Proceeding S.Z.P.G.M.I vol: 8(3-4) 1994, pp. 78-88.

Editorial Review

Salmonella Hepatitis: A Review

Farzana Shafqat, Anwaar A. Khan, Zafar Iqbal
Department of Medicine and Gastroenterology, Shaikh Zayed Hospital, Lahore

INTRODUCTION

The clinical picture of typhoid is extremely variable with increasing reports of atypical features[1-6]. Toxic manifestations like headache, step ladder temperature, coated furred tongue, cough, abdominal symptoms, malaise etc. may be observed in only 50% of cases[5]. A special problem is the occurrence of typhoid hepatitis.

Typhoid hepatitis is one of the atypical presentations of typhoid fever and can be defined as reversible involvement of liver during the course of typhoid fever.

Diagnosis of typhoid should always be considered in patients presenting with fever and features of liver involvement especially in endemic areas, because it can mimick other diseases occurring commonly in these areas, like acute viral hepatitis, amoebic hepatitis or malaria.

Epidemiology

Involvement of liver in typhoid is more commonly seen in endemic areas but has also been reported from non-endemic areas[7].

No age is exempt from typhoid hepatitis, but it is commonly seen between second and fourth decade[5] and in patients belonging to lower socio-economic class[4]. Complications like hepatitis occur more in patients with depressed cellular immunity and in those with relapse of typhoid fever[4,8,9].

Bacteriology

Infection in India and Pakistan occurs more commonly with salmonella typhi as compared to paratyphi A, B and C[4,10]. Similarly, liver involvement occurs more commonly with salmonella typhi infection[11]. Salmonella group of organisms belong to the family enterobacteriaceae. Salmonella typhi are gram negative, actively motile organisms. They do not ferment lactose, sucrose and salicin. Salmonella typhi only produce acid but no gas from dextrose and other carbohydrates. Their colonies stand out pale against the coloured colonies of lactose fermenters in media containing lactose and a pH indicator. There are three groups of antigens that are important for the identification of salmonella typhi in the laboratory and also for the serological diagnosis of infection. These are O antigen, H antigen and Vi antigen.

Somatic or O antigen is present within the bacterial cell wall. This is lipopolysaccharide, protein and lipid complex. This constitutes the endotoxin. Group classification is done on the basis of this antigen, Salmonella typhi belongs to 'Group D'. Further typing of S. typhi is done on the basis of flagellar antigen called 'H' antigen. Surface antigen which covers O antigen, is called Vi antigen. Vi antigen increases the virulence of the organism. This antigen is also present in Paratyphi C, though their group factor and flagellar antigen are different.

These bacteria are readily killed by heat in one hour at 55 ° C, in 15-20 minutes at 60 ° C and within 5 minutes by boiling. Baking also kills these organisms and other salmonellae. Growth stops below 55 ° C but survival is possible. Contamination during preparation of food or after cooking may not be harmful if the food is quickly cooled and kept at refrigerator temperature below 5 ° C but if left for an hour or two before cooling, bacteria may multiply rapidly and food becomes contaminated for safe consumption before it is put in the refrigerator. S. typhi and other Salmonellae can be destroyed by a number of chemicals including phenols, mercuric chloride, formaldchyde and quaternary ammonium compounds. Chlorine and potassium permanganate can be used for treating food.

Pathogenesis of salmonella hepatitis

The exact mechanism of hepatic damage in typhoid fever is not clear. It has been seen that this complication, like other complications occurring in typhoid, is more commonly seen in malnourished people belonging to lower socio-economic group[4].

Bacteremia may be the cause of liver damage as bacteremia occurs in most patients with typhoid fever[3]. It definitely has a diagnostic significance but clinical severity and development of complications of the disease have no significant association with the concentration of bacteria in blood[12].

Salmonella endotoxin has been implicated in

causing salmonella hypatitis like other features of typhoid fever. When these bacilli enter the circulation after considerable multiplication in lymphoid tissue of intestine, they undergo destruction with the result of liberation of endotoxin which produces the symptoms of typhoid fever[13]. But rapid development of tolerance to endotoxin in volunteers can not explain the protracted course of the disease[14].

Human volunteer studies showed that endotoxins did not play much role in the production of sustained pyrexia and toxemia of typhoid fever[14,15]. While evidence continues to accumulate that endotoxins do not play a major role in the pathogenesis of typhoid fever and its complications, but in fact there are indicators favouring its local effect in the vicinity of the salmonella typhi infection. At these local sites, where salmonella typhi are multiplying, the highest concentration of endotoxins might be expected[14].

Salmonella endotoxin is a potent inflammatory agent and is chemotactic for polymorphonuclear leucocytes. Very minute concentration as low as 1 ng/dl can produce local dermal responses during typhoid fever[15]. Therefore, sustained pyrexia and toxemia may be explained by the ability of S. typhi and its endotoxin component to stimulate the synthesis and release of endogenous pyrogens from mononuclear cells and polymorphs accumulated at the site of inflammation in tissues.

Demonstration of salmonella bacilli within the liver by indirect immunoflurescence strongly favours the possibility of damage caused by locally released endotoxins by the proliferating organisms and by invoking local inflammatory reactions[16]. Hepatic damage seen in patients with gut perforation and peritonitis was considered to be due to ascending cholangitis[17].

Hornick et al.[14] also considered the possibility of localized intravascular coagulation and arteritis in the pathogenesis of clinical features of typhoid fever. Hepatic injury in typhoid fever could be due to vascular hyperreactivity to catecholamines. In man and animals, intestinal mucosa possesses high serotonin concentrations and a variety of inflammatory lesions of the intestine cause vascular hyperactivity to catecholamines in man. Therefore, release of serotonin from the inflammed intestinal mucosa could be responsible for the vascular hyperreactivity to the catecholamines.

The clinical significance of the vascular hyperreactivity to catecholamines during typhoid fever is not clearly understood but it may represent a contributing mechanism to the pathogenesis of the focal necrotic lesions and arteritis that occur in typhoid[14].

Immune complexes and high ratio of antitrypsin to C_3 have been seen in typhoid fever and more frequently in patients with complications including hepatitis[18]. Cell mediated immune response (CMIR) appeared to play an important role in typhoid and its complications[9]. It can be measured by leucocyte migration test and delayed hypersensitivity[8]. Recovery of the complicated cases was associated with change of negative L.M.T to positive[8,9]. Mebel and Paniker[19] found increased incidence of typhoid and severe toxemia in patients with negative L.M.T cell mediated immune response. Rajagopalan et al.[9] also found intact CMIR in uncomplicated cases of typhoid fever as compared to complicated cases. The ratio of T lymphocyte sub-populations was grossly imbalanced in typhoid patients, the number of T lymphocytes and their sub-population was further altered in the complicated cases as compared to uncomplicated cases. Increased proportions of T suppressor cells and reduced population of T helper cells especially in complicated cases suggest that high levels of suppressor T cells and circulating immune complexes may be responsible for a negative L.M.T. Simultaneous presence of these two factors is to be expected since it has been reported that immune complexes stimulate the formation of suppressor T cells and other suppressor factors. Further confirmation of the involvement of circulating immune complexes and suppressor T cells in producing immunological abnormalities in typhoid fever would help in deciding therapeutic approach to correct these abnormalities. Thus, there is found to be a close correlation between the development of leucocyte migration test (L.M.T), recovery and inverse correlation with complications and a prolonged illness in typhoid fever.

Clinical features of salmonella hepatitis

Clinical features would be both of typhoid fever and that of hepatic involvement. Onset of fever in typhoid is slow and insidious in most of the cases[3] but rapid onset with or without chills has also been observed[17].

The most common prodromal symptoms which precede the actual onset of fever were headache,

Table 1: Reports of liver involvement in typhoid fever (in percentage)

Study	*No. of patients*	*Jaundice*	*Hepatomegaly*	*Abnormal LFTs (%)*	*Abnormal liver histology*
Stuart and Pullen 1946	360	3.6	25	NR*	NR
Rowland 1961	530	1.1	NR	NR	NR
Gulati et al. 1968	98	0	0	NR	NR
Wicks et al. 1971	243	1.6	NR	NR	NR
Ramachandran et al. 1974	58	7.6	29	-	-
Diem et al. 1976	15	26.6	10	93.3	100
Samantray et al. 1977	500	0	18	NR	NR
Singh et al. 1978	460	1	NR	NR	NR
Nasrallah and Nassar 1978	104	23	33	17	NR
Johnson and Aderele 1981	117	6	27	5	NR
Gupta et al. 1985	125	5.6	8.8	5.6	NR
Khosla et al. 1988	36	8.3	55	55	40
Ishaq et al. 1990	30	0	63	NR	NR
Arif et al. 1990	9	66	77	100	44
Shafqat et al[75]. (1994)	31	45	70	NR	32

*Not recorded.

malaise and anorexia[3,17]. Abdominal pain, constipation, diarrhoea abdominal distension, body aches and pains and symptoms pertaining to chest e.g. cough, sore throat may be present[3,17,20] (Table 1).

Common physical signs are fever, toxaemia, typhoid tongue, splenomegaly, hepatomegaly, bronchitic signs, relative-bradycardia, rose spots and abdominal tenderness[1,2,3,17] (Table 2).

Table 2: Common symptoms in typhoid.

- Headache
- Anorexia
- Nausea and vomiting
- Malaise
- Bodyache
- Rigors
- Diarrhoea
- Constipation
- Abdominal pain
- Abdominal distension
- Cough
- Sore throat

Features indicative of hepatic involvement which may be present alone or in combination are, hepatomegaly, jaundice, disturbed liver function tests and abnormal histology[4,21,22].

Salmonella hepatitis is usually mild and runs a benign course and may even be missed by the physician or it can be severe presenting with severe bleeding syndrome, haematemesis, or hepatic encephalopathy.

Osler first reported hepatomegaly in typhoid fever in 1899[4]. Subsequently incidence of liver enlargement more than 14 cm was reported in different series varing from 13-63%[4,10]. Hepatomegaly is seen more commonly in patients with salmonella typhi infection as compared to salmonella paratyphi, and in patients with relapse of typhoid fevere[4,11]. Hepatomegaly appears after the first week of illness and remains during the height of temperature and disappears with treatment[11]. Enlargement has been varying from 1-10 cms below right costal margin[23]. It is usually non tender but tender hepatomegaly has also been reported[24]. Patients with enteric hepatitis may or may not have hepatomegaly. Ramachandran et al.[11] described hepatomegaly in all cases of enteric hepatitis whereas it was absent in 15% of patients with biochemical evidence of hepatic damage reported by others[4].

Jaundice in typhoid fever occurs rarely[3]. Incidence reported in various series ranges between 1% and 26.6%[6,23]. This complication occurs earlier in the illness, especially in people who are malnourished. Rowland (1961) found jaundice in

Table 3: Frequency (in percentage) of different clinical featuresfor various reported series.

Signs	*Start and Pullen 1946*	*Huckstep 1960*	*Gulati et al. 1968*	*Samantary 1977*	*Gupta et al. 1985*
Fever	100.00	100.00	100.00	100.00	100.00
Toxemia	-	54.0	37.0	45.6	60.0
Typhoid tongue	-	-	35.0	43.6	60.0
Splenomegaly	63.1	14.0	38.0	65.0	44.0
Hepatomegaly	25.2	6.3	-	18.0	8.8
Bronchitic signs	40.2	21.0	50.0	11.0	52.0
Rose spots	59.8	45.0	-	41.6	9.6
Relative bradycardia	88.0	-	22	50.0	38.4
Abdominal tenderness	45.0	45.0	-	41.6	27.2

five (0.9%) of his patients at the time of admission[6]. Jaundice was also observed in 8% of patients in a review of 214 patients in Ibadan. In 6% of cases it was definitely due to hepatocellular damage[25]. Many workers have reported typhoid patients presenting with profound jaundice as shown in Table 4. In a recent epidemic in India in 1989, 2.5% of patients came to hospital with jaundice[26]. Jaundice in typhoid fever could be due to ascending cholangitis. All 7 cases with jaundice reported by Gupta et al. had gut perforation and septic peritonitis and jaundice was ascribed to ascending cholangitis[17]. Ramachandran et al.[11] reported that cholangitis and bile stasis do not occur in hepatic involvement in typhoid fever. Uncommonly, typhoid cholecystitis with bile duct obstruction may occur[1]. Hepatic involvement and icterus in typhoid fever can be due to suppurative pyelophlebitis and Salmonella liver abscess[27]. Hemolysis in typhoid can occur and hemolytic jaundice can result[1].

Table 4: Case report of typhoid patients presenting as "fever with jaundice".

Reports	*Year*	*Country*	*No. of case*
Ramachandran et al.	1974	Sri Lank	1
Kar et al.	1985	India	1
Faierman et al.	1972	New York	1
Gandapur et al.	1988	Pakistan	1
Singh et al.	1978	India	5
Shankar and Kejriwal	1988	India	1
Rao et al.	1978	India	1
Greig and Naidoo	1981	South Africa	1

Hemolysis can occur especially in people with glucose-6-phosphate dehydrogenase deficiency and haemoglobinopathies[25,28]. Jaundice is usually mild but profound jaundice can occur indicating severity of illness[29]. It is reversible with treatment and complete recovery results[11,27].

This presentation creates diagnostic problem and typhoid should always be considered in a patient presenting with fever and jaundice of more than one week duration, even in non endemic areas[7]. Rarely patients with typhoid hepatitis can deteriorate and can develop confusion, somnolence and asterixis along with presence of jaundice. Such cases have been reported[7,27,29].

Faierman et al.[7] reported a case of a young man who migrated from Peru to the United States five weeks prior to his illness; developed typhoid hepatitis characterized clinically by profound jaundice and hepatic encephalopathy. He also had other life threatening complications of typhoid like acute renal failure due to typhoid nephritis, and thrombocytopenia resulting in bleeding from different sites. He recovered fully after treatment and was discharged from hospital after six weeks.

Another case of typhoid was reported from India presenting with jaundice and encephalopathy[29]. This patient also recovered fully after treatment. Singh et al[27]. reported 5 cases of typhoid fever presenting at the time of admission with moderate jaundice and were toxic, deteriorated during stay in hospital, developed hepatic encephalopathy and hepatorenal syndrome and died. Hematemesis, and epistaxis have been seen very rarely in typhoid patients[7,28].

Atypical presentations could also be due to

neurological disturbances like encephalopathy[5] meningitis[6] intracerebral or subdural abscess[30], myocarditis[31], or acute renal failure[28,32].

Severe bleeding syndrome occurred in a young female due to deficiencies of factors II, VII, IX and X resulting from defective synthesis in a patient with typhoid hepatitis[33]. Other serious complications of typhoid are intestinal haemorrhage, intestinal perforation or peripheral circulatory failure[2,17].

Diagnosis

Diagnosis of salmonella hepatitis is based on confirmation of typhoid fever and that of liver involvement.

Typhoid fever can be confirmed by isolation of the organisms from culture of different media, e.g., blood, bone marrow aspirate, rose spots, urine, faeces and bile. Most important of these are blood and bone marrow cultures.

Blood is the most important and accessible media for the isolation of organisms. Therefore, it is important to take two, three specimens before starting any treatment[20]. In the absence of antimicrobial therapy, blood cultures are positive in over 80% of patients during first week of illness[3]. Bacteremia persists even after the first week and in most severe cases it may not reach its height till the third week, while it may persist till the end in patients dying from toxemia. Positive cultures have been obtained in high percentage of patients presenting with two or three weeks history of fever[5,20]. During clinical relapse orgaisms can be isolated as frequently as from the acute case but may be for a shorter period[26]. Blood cultures should not be discarded for 10-12 days, as the number of organisms in blood may be very small, even as low as one organism per ml resulting in delayed positivity. Blood should be diluted as it contains bactericidal substances. It is, therefore, diluted at least four times by the culture medium to reduce its bactericidal properties. Ten times dilution of 8 ml have been recommended[34]. Blood from patients, already, on chloramphenicol may have to be diluted further to obtain better results. In some cases bile and liquid (Sodium polyanethol sulphonate) have been added to the medium which helps to counteract the action of blood.

Bone marrow culture is considered to be the most sensitive single method for isolating these organisms especially in patients who have already used antibiotics. In a comparative study of 62 patients, bone marrow cultures were positive in 56 (90%) while S. typhi was recovered from blood in only 25 (45%)[35]. Most of these patients had taken antibiotics. Bone marrow aspirate culture was found to be superior to strepotkinase clot culture and 8 ml 1:10 blood:broth ratio of blood culture[34]. It was also found to give better results as compared to duodenal string capsule culture and rectal swab culture[36].

Diagnosis can also be confirmed by changes in biopsy specimens from liver or kidney. Changes characteristic of typhoid were seen in 100% of cases by some workers[22,23]. Calva and Ruiz-Palacios observed histological changes in 88% of their patients suffering from typhoid hepatitis[16]. Fluorescein stained bacilli can be seen in the tissues. Intact fluorescent bacilli were seen to be spread through out the parenchyma of the liver in numbers of four to six bacteria in all (8) biopsy specimens[36].

Changes of acute tubulo-interstitial nephritis have been seen in patients with acute renal failure due to typhoid fever[7]. Salmonella typhi VI antigen have been demonstrated in three consecutive typhoid patients who did not have any symptoms pertaining to urinary tract involvement. They only had mild proteinuria[37].

Serological tests e.g., widal test may help in diagnosis though with certain reservations. Formation of agglutinins (antibodies) against their antigens within the body, form the basis of this test.

In developing countries, where facilities for isolation and culture are not freely available especially in smaller hospitals, diagnosis depends upon clinical features and the detection of agglutinating antibodies to S. typhi i.e. the widal test. Numerous studies, however, have produced data which have resulted in serious doubts on the value of the Widal test in the diagnosis of typhoid fever[1,3,28]. Several factors have contributed to this problem. These include poorly standarized antigens, the sharing of antigenic determinants with other salmonellae, the effect of treatment with antibiotics and previous immunization with TAB vaccine. Another major problem relates to the difficulty of interpreting Widal test results where the disease is endemic and where the antibody titres of the normal population are often not known. Also possibility of false positive reactions to non-typhoid fevers exists in areas where fever due to infectious causes is a common occurrence[39].

Therefore, the diagnostic value of the widal test in any given case varies considerably with the

knowledge and experience of the interpreter[39]. In an area where typhoid fever is uncommon, a titre of 1/40 for either H or O antibodies, or both, in an uninoculated febrile patient should suggest the possibility of acute infection, titres over that levels have increasing diagnostic significance. In endemic areas where antibodies due to previous infection will be common in the population, it is important to know the average level of antibodies in normal, healthy people in that area[38]. High O antibody titres especially rising titres have greater significance. In a previously inoculated person, within six months, interpretation should be made carefully. Clinical picture of the patient and a rising titre would be helpful in such cases. Widal test still remains the vital investigation in developing countries where typhoid is endemic.

Other serological tests have been tried but none of these has been accepted as a routine test in microbiology laboratories in endemic areas. These include passive agglutination test[39], counter immuno electrophoresis[39], (ELISA) enzyme linked immunosorbent assay[40], and DNA probes[41].

Another test of great diagnostic value especially in the absence of laboratory facilities is diazo reaction in urine[1].

Involvement of liver in typhoid fever can be confirmed by clinical, biochemical, and histological abnormalities. There should be high index of suspicion in patients with prolonged fever and showing features of liver involvement like hepatomegaly, jaundice, hepatic encephalopathy and bleeding from any site.

Liver injury in typhoid is usually hepatocellular. But mixed cholestatic and hepatocellular and pure cholestatic type can also be seen[42]. Raised levels of bilirubin with increased conjugated bilirubin is the characteristic feature of patients with jaundice in typhoid. Levels of bilirubin increase during the course of illness but decrease and finally return to normal with improvement of patient after treatment[27].

Rise in transaminases especially serum (SGPT) aminotransferases (ALT) indicates definite hepatocellular damage. Sometimes their rise is the only indication of liver damage in typhoid, there may not be any other feature present like hepatomegaly or jaundice[4]. Biochemical alteration suggestive of hepatic damage and dysfunction have been reported in 23-60% of the cases in various series[4,11]. Alkaline phosphatase and 5-adenosine nucleotidase have also been found raised indicating billiary stasis[4]. Prolonged prothrombin time can occur. Profound deficiencies of clotting factors, II, VII and X have been reported[33].

Diem et al[23]. described histological changes in 100% of their culture proven typhoid cases. These changes consisted of hepatocyte swelling. Kupffer cell hyperplasia, mononuclear infiltrations of presinusoidal space and portal space and fatty degeneration of liver cells. Spotty necrosis was observed in eight out of fifteen patients. Ayhan et al.[22] from Turkey also described similar type of changes in all of their 16 patients. These changes were found to be reversible after treatment. Absence of diffuse inflammation is the characteristic feature of salmonella hepatitis.

Treatment

Treatment of salmonella hepatitis is the same as that of typhoid fever. The management of typhoid patients remained symptomatic and supportive until the discovery of specific chemotherapy in 1948[13]. Before the antibiotic era, the disease used to run a long and protracted course lasting for several weeks to several months and the mortality was high[3].

Chloramphenicol

Chloramphenicol was the specific therapy discovered in 1948[13]. It is still the drug of choice in patients suffering from typhoid fever due to sensitive strains of salmonella typhi[44]. Treatment with chloramphenicol has definitely shortened the course of the acute illness[1]. Mortality and complications especially intestinal haemorrhage have decreased[6]. Complications primarily due to a long and severe febrile illness, like pneumonia, secondary infections, bed sores, parotitis and venous thrombosis are also less common[6].

Relapse rate and carriers are found to be increasing with chloramphenicol treatment[2]. But this problem is attributed by some workers to inadequate dosages and short course of treatment[17]. Bone marrow damage and sensitivity to chloramphenicol can occur but the incidence of both these side effects is very low[6].

Major problem which has created difficulties is the emergence of chloramphenicol resistant strains, and now occurrence of multiple drug resistance[10,45,46]. Different drug regimens have been tried depending upon the need and availability of the drug[1,6]. It should be used in adequate doses and for a sufficient

period. Divided doses are not recommended[1,17]. Doses recommended by Huckstep varies with the severity of disease. In severe cases, one gram 6 hourly can be given initially for three days and then can be reduced to 500 mg 6 hourly for at least 12 days. In ordinary acute or subacute cases 0.5 g 6 hourly for three days and then 0.25 g 6 hourly for 12 days have been recommended.

Cotrimoxazole

Cotrimoxazole is also considered to be an effective drug in the treatment of typhoid fever[10]. The carrier state seems less common but frequency of relapses after treatment with this drug is not clear. Again the danger is because of its effect on blood cells formation and development of resistance to it[10]. The mean duration of fever in typhoid after co-trimoxazole therapy varies between 5 and 8 days, longer as compared to that of chloramphenicol[17]. The dosage schedule in adults is 960 mg twice daily for 2 weeks. Children are given a dose according to their body weight, with a recommended average daily dose of 6 mg to 8 mg of trimethoprim and 30 to 40 mg of sulphamethoxazole per kg of body weight.

Amoxycillin

Amoxycillin has been used successfully in the treatment of typhoid. It was also found to be useful in children who had glucose 6-phosphate dehydrogenase deficiency and typhoid fever[48]. Recommended dose is 1 g 6 hourly for 14 days, 2 g a day for 21 days gave better results than chloramphenicol with no carriers and a 2% relapse rate[49]. Relapses are apparently infrequent and carrier rate is not much after treatment with amoxycillin.

Second line of treatment in resistant cases

Emergence of resistant strains of salmonella typhi have created a lot of difficulties. After isolation of bacteria, sensitivity of the organism has also to be checked[10]. Chloramphenicol resistance in salmonella typhi was apparently first reported in England[50]. Subsequently it was observed in other countries. First epidemic due to chloramphenicol resistant strains of salmonella typhi occurred in Mexico[51]. Until recently, resistance was seen only to chloramphenicol but now incidence of multiple durg resistance of salmonella typhi strains had been increasing[52]. Recently an outbreak of multi-resistant typhoid has occurred in Eastern India. This illustrates potential for epidemic spread of these strains[26,45].

The resistance appears as a result of either mutation or acquisition of R factor. The frequency of infection due to resistant strains is likely to increase in countries where typhoid is endemic and chloramphenicol is used indiscriminately. For treatment of the highly resistant strains of salmonella typhi, quinolones or third generation cephalosporins are the drugs of choice[26,46].

Quinolones

Quinolones are synthesized chemically. These agents are bactericidal against salmonella typhi and penetrate into phagocytes[54]. In comparative clinical trials, ciprofloxacin, ofloxacin, pefloxacin or fleroxacin have been found to be equivalent or superior to standard antityphoid therapy[54].

Ciprofloxacin have been found to be effective in patients with multi drug resistant typhoid fever by many workers[55]. Seven days short course ciprofloxacin therapy has been recommended[56].

Ofloxacin, another antibiotic belonging to quinolones, has been tested in Pakistan for its efficacy against salmonella typhi in vitro. Salmonellae typhi responsible for causing typhoid fever was found to be highly susceptible to ofloxacin and this antibiotic possessed a low and very narrow range of minimum inhibitory concentrations[57]. It has been used effectively in resistant cases of typhoid fever. When a dose of 400 mg twice a day of ofloxacin was given, fever subsided within 72 hours after administration of this therapy. Treatment was continued for 14 days, without any untoward effects[10]. Major problem with these drugs is high cost and their contraindication in children and pregnant women.

Cephalosporins

Numerous third generation cephalosporins have demonstrated good results against S. typhi. These are cefotaxime, ceftriaxone, moxalactam, and ceftizoxime. Cure rates with these have been considerably high and relapses low[53]. Ceftriaxone in a dose of 1 g every 12 hours for 14 days have been found to be a reasonable alternative to quinolones for the treatment of highly resistant cases of typhoid fever, especially in patients under 16 years of age and in pregnant or lactating women. An alternative regimen commonly used in endemic areas is administration of ceftriaxone 3 g once a day for 7

days[58].

Cefoperazone is another cephalosporin found to be as effective as chloramphenicol in the treatment of severe typhoid fever. It can also be given to children with severe typhoid fever[59]. Defervescence was found to be more rapid and blood cultures tended to become negative faster with cefoperazone as compared to chloramphenicol[59]. This drug is, however, expensive and can only be given intravenously, it should be reserved for the treatment of S. typhi strains resistant to standard therapy. Dosage is 100 mg/kg/day IV 12 hourly till daily temperature is below 38 °C then 50 mg/kg/day/IM 12 hourly for upto 14 days.

Cefixime has also been found very effective in typhoid fever caused by multiple drug resistant strains in childern. It was given orally in a dose of 20 mg/kg/day in two divided doses 12 hourly for a minimum of 12 days. All patients responded rapidly to treatment and were cured clinically and bacteriologically. No serious adverse reactions attributable to the drug were observed[60].

Corticosteroids in typhoid fever

Corticosteroids have been used in cases of severe typhoid fever but their role has been controvertial since it was first described in 1951[36]. Steroid therapy definitely shortens the duration of fever and improves the sense of well being of the patient[61].

Initially they were used in smaller doses and for a shorter period i.e. 300 mg cortisone or equivalent dose of prednisolone for 3-5 days. Such short term steroid therapy has not been associated with higher incidence of perforation or haemorrhage from intestinal ulcer[61]. But the use of steroids in severe typhoid fever in small doses have not been found to decrease mortality[6], but on the contrary it has been found to increase the relapse rate especially when used later in the course of the disease[62]. Steroids in small doses, therefore, are not recommended in typhoid fever.

Corticosteroids used in high doses have been found beneficial in patients suffering from severe typhoid fever. They reduce mortality significantly without any increase in complications[36]. The mechanisms in decreasing fatality rate is not well understood. Steroid therapy is found to reduce the production of arachidonic acid and its metabolites, act as antioxidant, reduce the level of macrophage-derived lysosomal enzymes, and render normal macrophages unresponsive to lymphokines[36].

In addition to receiving treatment with antibiotics, patients with severe typhoid fever should receive dexamethasone in a dosage of 3 mg/kg initially, followed by eight doses of 1 mg/kg every 6 hours. The use of dexamethasone decreased mortality from 55% in the placebo group to 10% in the treatment group in a randomized double blind trial in severe typhoid fever[36].

Treatment of carriers

For the control of typhoid fever, identification and treatment of chronic carriers is very important[63]. Carrier state is usually associated with underlying biliary tract or urinary tract abnormality. Chloramphenicol does not help in the treatment of carriers. Ampicillin is the drug of choice. Larger doses for longer period should be used[48]. Amoxicillin given for a 28 day course cured the carrier state even in the presence of gallstones[64].

Trimethoprim sulphamethoxazole (co-trimoxazole) seems to be effective in the clearing of carriers[48]. Salmonella typhi carriers have also been treated successfully with 750 mg of ciprofloxain given for 28 days in a patient with associated gallbladder disease who refused surgery and was sensitive to ampicillin and co-trimoxazole[65]. Typhoid carrier state when associated with chronic cholelithiasis can only be cured in most cases by cholecystectomy with or without antibiotics supplementation[66]. Schistosomiasis also favours carrier state and eradication of S. typhi needs treatment of schistosomal infection along with treatment of S. typhi infection[67].

Prevention

Typhoid fever is a serious illness and can lead to life threatening complications, therefore, needs to be controlled. Incidence in developed countries has decreased during this century because of improvement in their hygienic conditions. Control of the disease in endemic areas requires supply of clean water, effective sewage disposal, early diagnosis, and treatment of patients and of asymptomatic carriers. Achievement of these ideal conditions is not possible in the near future therefore the only alternative for the control of disease is by vaccination.

Commonly used parentral vaccines consist of inactivated bacilli. Out of the available vaccines, heat killed phenol preserved (Phenolized), alcohol killed and acetone killed, acetone dried (Acetone vaccine),

the acetone vaccine is found to be superior to others[69]. These vaccines are efficacious in preventing typhoid fever but they have three major limitations. They are 70% effective, immunity produced does not persist for more than three to five years and vaccination results in local and systemic reactions in most recipients[14].

The development of a safe effective oral vaccine has been considered the ultimate goal. This vaccine is made from an attenuated mutant strain of S. typhi Ty21a which lacks the enzyme UDP-galactose-4 epimerase. This live oral vaccine has been evaluated for its efficacy in human volunteers. The ingestion of five to eight doses of vaccine (equivalent to $3\text{-}10 \times 10^{10}$ live organisms) caused no significant side effects, gave a protection rate of 87% against a dose that caused typhoid fever in 53% of unimmunized control volunteers[69]. In earlier studies, parenteral vaccines that had been found effective in the field demonstrated no protection against such a high challenge dose[14]. The large field trials in Egypt and Chile also provided favourable information regarding oral vaccine. The first large trial in Egypt with three doses of live oral vaccine of Ty21a given in liquid formulation proved it to be a stable and safe vaccine and provided 96% protection for a period of at least 3 years[70]. Oral vaccine Ty21a has also been used in enteric coated capsules with which no buffer is required as these capsules open only in a surrounding pH of 6.0 or more. Levine et al[71]. showed 67% protection in school children for three years and 66% for five years follow-up after giving three doses of enteric coated capsules within a week in a large field trial. An immunization schedule of four doses of Ty21a given within 8 days was found to be significantly more protective than three doses[72].

Based upon these results, food and drug administration in the USA licensed the enteric coated capsule formulation of Ty21a with a recommended immunization schedule of four doses to be given on days 1, 3, 5 and 7.

Then the efficacy of two formulations was compared in Chile, as these showed different results in two large field trials conducted at different places[73]. Levine et al[73]. compared the efficacy of two formulations of oral vaccine Ty21a in Chile recommended the liquid formulation for use in endemic areas, especially for children. It was effective at all ages, and was easier for immunizing the youngest children.

Another vaccine prepared from capsular polysacharide of S. typhi (vi) has been found to produce specific immune response and confer immunity, in a pilot study followed by a large clinical trial in Nepal[69]. The efficacy of vi was 75%, only one injection was given and adverse reactions were rare.

CONCLUSION

Salmonella hepatitis is a well recognized entity and has variable clinical features. It should always be considered in patients with fever and hepatic dysfunction especially in endemic areas, as earlier recognition and management results in complete recovery[75].

REFERENCES

1. **Huckstep RL.** Recent advances in the surgery of typhoid fever. *Ann R Coll Surg Engl 1960;* 207-30.
2. **Gulati PD, Saxena SN, Gupta PS, Chuttani HK.** Changing pattern of typhoid fever. *Am J Med 1968;* **45**: 544-48.
3. **Stuart BM, Pullen RL.** Typhoid: Clinical analysis of 360 cases. *Arch Intern Med 1946;* **78**: 629-61.
4. **Khosla SN, Singh R, Singh GP, Trehan VK.** The spectrum of hepatic injury in enteric fever. *Am J Gastroenterol 1988;* **83**: 413-16.
5. **Khosla SN.** Changing pattern of typhoid (a reappraisal). *Asian Med J 1982;* **25**: 185-98.
6. **Rowland HAK.** The complications of typhoid fever. *J Trop Med Hyg 1961;* **64**: 143-52.
7. **Faierman D, Ross FA, Seckler SG.** Typhoid fever complicated by hepatitis, nephritis and thrombocytypenia. *JAMA 1972;* **221**: 60-61.
8. **Sarma VNB, Malaviya AN, Kumar R, Ghai OP, Bakhtar MM.** Development of immune response during typhoid in man. *Clin exp Immunol 1977;* **28**: 35.
9. **Rajagopalan P, Kumar R, Malaviya AN.** Immunological studies in typhoid fever II. Cell mediated immune responses and lymphocyte subpopulations in patients with typhoid fever. *Clin exp Immunol 1982;* **47**: 269-74.
10. **Ishaq M, Farooqui BJ, Ashfaq MK, Khan MA.** Therapeutic implications of ofloxacin in the treatment of typhoid. *JPMA 1990;* 176-78.
11. **Ramachandran S, Godfrey JJ, Perera MVF.** Typhoid hepatitis. *JAMA 1974;* **230**: 236-40.
12. **Butler T, Bell WR, Levin J, Linh NN, Arnold K.** *Arch Intern Med 1978;* **138**: 407-10.
13. **Hornick RB, Greisman SE.** On the pathogenesis is typhoid fever [Editorial]. *Arch Inter Med 1978;* **138**: 357-59.
14. **Hornick RB, Greisman SE, Woodward TE, Dupont HL, Dawkins AT, Synder MJ.** Typhoid fever: Pathogenesis and immunological control (second of two parts). *N Engl J Med 1970;* **283**: 739-46.
15. **Greisman SE, Hornick RB, Wagner HN Jr, et al.** The role of endotoxin during typhoid fever and tuleremia in man: IV the integrity of the entotoxin tolerance mechanisms during infection. *J Clin Invest 1969;* **48**: 613-29.
16. **Calva JJ, Rulz-Palacios GM.** Salmonella hepatitis: Detection of salmonella antigens in the liver of patients

with typhoid fever. *J Infect Dis 1986;* **154**: 373-74.

17. **Gupta SP, Gupta MS, Bhardwaj S, Chugh TD.** Current clinical patterns of typhoid fever: a prospective study. *J Trop Med Hyg 1985;* **88**: 377-81.
18. **Rajagopalan P, Kumar R, Malaviya AN.** Immunological studies in typhoid fever I. Immunoglobulins, C_3, antibodies, rheumatoid factor and circulating immune comlexes in patients with typhoid fever. *Clin exp Immunol 1981;* **44**: 68.
19. **Mebel TJ, Pankier KJ.** The role of cell mediated immunity in typhoid. *Asian J Infect Dis 1979;* **3**: 69-75.
20. **Samantray SK, Johnson SC, Chakrabarti AK.** Enteric fever: An analysis of 500 cases. *Practitioner 1977;* **218**: 100-8.
21. **Arif N, Khan AA, Iqbal Z.** Hepatic involvement in *JPMA 1990;* **40:** 4-8.
22. **Ayhan A, Gokoz A, Karacadag S, et al.** The liver in typhoid fever. *Am J Gastroenterol 1973;* **59**L 141-46.
23. **Diem LV, My TQ, Chi NV, Nhon Nt, Thuc TK.** Thyphoid fever with hepatitis. *J Tropic Med Hyg 1976;* **79**: 25-7.
24. **Kar P, Bhargava DK, Tandon BN.** Enteric hepatitis: A case report. *J Assoc Physician India 1985;* **33**: 430-1.
25. **Ikeme AC, Anan CO.** A clinical review of typhoid fever in Ibadan, Nigeria. *J Trop Med Hyg 1966;* **69**: 15-21.
26. **Anand AC, Kataria VK, Singh W, Chatterjee SK.** Epidemic multiresistant typhoid fever in eastern Indian [Letter]. *Lancet 1990;* **335**: 352.
27. **Singh DS, Nair PNR, Krishnasamy S, Aurora AL, Chandrasekar S, Bisht DB.** Jaundice in typhoid fever. *J Trop Med Hyg 1978;* **81**: 68-70.
28. **Wicks ACB, Holmes GS, Davidson L.** Endemic typhoid fever: A diagnostic pitfall. *Quart J Med 1971;* **159**: 341-51.
29. **Rao PN, Bhusnurmath SR, Naik SR.** Typhoid fever manifesting with haematamesis, hepatitis and haemolysis. *J Trop Med Hyg 1978;* **81**: 146-50.
30. **Mahapatra AK, Bhatia R.** Salmonella intracerebral and subdural abscess report of two cases. *Post Grad Med J 1987;* **63**: 373-75.
31. **Khosla SN.** The heart in enteric (typhoid) fever. *J Trop Med Hyg 1981;* **84**: 125-31.
32. **Baker NM, Mills AE, Rachman I, Thomas JEP.** Haemolytic-uraemic syndrome in typhoid fever. *Br Med J 1974;* **ii**: 84-87.
33. **Greig HBW, Naidoo PD.** A case of typhoid fever complicated by a severe bleeding syndrome due to deficiency of the prothrombin group of coagulation factors. *J Trop Med Hyg 1981;* **84**: 253-57.
34. **Hoffman SL, Edman DC, Punjabi NH, et al.** Bone marrow aspirate culture superior to streptokinase clot culture and 8 ml 1:10 blood to broth ratio blood culture for diagnosis of typhoid fever. *Am J Trop Med Hyg 1986;* **35**: 836-39.
35. **Gilman RH, Terminel M, Levine MM, Hernandez-Mendoz P, Hornick RB.** Relative efficacy of blood, urine rectal swab, bone marrow and rose-spot cultures for recovery of salmonella typhi in typhoid fever. *Lancet 1975;* **1**: 1211-13.
36. **Hoffman SL, Punjabi NH, Kumala S, et al.** Reduction of mortality in chloramphenicol treated severe typhoid fever by high dose dexamethesone. *N Engl J Med 1984;* **310**: 82-6.
37. **Sitprija V, Pipatanagul V, Boon Pucknavig V, Boon Pucknavig S.** glomerulitis in typhoid fever. *An Intern Med 1974;* **81**: 210-13.
38. **Pang T, Puthucheary SD.** Significance and value of the widal test in the diagnosis of typhoid fever in an endemic area. *J Clin Path 1983;* **36**: 171-75.
39. **Coovadia YM, Singh V, Bhana RH, Moodley N.** Comparison of passive hemagglutination test with widal agglutination test for serological diagnosis of typhoid fever in an endemic area. *J Clin Path 1986;* **39**: 680-83.
40. **Appassakij H, Bunchuin N, Sarasombath S, et al.** Enzyme linked immunosorbent assay for detection of salmonella typhi antigen. *J. Clin Microbiol 1987;* **25**: 273-77.
41. **Rubin FA, Mcwhirter PD, Punjabi NH, et al.** Use of a DNA probe to detect salmonella typhoid in the blood of patients with typhoid fever. *J Clin Microb 1989;* **27**: 1112-14.
42. **Adinolfi LE, Utili R, Gaeta GB, Perna P, Ruggiero G.** Presence of endotoxemia and its relationship to liver dysfunction in patients with typhoid fever. *Infection 1987;* **15**: 55-8.
43. **Woodward TE, Smadel JE, Ley HL, Jr, Green R, Mankier DS.** Preliminary report on the beneficial effect of chloromycetin in the treatment of typhoid fever. *Ann Intern Med 1948;* **29**: 131.
44. **Anderson ES.** Chloramphenicol resistant salmonella typhi. *Lancet 1973;* **2**: 1194.
45. **Anand AC.** The anatomy of an epidemic (the final report on an epidemic of multidrug resistant enteric fever in eastern India). *Trop. Gastroenterol 1993;* **14**: 21-7.
46. **Gupta B, Kumar R, Khurana S.** Multi drug resistant salmonella typhi in Ludhiana (Punjab). *Indian J Pathol Microbiol 1993;* **36**: 5-7.
47. **Nasrallah SM, Nassar VH.** Enteric fever: A clinicopathological study of 104 cases. *Am J Gastroenterol 1978;* **69**: 63-9.
48. **Christie AB.** Typhoid fever and paratyphoid fevers. In: **Christie AB ed.** Bacterial infections of human epidemiology and clinical practice. 4th ed. New York. Churchill-livingstone, 1987: 100-164.
49. **Scragg JN, Rubidge CJ.** Amoxycillin in the treatment of typhoid fever in children. *Br Med J 1975;* **4**: 1031.
50. **Anderson ES, Smith HR.** Chloramphenicol resistance in the typhoid bacillus. *BMJ 1972;* **3**: 329.
51. **Gonzalez-Cortes A, Bessudo D, Sanchez-Leyvar R, Fragoso R, Hinojosa M, Becerril P.** Water borne transmission of chloramphenicol-resistant salmonella typhi in Mexico. *Lancet 1973;* **1**: 605-7.
52. **Wallace M, Yousif.** Spread of multi salmonella typhi. *Lancet 1990;* **336**: 1065-66.
53. **Oldfield III, Edward C, Mark R.** Endemic infections diseases of the Middle East. *RID 1991;* **13**: S202-S203.
54. **DuPont HL.** Quinolones in salmonella typhi infection. *Drugs 1993;* **45**: 119-24.
55. **Rao PS, Rajashekar V, Varghese GK, Shivananda PG.** Emergence of multidrug resistant salmonella typhi in rural southern India. *Am J Trop Hyg 1993;* **48**: 108-11.
56. **Mathai D, Kudva GC, Keystone JS, et al.** Short course ciprofloxacin therapy for enteric fever. *J Assoc Physicians India 1993;* **41**: 428-30.
57. **Hannan A.** In vitro activity of ofloxacin against 210 isolates of typhoid salmonellae. *Infection 1986;* **14**: 5243.
58. **Islam A, Butler T, Nath SK, et al.** *J Infect Dis 1988;* **158**: 712-17.
59. **Pape JW, Gerdes H, Oriol L.** Typhoid fever: successful therapy with cefoperazone. *J Infect Dis 1986;* **153**: 272-76.
60. **Girgis NI, Kilpatrick ME, Farid Z, Sultan Y, Podgore JK.** Cefixime in the treatment of enteric fever in children. *Drugs Exp Clin Res 1993;* **19**: 47-9.
61. **Woodward TE, Smadel JE.** Management of typhoid fever and its complications. *Ann Intern Med 1986;* **60**: 144-57.
62. **Cooles P.** Adjuvant steroids and relapse of typhoid fever. *J*

Trop Med Hyg 1986; **89**: 229-31.
63. **Dunlop JM.** Salmonella infection in the community. *Publ Hlth Lond 1985;* **99**: 79-84.
64. **Levine MM, Myron M, Robert F.** Claudio Lanata and the chilean typhoid committee. Precise estimation of the numbers of chronic carriers of salmonella typhi in santiago, chile and endemic areas. *J Infect Dis 1982;* **146**: 724-26.
65. **Hudson SJ, Ingham HR, Snow MH.** Treatment of salmonella typhi carrier state with ciprofloxacin [letter]. *Lancet 1985;* **5**: 1047.
66. **Pleydell M.** One small slip and its consequences. *BMJ 1984;* **289**: 1729-31.
67. **Gendrel D, Richard-Lenoble D, Kombila M, et al.** Schistosoma intercalatum and relapses of salmonella infection in children. *Am J Trop Med Hyg 1984;* **33**: 116-69.
68. **Yugoslav Typhoid Commission.** *Bull WHO 1964;* **30**: 623-30.
69. **Gilman RH, Hornick RB, Wood Ward WE, et al.** Immunity in typhoid fever. Evaluation of Ty 21a an epimeraseless mutant of S. typhi as a live oral vaccine. *J Infect Dis 1977;* **136**: 717-23.
70. **Wahadan MH, Serie C, Cerisier Y, Sallam S, Germanier R.** A controlled field trial of live salmonella typhi strain Ty 21a oral vaccine against typhoid: three year results. *J Infect Dis 1982;* **145**: 292-5.
71. **Levine MM, Ferreccio C, Black RE, Germanier R.** Large-scale field trial of Ty 21a live oral vaccine in enteric coated capsule formulation. *Lancet 1987;* **2**: 1049-52.
72. **Ferreccio C, Levine MM, Rodriquez H, Contreras R.** Chilean typhoid committee. Comparative efficacy of two, three or four doses of Ty 21a live oral typhoid vaccine in enteric coated capsules. A field trial in an endemic area. *J Infect Dis 1989;* **159**: 766-69.
73. **Levine MM, Ferreccio C, Cryz S, Ortiz.** Comparison of enteric coated capsules and liquid formulation of Ty 21a typhoid vaccine in randomized controlled field trial. *Lancet 1990;* **336**: 891-94.
74. **Acharya II, Lowe CU, Thapa R, et al.** Prevention of typhoid fever in Nepal with the vi capsular polysaccharide of salmonella typhi. A preliminary report. *N Eng J Med 1987;* **317**: 1101-4.
75. **Shafqat F, Iqbal Z, Khan, AA, et al.** Hepatic involvement with typhoid fever. *Proceedings SZPGMI 1994*; **8** 38-42.

The Authors:

Farzana Shafqat,
Senior Registrar
Department of Medicine,
Shaikh Zayed Hospital,
Lahore.

Anwaar A. Khan
Professor of Gastroenterology
Shaikh Zayed Hospital,
Lahore.

Zafar Iqbal,
Professor of Medicine,
Shaikh Zayed Hospital,
Lahore.

Farrukh Iqbal,
Assistant Professor of Medicine,
Shaikh Zayed Hospital,
Lahore.

Address for Correspondence:

Farzana Shafqat,
Senior Registrar
Department of Medicine,
Shaikh Zayed Hospital,
Lahore.