symptomatic, and asymptomatic, people who are: Food handlers, healthcare/daycare staff who are involved in patient care and/or child care, children attending unsanitary daycare centers, and older children who are unable to implement good standards of personal hygiene. The exclusion applies until two consecutive stool specimens are taken from the infected patient and are reported negative. Control requires treatment of antibiotics and vaccines prescribed by a doctor. Major control treatments for Typhoid fever include Ciprofloxacin for seven to eight days or Ceftriaxone/Cefotaxime for 5 to 6 days or Azithromycin.

(Fery J Rebecca, Oct 2008).

Chapter - 2

OBJECTIVE OF THE STUDY

Typhoid fever is a bacterial disease, caused by *Salmonella typhi*. It is transmitted through the ingestion of food or drink contaminated by the faeces or urine of infected people. Symptoms usually develop 1–3 weeks after exposure, and may be mild or severe. Typhoid fever can be treated with antibiotics. However, resistance to common antimicrobials is widespread.

In developing world food or water can be contaminated by a food handler with S. typhi, or may be contaminated if sewage accidentally gets into the food or water. Some infected persons may not show any symptoms of typhoid fever but can shed the S. typhi bacteria in their faeces for many years. These persons are called typhoid fever "carriers". *S typhi* is only found in humans. Patients with acute illness can contaminate the surrounding water supply through the stool, which contains a high concentration of the bacteria. Also, about 3-5% of patients become carriers of the bacteria after the acute illness. Some patients suffer a very mild illness that goes unrecognized. These patients can become long- term carriers of the bacteria. The bacterium multiply in the gallbladder, bile ducts, or liver and passes into the bowel. The bacteria can survive for weeks in water or dried sewage. These chronic carriers may have no symptoms and can be the source of new outbreaks of typhoid fever for many years. Thus it can be very fatal and risky.

In this scenario, the present study was undertaken to evaluate the impact of infection and sensitivity of various antibiotics on clinical outcomes in patients with typhoid fever.

The present study was designed to assess:

- Widely used antibiotics in treating typhoid fever.
- The sensitivity pattern of various antibiotics against typhoid fever.
- The resistance pattern of various antibiotics against typhoid fever.

SIGNIFICANCE OF THE STUDY

Typhoid fever, also known as enteric fever, is a potentially fatal multisystemic illness caused primarily by *Salmonella typhi*. The protean manifestations of typhoid fever make this disease a true diagnostic challenge. It is a global health problem that can have a devastating impact on resource-poor countries. Typhoid fever is both a water-borne and food-borne gastrointestinal infection.

Typhoid fever occurs worldwide, primarily in developing nations whose sanitary conditions are poor. Typhoid fever is endemic in Asia, Africa, Latin America, and the Caribbean countries. Typhoid fever infects roughly 21.6 million people and kills an estimated 200,000 people every year.

The epidemiology of typhoid fever and other enteric fevers primarily involves person-to-person spread because these organisms lack a significant animal reservoir. Contamination with human feces is the major mode of spread, and the usual vehicle is contaminated water. Occasionally, contaminated food (usually handled by an individual who harbors *S. typhi*) may be the vehicle.

Prevalence of typhoid fever in Bangladesh is increasing day by day and mostly children's are affected rather than older person. Environmental factors such as, lacking of health hygienic, poor sanitation water, street food habits are mainly associated with typhoid fever.

This study is expected to provide important information to better understand the sensitivity and resistant pattern of various antibiotics associated with typhoid fever. Also on the types of antibiotics used to treat this infection. Thus, the result of the study is expected to improve the knowledge of management of typhoid disease and people's health consciousness, which ultimately will help to improve the disease management process. On the other hand it will help us to understand the effect of irrational uses of drugs that lead to resistant. Thus we move on to the search of better antibiotics in the treatment of typhoid.

Chapter - 3

MATERIALS AND METHODS

3.1 Place of study

The study was a retrospective study and all the case histories were collected from the library of Institution of Child Health & Shishu Sasthya Foundation Hospital, Mirpur-2, Dhaka. Only old and stored files of *Salmonella typhi* positive patients were collected.

3.2 Study Period

The study period was one and half year.

3.3 Project Protocol/ title

Before making and formatting the data collection paper project protocol was made comprising of all important criteria's.

3.4 List of antibiotics used in the treatment of Typhoid fever

All antibiotics used in the treatment of typhoid fever caused by *Salmonella typhi* was found and listed accordingly with correct dose and dosage form. The following antibiotics are:

Ceptazidime, Netilmicin, Ceftriaxone, Ciprofloxacin, Cephradine, Cotrimoxazole, Cloxacillin, Amikacin, Cephalexin, Ampicillin, Gentamicin, Chloramphenicol, Amoxicillin, Cefotaxime, Trimethoprim, Sulphamethoxazole.

3.5 Research Design

The study was a descriptive and retrospective (history) study; in which 50 patients with Typhoid Fever were taken within the age limit of 0-10 years old.

3.6 Data Collection and Sample Characteristics

The sample was collected from the Institution of Child Health & Shishu Sasthya Foundation Hospital, Mirpur-2, Dhaka from 1st January to 30th June, 2008. Fifty subjects meeting the following inclusion and exclusion criteria were sampled from patient's history booklet:

Inclusion criteria:

- Patient : With Typhoid Fever
- Age : From 0-10 years
- Weight
- Sex: Both male and female
- The case history will include the following parameters:
- Clinical
- Non – clinical
- Clinical parameters includes:
- Sign and symptoms.
- Pathological state.
- Past history.
- Patient complains.

Exclusion Criteria:

Patients with other clinical complication other than Typhoid Fever were excluded from the study. E.g. Non-Salmonella Typhoid or other clinical and pathological conditions.

3.7 Data collection paper (DCP)

The data collection paper was them made in order to compile all the information and clinical history of the patient in an organized manner.

The data collection paper (DCP) contains the following initial evaluation data:

- Name of the patient
- Address
- Date of admission
- Date of discharge
- Present complaints
- Fever
- Abdominal pain
- Vomiting
- Diarrhea
- Constipation
- Cough
- Respiratory distress
- Maximum temperature reached
- Drug received before admission
- Others
- History of illness

- Feeding history
- Immunization history
- History of past illness
- History of past medication
- Socio – economic history
- General examination
- Provisional diagnosis
- Differential diagnosis
- Investigations
- Final diagnosis
- Culture and sensitivity pattern
- Treatment
- Day at which temperature become a febrile.

From the patient history booklet (Institution of Child Health & Shishu Sasthya Foundation Hospital) the data collection paper is filled correctly. Then all the information in the sheet is summarized and all the parameters are tabulated to organize the information uniformly so that statistical analysis can be done to draw conclusion and to find the result of the whole study.

3.8 Laboratory Investigation

After collecting all the blood samples and stool, laboratory analysis were done in Institution of Child Health & Shishu Sasthya Foundation Hospital, Mirpur; Dhaka. The semi-automated machine, automated machine, other devices and chemical reagents were used for the determination of microorganism and the causative agent.

The **following procedures were involved while laboratory investigation**:

- Collection of specimens
- Isolation of the organism
- CBC
- Urine Diazo Test
- Blood culture
- Clot culture
- Culture of faeces
- Urine culture
- Cultural characters
- Slide agglutination
- Antimicrobial susceptibility testing
- Detection of antibodies
- Widal test
- Preparation of antigen
- Diagnosis of chronic typhoid carriers

3.9 Demographic history of the patient

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

3.10 Patient's Family History

The family history of the patient contains:

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

3.11 Patient's Personal Information

Patient's personal information contains the following features:

- Name
- Age
- Sex
- Weight
- Education
- Address
- Date of admission
- Discharge date
- Maximum temperature reached
- Fever start (day)
- Fever end (day)
- Hand washing practice
- Nail cutting practice
- Personal cleanliness
- Vaccination status
- Outer food habits (street or open food)
- Sanitation and hygiene

3.12 History of present illness (complains during admission)

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

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

- Hours before passed last urine
- What vaccine has the child received (dose and booster)
- Drugs/ antibiotics (dose) received before admission.

3.13 Different Antibiotics used before admission by the patient

Various antibiotics were being used by the patient before admission to the hospital. The names of the antibiotics are:

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

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

3.14 Hospital treatment and courses

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

3.15 Use of Different Antibiotics during treatment course

All patients did not receive the same antibiotics and also the dosage forms. Antibiotic therapy was given according to the protocol. However, receiving of the antibiotics to the patients mainly depends on the patient's condition. In most of the cases antibiotics that were given are:

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

3.16 Table 3 Sensitivity pattern paper and its format

Name of the Patient.and ID	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Ceftazidime (CAZ)							
Netilmicin (NET)							
Ceftriaxone (CRO)							
Ciprofloxacin (CIP)							

furatoin F)							
penem IPM)							
thromycin TH/AZM)							
phradine CRD)							
idixic Acid A)							
rimoxazole S)							
reonam TM)							
phalexin L)							
picillin MP)							
ntamicin N/CN/GM)							
lorampheni l (C)							

Sulphamethoxazole Trimethoprim (SXT)							
Sulfamethoxazole (RL/ SXT)							
Cefotaxime (CTX)							

3.17 Statistical Analysis (Graphical/ statistical form)

Data were analyzed by using Microsoft Excel. All the data of the study sample was entered from each patient's data collection paper (DCP). Descriptive statistics were done for major variables of interest including the age, weight, sex, clinical improvement, drugs/ antibiotics used before admission, day on which temperature subsided, max temperature reached, day on which temperature became a febrile, sign and symptoms, day on which patient discharge, duration of hospitalization in days of patients and sensitivity and resistant pattern of different antibiotics that are used against typhoid fever. Finally a data summarization chart has been made from the data on the data collecting paper.

3.18 Table 4 Data summarization paper and its format

ient name and pital ID	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
e							
ight (kg)							
x							
ver (days)							
dominal Pain							
miting							
rrhea							
nstipation							
spiratory stress							
ghest mperature ched							
hers							
dicine given ore admission							
tment given							
sitivity pattern							

al test							
at which erature e afebrile							
of discharge							

3.19 Variables Outcome

The following factors were considered to find outcome variables from the whole study:

- ✓ Clinical improvement of patient
- ✓ Improvement in sign and symptoms
- ✓ Antibiotics used (Multiple/ Single therapy)
- ✓ Max temperature reached
- ✓ Day on which body temperature subsided
- ✓ Day on which body temperature became a febrile
- ✓ Pulse rate
- ✓ Day on which patient discharge
- ✓ Sensitivity and resistant pattern of various antibiotics against typhoid fever.

3.20 Final outcome

Finally after data collection, sorting, tabulation, statistical and graphical presentation, etc conclusion and summarization of this study is drawn and the result is thus found. Then considering all the parameters like age, weight, gender, temperature, sign & symptoms, complications, day at which afebrile, previously used drugs & antibiotics, treatment received, etc statistical analysis was done to get a clear idea about the outcome of this study.

3.21 Table 5 Case Report form

Study Name: Investigation on the sensitivity of various antibiotics against Typhoid fever

PATIENT HISTORY

1. 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:.....

12. PRESENT COMPLAINTS:

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

13. HISTORY OR PRESENT ILLNESS (Elaborate history):

.....

.....

.....

14. FEEDING HISTORY:

Breast Milk ☐ Milk Formula ☐ Mixed Feeding ☐

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

15. IMMUNIZATION HISTORY:

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

5. MMR ☐ 6. Chicken pox ☐ 7. Others ☐

16. HISTORY OF PAST ILLNESS:

.....

.....

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

.....

8. SOCIO-ECONOMIC HISTORY: .....

.....

9. GENERAL EXAMINATION:

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

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

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

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

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

10. PROVISIONAL DIAGNOSIS:.....

.....

.....

11. DIFFERENTIAL DIAGNOSIS: .....

.....

12. INVESTIGATIONS: .....

.....

.....

.....

3. FINAL DIAGNOSIS:

.....

.....

.....

.....

4. TREATMENT **DOSE**

1. Ciprofloxacin (Inj / Syr / Tab / Cap) ☐ .....
2. Cefixime (Inj / Syr / Tab / Cap) ☐ .....
3. Ceftriaxone (Inj / Syr / Tab / Cap) ☐ .....
4. Ceftazidime (Inj / Syr / Tab / Cap) ☐ .....
5. Cotrimoxazole (Inj / Syr / Tab / Cap) ☐ .....
6. Cephalexin (Inj / Syr / Tab / Cap) ☐ .....
7. Cefotaxime (Inj / Syr / Tab / Cap) ☐ .....
8. Chloramphenicol (Inj / Syr / Tab / Cap) ☐ .....
9. Ampicillin (Inj / Syr / Tab / Cap) ☐ .....
10. Azithromycin (Inj / Syr / Tab / Cap) ☐ .....
11. Amoxicillin (Inj / Syr / Tab / Cap) ☐ .....
12. Aztreonam (Inj / Syr / Tab / Cap) ☐ .....
13. Gentamicin (Inj / Syr / Tab / Cap) ☐ .....
14. Imipenem (Inj / Syr / Tab / Cap) ☐ .....
15. Levofloxacin (Inj / Syr / Tab / Cap) ☐ .....

16. Ofloxacin (Inj / Syr / Tab / Cap) ☐ .....

17. Netilmicin (Inj / Syr / Tab / Cap) ☐ .....

18. Others: (Inj / Syr / Tab / Cap) ☐ .....

15. IDENTITY OF DATA COLLECTOR:

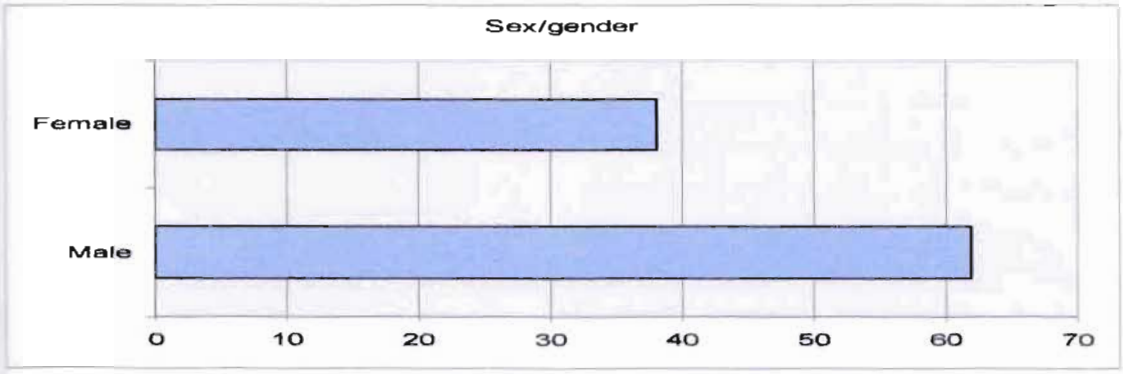
Name:..... Signature:.....

Date of data collection: .....

Chapter 4

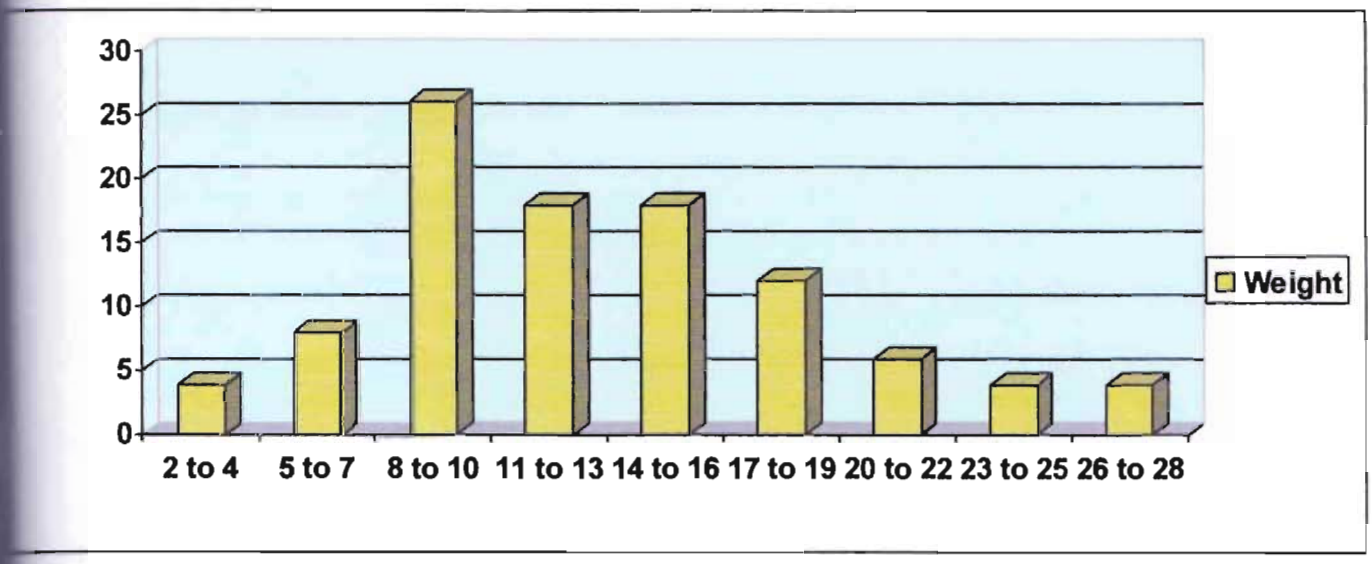
Results

Fig: 4.1 % Distribution of Typhoid fever among male and female children patients (n=50)



In fig: 4.1 62 % male and 38 % female patients out of 50 patients.

Fig: 4.2 % distribution of weight (Kg) among the patients (n=50)



In fig: 4.2 the weight of 26% patients was within the range 8-12 kg.

Table: 4.3 % Distribution of age (years) among the patients (n=50)

Range (years)	Percentage (%)
1-2	42
3-4	32
5-6	12
7-8	10
9-10	4

In fig: 4.3 the age of 42 % patients were within the range 1-2 years.

Fig: 4.4 Statistical representation of age (years) (n=50)

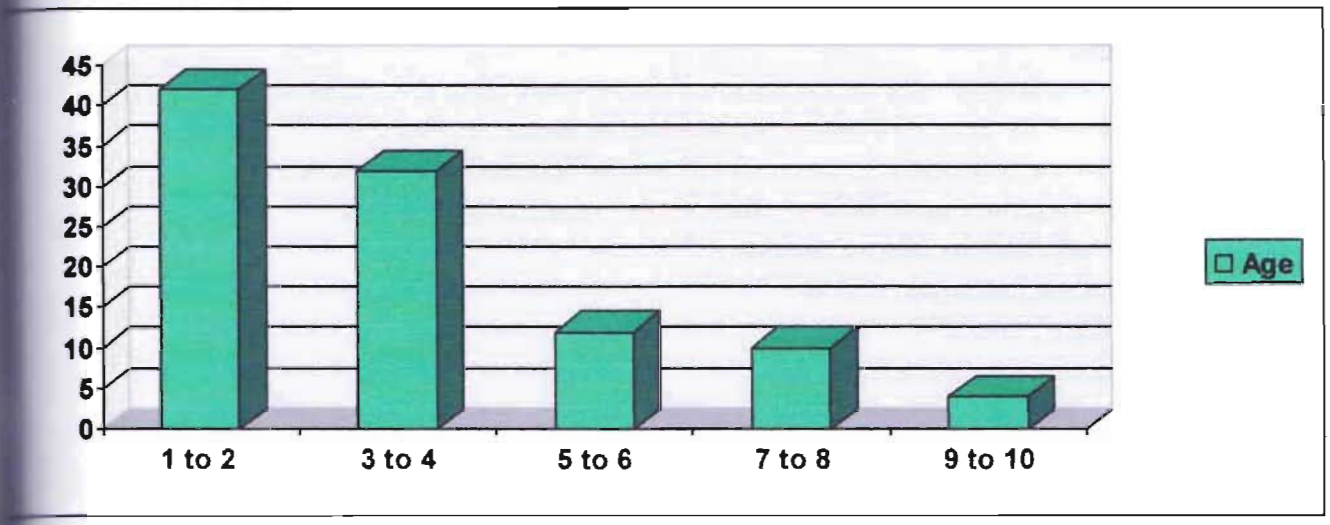
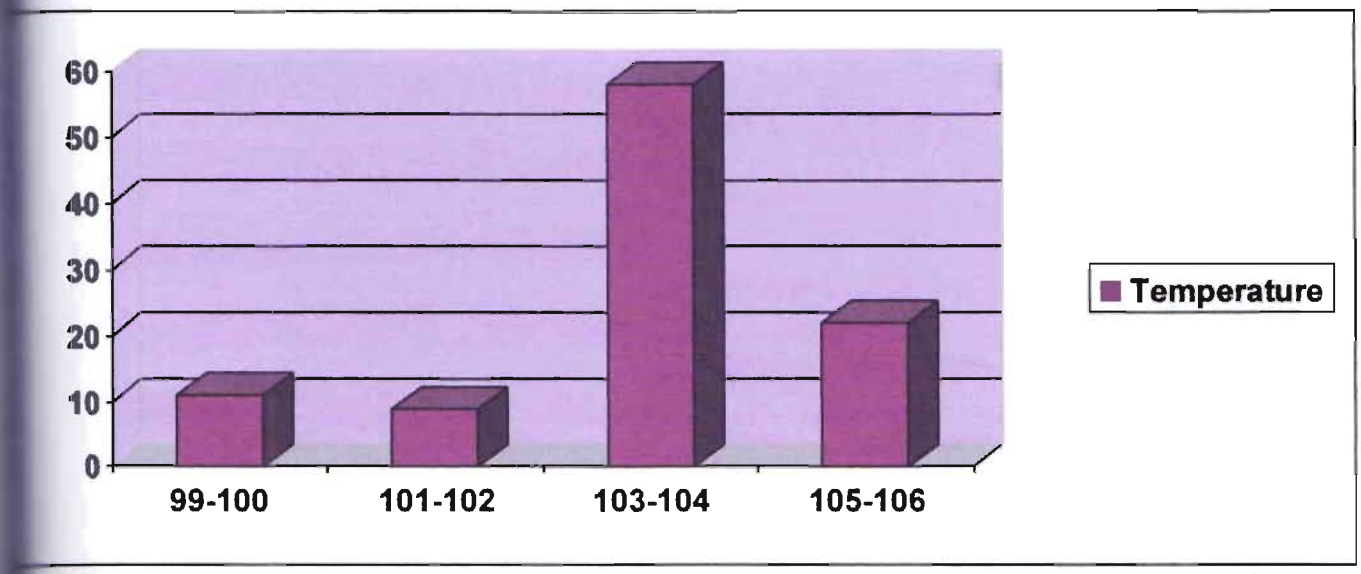


Fig: 4.4 show that the age of 42 % patients were within the range 1-2 years.

Fig: 4.5 Max temperature (°C) reached by the patient (n=50)



In fig: 4.5 show the max. temperature recorded was within the range 103-104 °C by 58 % patients

Table: 4.6 The day at which the temperature became afebrile after treatment has been given

Range (days)	Percentage (%)
2-3	10
4-5	38
6-7	37
8-9	5
10-11	10

Table: 4.6 show that 38 % patient's temperature became afebrile with 4-5 days after treatment has been given.

Fig: 4.6.1 The day at which the temperature became afebrile

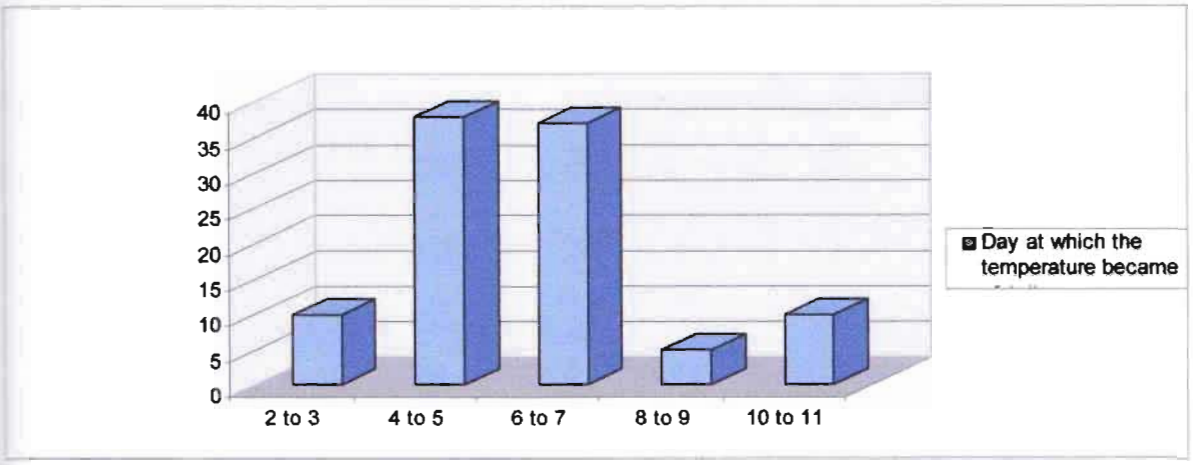


Fig: 4.6.1 shows the statistical representation of the day at which the temperature became afebrile.

(Where 37 % patient's temperature became afebrile on 4^{th} to 5^{th} day and 34.5 % patient's temperature became afebrile on 6^{th} to 7^{th} day)

Fig: 4.7 Graphical Representation of sign and symptoms of the patients (n= 50)

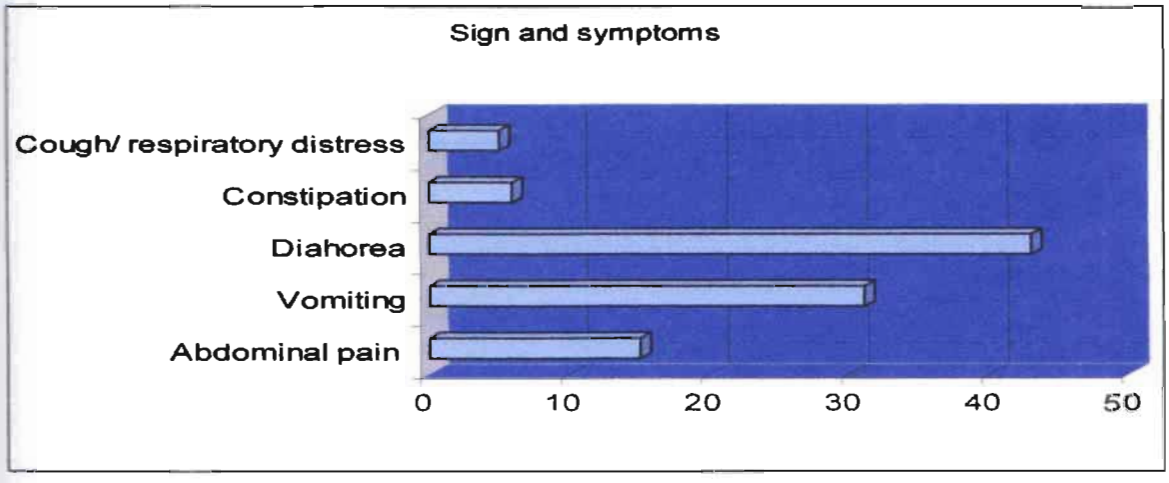


Fig: 4.7 show the graphical representation of sign and symptoms of the patients.

Table: 4.8 Drugs used before admission by the patient

Name of the drugs used	Percentage (%)of the patient
Paracetamol	52
Antihistamine	2
Ciprofloxacin	12
Cephradine	7
Ceptazidime	2
Ceftriaxone	2
Azithromycin	5
Ampicillin	3
Reported Nil (No drugs used)	15

Table 4.8 shows the % of the name of the Drugs used before admission by the patient.

(52 % patient received paracetamol before admission)

Fig: 4.9 Previously used drug before admission by the patient

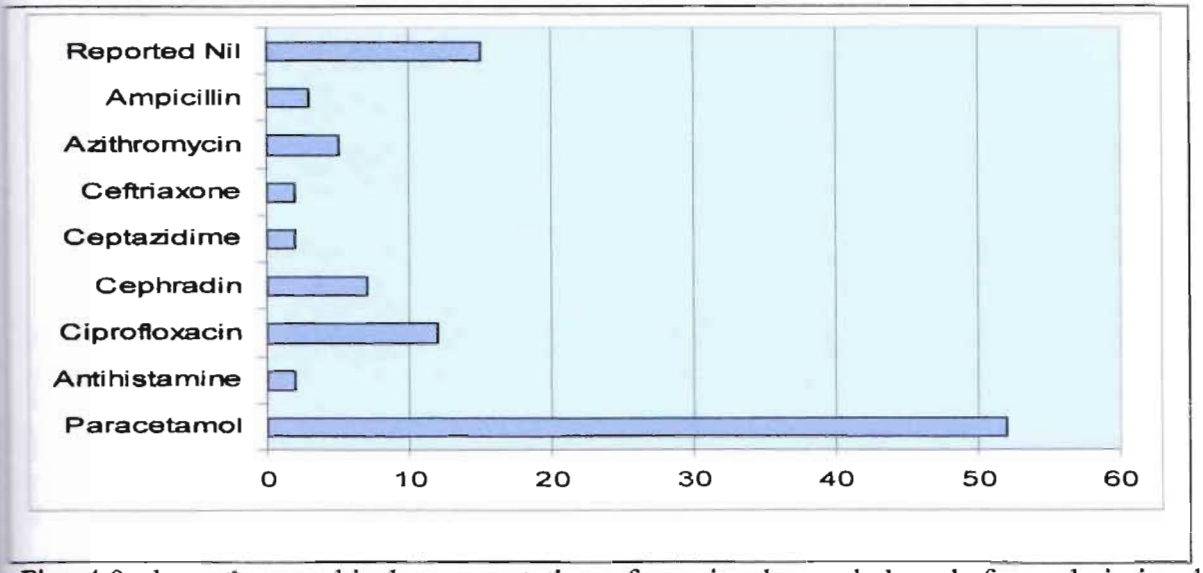


Fig: 4.9 show the graphical representation of previously used drug before admission by the patient.

Table 4.10 Drugs (antibiotics) used and the day at which the temperature became afebrile.

Name of the antibiotics (generic)	Day at which the temperature became afebrile
Amoxicillin	6th day
Ceftriaxone	7th day
Ciprofloxacin	6th day
Gentamicin	6th day
Levofloxacin	6th day
Ofloxacin	6th day

Table 4.10 shows the drugs used and the day at which the temperature became afebrile.

Fig: 4.10.1 Antibiotics used for the treatment

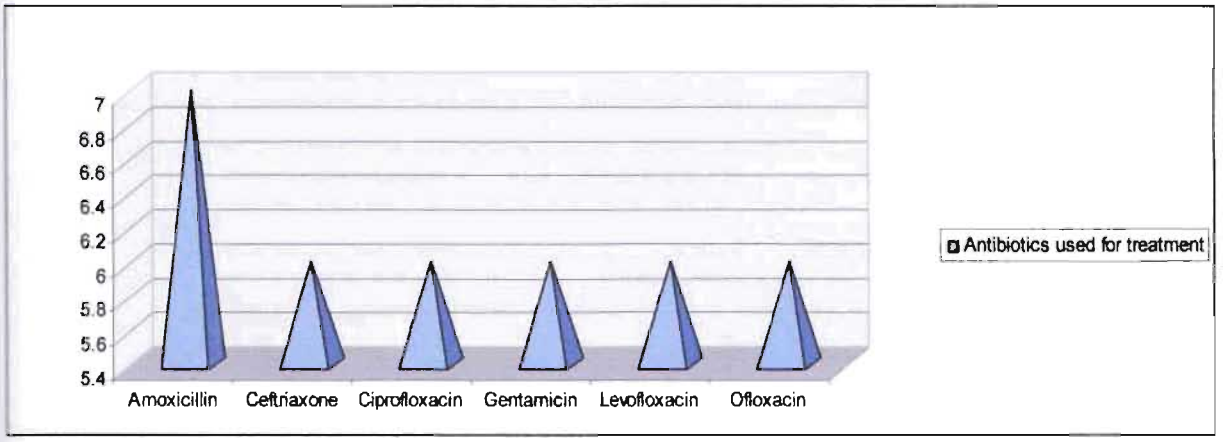


Fig: 4.10.1 shows the graphical representation of the names of antibiotics used for the treatment.

Table 4.11 The percentage of days the patient received treatment in the hospital

No of Days	Relative percentage (%)
4	18.9
5	24.3
6	16.2
7	13.5
8	10.8
9	16.3

Table 4.11 shows the relative percentage of days the patient received treatment in the hospital.

24.5 % patient received treatment for 5 days in the hospital.

Fig: 4.11.1 The no. of days of treatment received in the hospital

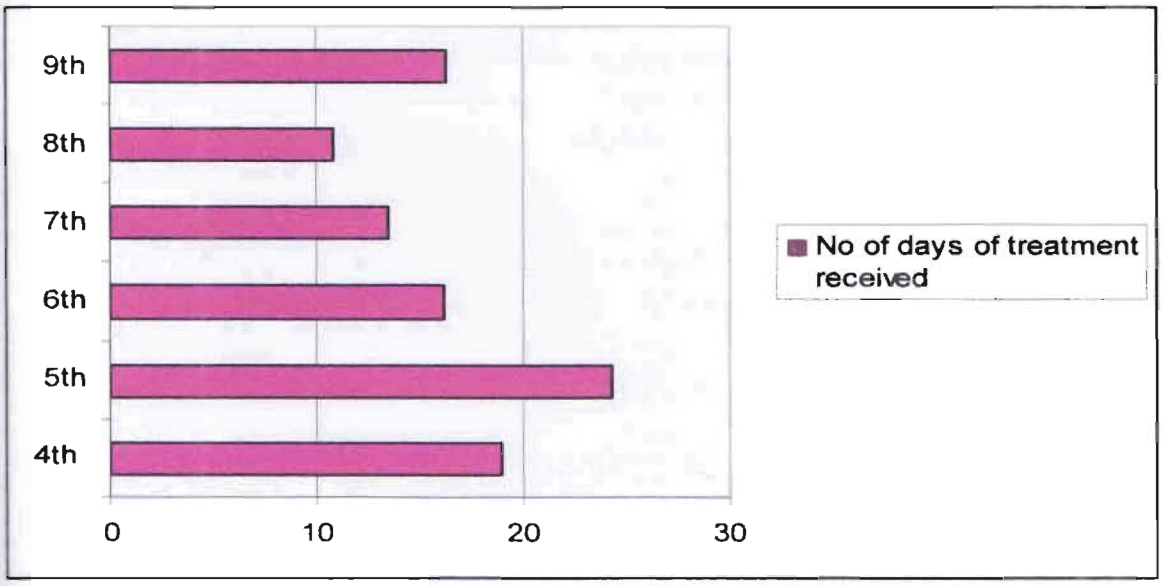


Fig: 4.11.1 Graphical representation of the days of treatment received in the hospital.

Fig: 4.12 The sensitivity pattern of Chloramphenicol

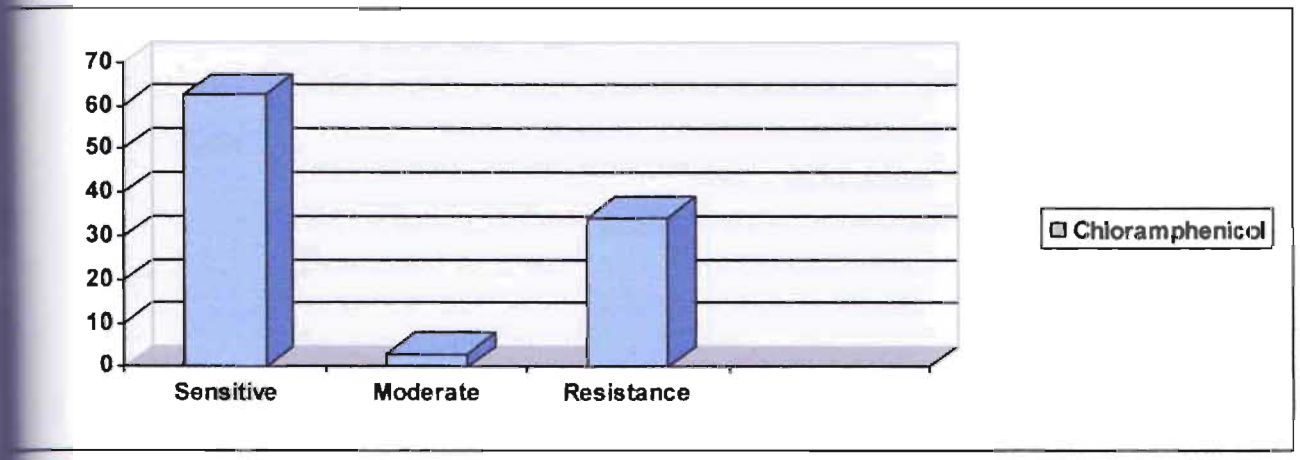


Fig: 4.12 Shows the sensitivity pattern of Chloramphenicol (sensitive 62%, moderate 5% & resistance 33%)

Fig: 4.13 The sensitivity pattern of Ceftriaxone

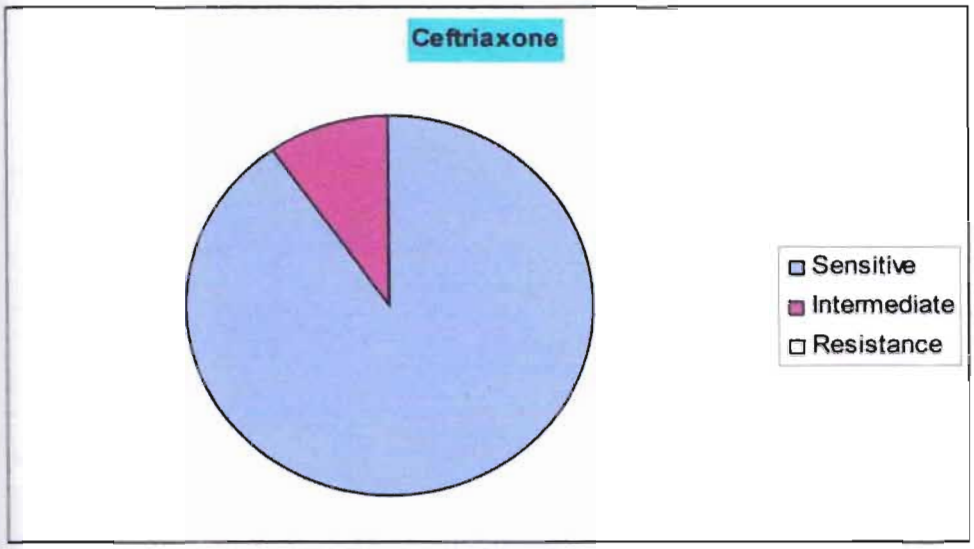


Fig: 4.13 Shows the sensitivity pattern of Ceftriaxone (sensitive 90% & intermediate 10%)

Fig: 4.14 The sensitivity pattern of Azithromycin

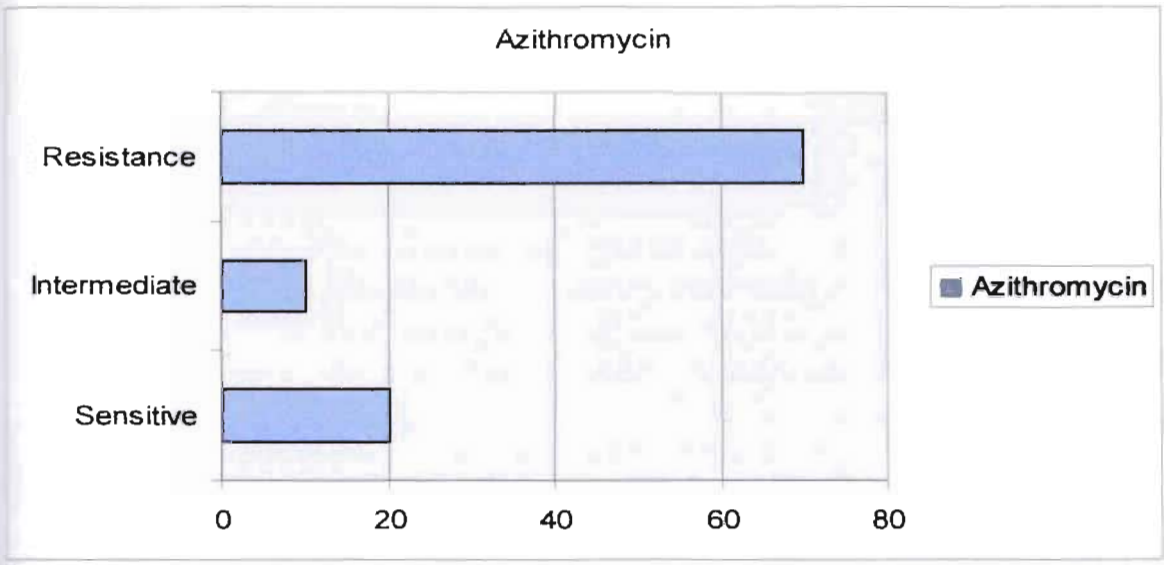


Fig: 4.14 Shows the sensitivity pattern of Azithromycin (sensitive 20%, intermediate 10%, & resistance 70%)

Fig:4.15 The sensitivity pattern of Ciprofloxacin

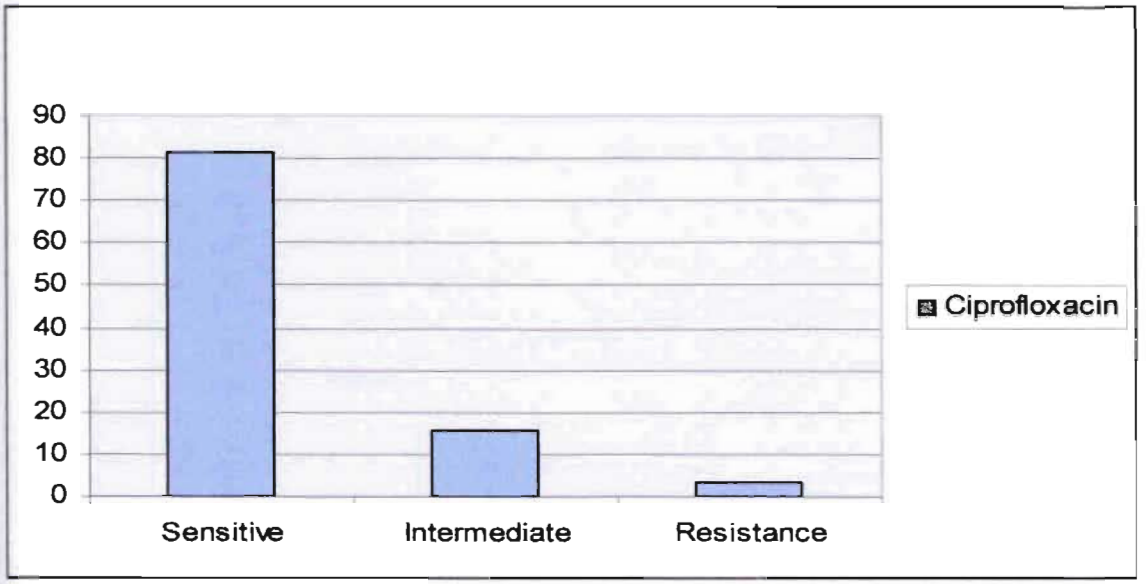


Fig: 4.15 Shows the sensitivity pattern of Ciprofloxacin (sensitive 81%, intermediate 18%, &

Resistance 1%)

Chapter 5

DISCUSSION

The discovery of antibiotics was a blessing in modern medicine. Powerful antibiotics first became commercially available in the 1940s and have saved untold millions of lives suffering from infectious diseases. They have been able to stop the growth or kill many different kinds of microorganisms. However, bacteria have proven to be much more innovative and adaptive than we imagined and have developed resistance to antibiotics at an ever increasing pace. Bad practices and mismanagement have only exacerbated the situation resulting development (Kotton C. 2007).

Definitive treatment of typhoid fever (enteric fever) is based on susceptibility. As a general principle of antimicrobial treatment, intermediate susceptibility should be regarded as equivalent to resistance. Antibiotic susceptibility varies widely among *S. typhi* and *S. paratyphi* strains, depending chiefly on geography. The initial antibiotic choice should be based on the sensitivity data of the area in which the infection was acquired.

Antibiotic resistance causes tens of thousands of deaths each year. Almost all infections could be controlled, but finding an effective antibiotic (because of widespread drug resistance) typically requires two to three days. Labs use bacterial cultures to test antibiotic susceptibility and resistance. Cultures require extensive growth and thus cause significant delays (Kotton C. 2007).

With critically ill patients in the ICU, the physician cannot wait for lab results before attempting to control an infection. They must start therapy within a few hours of symptom onset. Therefore they try antibiotic combinations. These empiric antibiotic combinations fail in approximately 20% to 40% of cases. Switching drugs after receiving lab results fails to improve the outcome. ICU physicians urgently need rapid bacterial identification and antibiotic susceptibility testing that produces accurate results within a few hours after the patient presents with symptoms. Decreasing inappropriate antibiotic use is the best way to control resistance (Kotton C. 2007).

In our study 50 patients were included. We mainly observed the sensitivity pattern of different antibiotics which are associated with Typhoid Fever. We consider the variables like patient's age,

weight, sex, educational status, date of admission, date of discharge (in hospital), present complaints, history of past medication, general examination, culture and sensitivity pattern, temperature and the day at which temperature become a febrile. Along with it the most commonly used antibiotics and their sensitive, moderate and resistant criteria (Cooke FJ, Wain J, Threlfall 2006).

Thus from the above tables and graphs from the result section we can conclude by saying that the mostly used antibiotics for the treatment of typhoid was found to be Chloramphenicol, Ceftriaxone, Azithromycin & Ciprofloxacin.

Summary and findings of our study:

According to our study the sensitivity pattern of different antibiotics are shown below:

- Highly sensitive antibiotics against typhoid fever:- Ciprofloxacin(CIP), Ceftriaxone(CRO), Ceptazidime(CAZ), Cefotaxime(CTX), Cotrimoxazole(TS), Imipenem(IPM), Gentamicin(GM).
- Moderately active antibiotics against typhoid fever:- Azithromycin(AZM), Netilmicin(NET), Aztreonam(ATM), Nalidixic acid(NA)
- Highly resistance activity antibiotics against typhoid fever:- Ampicillin (AMP), Cephalexin(CL), Chloramphenicol.

Chapter 6

CONCLUSION

The annual incidence of typhoid is estimated to be about 17 million cases worldwide. Among those the percentage of incidence in Bangladesh is alarming and increases during monsoon season (May to August).

Typhoid fever can be treated with antibiotics. However, resistance to common antimicrobials is widespread. Healthy carriers should be excluded from handling food. Control measures to combat typhoid include health education and antibiotic treatment. A vaccine is available, although it is not routinely recommended except for those who will have prolonged exposure to potentially contaminated food and water in high-risk areas. The vaccine does not provide full protection from infection.

Typhoid fever is treated with antibiotics. A person will usually recover in 2-3 days with prompt antibiotic treatment. People that do not get prompt medical treatment may continue to have a fever for weeks or months, and as many as 20% may die from complications of the infection.

Resistance to Ampicillin, Chloramphenicol, Trimethoprim-sulfamethoxazole, Streptomycin, Nalidixic acid and Azithromycin are now common, and these agents have not been used as first line treatment for many years. Typhoid that is resistant to these agents is known as multidrug-resistant typhoid. Ciprofloxacin resistance is an increasing problem, especially in the Indian subcontinent and Southeast Asia. Many centers are therefore moving away from using ciprofloxacin as first line for treating suspected typhoid originating in India, Pakistan, Bangladesh, Thailand or Vietnam. For these patients, the recommended first line treatment is Ceftriaxone. Ceptazidime, Cefotaxime, Cotrimoxazole, Imipenem, Gentamicin can also be used for the treatment of Typhoid Fever (Cooke FJ, Wain J, Threlfall EJ 2006).

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