Typhoid is widely prevalent in all parts of the world but its incidence has considerably declined in developed counters due to improvement in sanitation, economic factors and quality of life.

The worldwide incidence of Typhoid is approximately 12.5 million cases annually with more than 62 per cent of the cases occurring in India and other Asian counters and 35 per cent in African countries.

Enteric diseases have been the scourge of civilization since days of yore and were of concern to Moses as shown by his insistence on appropriate sanitary laws. A disease entity having clinical features suggestive of Typhoid was known to Hippocrates, the father of medicine (about 460 to 377 BC) and to Galen (about 200 to 130 BC).

Typhoid has been a bane of nations and every nation in the world has paid a price because of this disease. Most of the wars in the world have borne brunt of Typhoid. In the Spanish American war one fifth of the troops belonging to U.S. Army had Typhoid and more than 1500 died of it. Similarly in Boer war the British Army lost more men to Typhoid than it did to wounds and other war injuries.

We have traveled a long time since then. For almost a century Typhoid fevers have been the bane of under developed and tropical countries with consequent high levels of morbidity and mortality. These did show signs of abating with the coming of chloramphenical in 1948 and case fatality rates declined but during the last few decades there came resurgence of disease with newer facets. The classical patterns of the disease started changing and cases of Typhoid presented with more serious profile and many the complications were masking the clinical profile. Diseases may show new facets depending on the pathogenicity of organisms, the introduction of newer therapeutic agents and other factors which change from time to time. This holds true for Typhoid also. The older classical textbook description of Typhoid seems to be the exception rather than the rule and the clinical profile of the disease is changing.

**CLINICAL PROFILE**

Distinctive clinical signs and symptoms are usually not present in a case of Typhoid, one more often sees cases with intermittent or remittent fever than the classical step ladder pattern. There is often tachycardia in contrast to the oft held view of bradycardia being an important sign in a case of Typhoid. Toxic manifestations such as headache, dry coated furred tongue, cough, abdominal symptoms, malaise etc. may be observed only in 50% of the cases while a great majority may be seen with atypical presentation.

The onset of the cases of Typhoid is not uniform and disease may start in any of the following ways:

a. Acute pyrexial onset which is seen in 50% of cases and is characterized by sudden onset of fever, headache, body ache, malaise, loss of appetite, abdominal discomfort and varying degree of toxemia. Some may start with high fever and severe toxemia, and a few rapidly go into a ‘Typhoid state’ in a period of one or two days.

b. Upper respiratory tract infection like onset (cough, sore and inflamed throat in about 25% of patients exceptionally a membrane over the tonsils) may be seen.

c. Gastrointestinal symptoms may sometimes predominate and are the major presenting feature. There is diarrhea and vomiting of varying severity which may mimic a classical case of gastroenteritis. Fever may be seen just before during or even after the onset of gastroenteritis. This type of presentation is seen on an average in 5 to 10 per cent of patients.

d. Slow insidious onset characterized by low fever rising in a step ladder fashion and reaching its peak in approximately a week with toxemia often appearing sometimes later on. On an average, 10 per cent of patients present with this type of onset.

e. Onset with complications is a very distinctive feature of cases of Typhoid with a serious profile. This may be in the form of neuropsychiatric manifestations (encephalopathy, psychosis, delirium, convulsions), peripheral circulatory failure, shock, hemorrhage, intestinal perforation, myocarditis etc.

Recognition of such cases is possible only if one keeps in mind the possibility of typhoid in any case of fever with odd manifestations. A careful history may reveal that the patient has had fever sometimes during the preceding 2 or 3 weeks; or fever may appear with
or immediately precede these complications. The whole clinical profile of typhoid is often so variable that one cannot specifically lay down rigid guidelines.

Splenohemorrhage is usually found in the majority of cases, the incidence ranging from 10 to 86 per cent. It usually becomes palpable during the second week of illness and may take from a few days to a week to recede.

Gurling caecum is an important sign and may be seen in majority of patients. It is an important diagnostic sign in a suspected case. The incidence of rose spots is variable especially in cases of dark skinned people. An incidence of 8% to 58% is reported from European countries with white populations; while a low incidence (1-6%) is reported from Africa, India and South Asia.1

With such a varied clinical picture it is no wonder that a case of typhoid may present features which are clinically indistinguishable from some other common ailments seen in tropics. Thus a case presenting with intermittent fever with rigors and chill is likely to be confused with a case of malaria while the case with predominant chest signs gets mimicked by acute bronchitis or lobar pneumonia. Cases where gastrointestinal symptoms predominate may look like cases of gastroenteritis. In the presence of perforation the case often presents a picture of acute abdomen. Cases of typhoid with predominant neuropsychiatric manifestations are often labeled as cases of encephalitis or land up in psychiatric units because of predominant psychosis.

Typhoid is a multisystem disease and there is hardly any organ in the body which is not involved due to typhoid. Very often fatal major complications occur which have a direct bearing in the causation of high mortality.

NEUROPSYCHIATRIC COMPLICATIONS: 2-5

During the last few years the incidence of neuropsychiatric complications in cases of typhoid is on the increase and the neuropsychiatric symptoms are now dominating the clinical picture to such an extent that the organic basis of the disorder is almost completely obscured.

Like many infectious diseases, typhoid also uses the central nervous system to express itself. Confusional states or delirium account for the highest incidence (54-76%). Various other manifestations include encephalopathic syndrome (acute, meningocerebral meningitis and neurologic deficits, hemiplegia, stupor, coma, convulsions, neuritis (cranial/peripheral) and psychosis (paranoid; melancholic; mania, hypomania, catatonie schizophrenia and non-specific psychosis) etc.

Neuropsychiatric manifestations present in the form of two major groups. In the first group there is acute onset characterized by delirium or confusional state, behavior disturbances, neck rigidity, involvement of organic reflexes and without much fever. The second group includes cases which present with slow insidious onset, and in which the degree of temperature varies with toxemia. There may be semicoma/coma and transient, Parkinsonism or Parkinsonian rigidity. Some cases of typhoid may present as acute brain syndrome or psychosis. Recognition of these cases as those of typhoid will to a long way in the diagnosis and prognosis of such cases.

Biochemical alterations in CSF and blood have been observed in cases of typhoid with neuropsychiatric manifestations. Low level of magnesium are known to produce restlessness, irritability, tremors and convulsions; while increased levels of calcium depress brain activity producing drowsiness and coma. Alterations in calcium and magnesium level act synergistically to produce the clinical profile but interestingly these revert to normal with recovery. It is possible that endotoxins from typhoid bacilli increase the susceptibility of the nervous system to changes in concentration of these ions. Malnutrition and anaemia may produce changes in the internal and external environment of cells so that clinically neurological manifestations may be seen at less severe levels of ionic alterations. Though a correlation between neuropsychiatric manifestations and electrolyte abnormalities is established yet it is difficult to say whether these have a casual role or are result of toxemia and encephalopathy.

The pathogenesis of neuropsychiatric manifestation in typhoid is difficult to explain. One can speculate that these may be result of endotoxia or S. typhi interfere transiently with the cholinergic dopaminergic control of the basal ganglia resulting in Parkinsonian rigidity. Some other factors such as enzymatic defects induced by bacterial endotoxia, direct invasion of brain cells by organisms causing altered metabolism, presence of pre-existing nervous disease, demyelination, hypoxia to poor nutrition and alterations in immune response have been postulated. Neurological involvement with its multifaceted picture has an important bearing on the profile of a case of typhoid.

HEART IN TYPHOID:7

The heart is quite frequently involved in cases of typhoid. There are no differences in the incidence within the prechloramphenicol (31-70%) and post chloramphenicol era (37-80%). Electrocardiographic abnormalities may be slight or severe and may show changes characteristics of myocarditis or rhythm alterations. These abnormalities are often related to severity of disease. The electrocardiogram returns to normal in patients who survive. Persistence of ECG changes and development of arrhythmias are indicators of bad prognosis. ECG alterations in cases of typhoid are due to structural damage to the myocardium produced by salmonella typhi infection. Abnormalities in tracings are expressions of typhoid myocarditis which is often the cause of death.

Clinically myocarditis in a case of typhoid should be suspected if the patient has inordinate tachycardia, diminished intensity and/or a soft quality of the first heart sound, gallop rhythm, rapidly developing cardiac enlargement, conduction defects and signs of congestive heart failure.

675
Myocarditis in typhoid always portends a serious prognosis. It is usually seen in severely ill patients, either during the acute period of the disease process, or when the disease process in fulminating.

INDENTINAL PERFORATION

Perforation in case of typhoid is another major complication which takes a great toll of life. Its incidence varies from 1.9 to 11.2%. Mortality is high in patients with late onset, poor nutrition, very high or low leucocyte count, delay in the diagnosis and institution of treatment. A case showing classical signs of perforation is usually the exception rather than the rule. When it does occur perforation tends to occur suddenly in a person who is apparently well, and who very after ignores the mild temperature he is running. This coupled with a dietetic indiscretion is another factor worsening the prognosis. When haemorrhage complicates perforation it makes the prognosis even more grave.

Other complications of typhoid which have bearing on high mortality includes intestinal hemorrhage, peripheral circulatory failure, typhoid pneumonia, toxic nephritis, and typhoidnephritis leading to renal failure.

TYPHOID HEPATITIS

Isolated hepatic enlargement in case of Typhoid is of no clinical significance unless it is associated with jaundice. Biochemical alterations or histopathological changes in liver. Typhoid hepatitis is an important complication and should be seriously considered in patients of fever with jaundice. Recognition of this entity is important since jaundice in a case of fever is likely to be confused with viral hepatitis.

Hepatic encephalopathy a manifestation of Typhoid hepatitis is very rare. Presence of neuropsychiatric features in a case of Typhoid hepatitis is likely to confuse the picture. A higher incidence of Typhoid hepatitis is seen in patients of anaemia and malnutrition as their immune response is poor. Histopathology of liver in cases of Typhoid hepatitis may ranges from non-specific changes to marked cloudy swelling, parenchymal degeneration, peripheral infiltration by mononuclear cells and central area of necrosis (Typhoid/Mallory nodule). Presence of Typhoid/Mallory nodule in histopathology is specific for Typhoid hepatitis.

REAL STATUS IN TYPHOID

Renal involvement in Typhoid can be either functional or pathological. It may be in the form of transient glomerular disease or acute renal failure due to hemolysis. Direct involvement of kidneys may be seen in those patients of typhoid who have some preexisting renal disease. In a severely ill and toxic patient of typhoid, a form of toxic nephritis occurs which to a large extent depends on alterations in immune system. Nephritis as such associated with Typhoid is rare and is observed in about 2% of patients.

Complement levels (C3) have been found to be altered in Typhoid fever patients and these circulating immune complexes represent the stage of immune elimination and are important indicators of injury to a target organ. As the renal parameter touch normal range, immune complexes can no longer be detected in the serum, indicating that renal dysfunction in patients of Typhoid is secondary to circulating immune complexes.

Direct role of salmonellae in the pathogenesis of glomerulitis is demonstrated by the detection of Salmonella V antigen in the damaged glomeruli.

Histopathological study of kidneys shows no glomerular or tubular abnormality since kidneys are transiently involved in very toxic and ill patients of typhoid. Only very moribund patients pass into irreversible renal damage.

IMMUNE RESPONSE IN TYPHOID

Both cell mediated immune (CMIR) and humoral immune responses develop in patients of Typhoid independent of each other. Specific CMIR appears by about second week of illness in patients with no complications while it is either delayed or remains absent in patients who have complications. Clinical recovery of patients with complications coincides with development of CMIR indicating that it is more important than humoral immune response. Humoral immune response is unrelated to complications, while a depressed cell mediated immune response is important in relation unrelated to complications like intestinal perforation, intestinal haemorrhage and pneumo typhoid. The hosts normal immune defence mechanism is at a lower level in all patients of Typhoid with a serious clinical profile. Poor nutrition, anaemia, deficiency state in addition to body's immune response play significant role in morbidity and mortality of Typhoid.

HAEMATOLOGICAL PROFILE IN TYPHOID

Haematological picture in Typhoid is well documented and comprises leucopenia with disappearance of eosinophilic cells and a relative increase of mononuclear cells.

Various haematological manifestations include acute haemorrhage, haemolytic uraemic syndrome, haemolytic anaemia and disseminated intravascular coagulation (DIC). Consumptive coagulopathy is commonly seen and there is often evidence of subclinical DIC in patients of typhoid.

Thrombocytopenia commonly seen is due to decreased production of platelets during acute infection or in part by increased destruction of platelets by the reticuloendothelial system. Subclinical DIC may be a contributing factor and drugs may also play a role. Bone Marrow is normocellular in most of the patients. Raised myeloid erythroid ratio suggests either increase in number of myeloid cells or decrease in number of erythroid cells or both. Rise in plasma cells suggests a non-specific humoral immunologic response to infection.

Blood changes seen in patients of typhoid can be correlated to direct effect of endotoxins on the bone marrow.
RELAPSE IN TYPHOID\textsuperscript{16}

It is one of the common complications of Typhoid which is often not considered by the clinician. Its incidence varies from 6-20\% and is more in cases who had prolonged duration of illness and not been treated adequately. Faulty nursing, inadequate rest and dietetic indiscretions further enhance the risk of relapse. Relapse is high in patients who had complications like hepatitis. Myocarditis, neuropsychiatric complications etc.

Adjuvant steroid therapy also increases relapse rate and it is high in patients treated with chloromycetin, trimethoprim – sulfhemethoxazole, amoxycillin, while it is low in patients treated with quinolones and cephalosporinics. Emergence of drug resistant strains of S. typhi has further increased chances of relapse.

Patients who relapse generally have poor nutrition and are malnourished. There is depression of CMIR in these patients. CMIR is a major defense mechanism to prevent relapse.

TYPHOID AND CARRIER STATE\textsuperscript{17}

An important aspect of Typhoid which often remains unidentified is the prevalence of carriers who pose danger to the community since they escape recognition and continue to live anormal life, but act as source of chronic infection in the community. Incidence of Typhoid carriers runs parallel to the disease and ranged from 2-5\% in pre-chloramphenicol era but there is no change in its incidence even now in the present age.

Carrier state is governed by age (higher at age 50 as at age 20) sex (twice in females as in males), etiological serotypes and patients defence mechanism. Most of these people go on shedding salmonella irregularly and infrequently.

Use of quinolones is an important weapon in the treatment of a typhoid carrier since the drug penetrates in most of the body tissues. A 4 weeks course gives good results.\textsuperscript{18}

DIAGNOSIS

Recognition of cases of Typhoid is important since a diagnosis of Typhoid can only be made if such a possibility is kept in any case of fever with odd presentation.\textsuperscript{12}

A careful history may reveal that the patient has had fever sometimes during the preceding two or three weeks or fever may appear with or immediately precede its various complications. Any patient with prolonged fever, bizarre symptoms and confusional state or delirium should alert a physician in tropics to suspect Typhoid. Gastrointestinal symptoms like diarrhea and vomiting may mimic a case of gastroenteritis. Fever may be seen before, during or even after the onset of gastrointestinal symptoms. Toxic manifestations such as headache, dry coated flurred tongue, cough, abdominal symptoms, beradycardia, malaise etc. may be observed in only 50\% of the cases. Splenic enlargement in the form of a soft tender spleen about two to three cm. below the costal margin is seen in 70-80\% of the cases. It usually becomes palpable during these second week and may take from a few days to a week for it to recede.

Gurgling caecum is an important sign and may be seen in majority of patients. Rose spots seen in fair coloured individuals is not commonly seen in dark coloured people. So the first and foremost step in making a diagnosis is strong suspicion about typhoidin a case of fever presenting with odd features. A simple total and differential leukocyte count shows leucopenia with relative lymphocytosis and eosinopenia. Sudden increase in total leucocyte count to 10,000/cmm\textsuperscript{3} or higher shall point to the development of intestinal perforation or haemorrhage.

Widal test is helpful in making a presumptive diagnosis. It has a low sensitivity because a significant number of culture positive patients do not develop antibodies as detected by the test. Of the two antigens, somatic antigen 0 is more important than Flagellar antigen ‘H’. A four fold or more increase in 0 antigen titre in excess of 1:160 shall provide presumptive diagnosis. ‘H’ antigens are not so specific since they remain elevated after a recent infection or immunization.

Blood culture is important in making a diagnosis of Typhoid. It is positive in 60-90\% of the cases during the first week and falls to 40\% in the third week of illness. The percentage of positive culture falls especially if the patient has taken prior antibiotics. Bone marrow cultures are very important in establishing a diagnosis of the disease, since they are specific and are not effected by prior intake of antibiotics or the duration of illness. The percentage of positivity with this tool is up to 95\%. It is a simple and safe method to establish the diagnosis and sensitivity of the organism.

Stool culture and urine culture now have become more of academic interest than of practical value. Stool culture for typhoid is positive in 10-15\% of cases in first week and its positivity goes up to 75\% in 3\textsuperscript{rd} - 4\textsuperscript{th} week. After eight weeks it is only 10\% and three percent of patients continue to excrete organism even after one year.

Urine culture positivity runs parallel with stool culture. Salmonella are shed in urine irregularly and infrequently and for just establishing diagnosis of typhoid in early weeks they may not be very useful. Because of irregular shedding of organisms in stools and urine, the cultures from these are helpful in identifying carriers.

A number of other methods like clot culture, duodenal string capsule culture, Elisa and detection of Salmonella antigens with monoclonal antibodies are also useful diagnostic helps. Culture for Salmonella typhi have been taken from Rose sports, suppurative lesions, CSF and sputum with variable degree of positivity. But for clinical practice, serial estimation of widal antibodies. Blood and bone marrow culture are important tools in establishing diagnosis of typhoid.

MANAGEMENT\textsuperscript{11,13}

An uncomplicated case of typhoid is not difficult to manage. General supportive measures include bed rest, maintenance of...
satisfactory fluid and electrolyte balance, adequate nutrition and general as well as personal nursing care. In acute stage of illness hyperpyrexia shall require hydrotherapy and if patient is unable to take sufficient fluids orally then intravenous hydration be employed. Presence of shock shall necessitate use of vasopressor drugs and steroids.

ANTIMICROBIAL AGENTS: 

One of the earliest and effective drug employed in the treatment of typhoid has been chloramphenicol which has been the first line of therapy in cases of typhoid. It has been effective in febrile toxic course of the disease in greater proportion of cases in shortest time and in reducing the fatality rates. But its major drawback is the production of toxic reactions in the form of bone marrow depression which may either be dose related or hypersensitivity reaction which is genetically controlled. Because of its toxicity and emergence of drug resistant, Strains of almonella the use of chloramphenicol in the treatment of typhoid has almost been reduced to nil.

Drugs like Ampicillin; Amoxycillin, Cotrimoxazole, Furazolidine, and Cotrimazine are good alternatives to chloramphenicol though inferior but again resistance to these drugs has also been encountered and poses a serious difficulty in some cases of typhoid. Combination of more than one antibacterial agents like quinolone derivative and an aminoglycoside attacking the organism acting at two different sites may prevent rapid emergence of resistance against these drugs.

Fluroquinolones have now emerged as potent drugs against Salmonella being effective both orally and parenterally and are able to attain appropriate levels in gut, liver and gall bladder. Ciprofloxacin has a wide antibacterial spectrum and is effective against resistant strains of Salomonella though occasional case of resistance to it is also being seen. The drug achieves rapid clinical and bacteriological cure and most of the patients become a febrile in 3-4 days. Dosage orally is 500 mg twice a day for 10-14 days. In seriously ill patients drug is employed parenterally.

Third generation cephalosporins and quinolones like Cetriaxone and Cefoperazone are the other drugs which are found to be effective in treating seriously ill patients of drug resistant salmonella.

Steroids: Use of steroids in case of typhoid often raises controversy. An uncomplicated case of Typhoid does not require any additional use of steroids and it is only in seriously ill patients where these are indicated. Oral predisol can in the dose of 40-60 mg per day is effective and in those who are very ill, toxic or in shock adequate doses of steroids parenterally be employed. Use of steroids is based on the assumption that adrenocortical functions are impaired in the acute stage of illness. It is a transient phenomenon and patients of typhoid who do not have severe toxemia do not require supplementation with steroids.

Management of Typhoid with Complications: Cases of Typhoid with predominant neuropsychiatric features will require in addition to general supportive measures, institution of appropriate antimicrobial agents (Ampicilline/Gentycin/Ciprofloxacin) along with steroids. Convulsions, psychotic features shall require drugs like dilantin, diazepam, prochlorperazine etc. No generalization can be made and the treatment will vary from patient to patient. Mortality shall depend on number of factors like nutrition of the patient, and the stage at which the patient comes. Intestinal haemorrhage in most cases is to be managed by general supportive measures and replacement of blood loss.

Cases of myocarditis, hepatitis have to be managed on conservative lines with the use of appropriate antimicrobial agents and steroids. Cases of typhoid with persistent arrhythmias shall require in addition use of antirrhythmic drugs.

Prognosis in any case of typhoid shall depend on severity of disease process, toxemia, state of nutrition of the patient, presence of complications and drug resistant organisms. A correct and early diagnosis coupled with institution of treatment shall go a long way in reducing morbidity and mortality in a case of Typhoid.

PROPHYLAXIS:

Immunization against Typhoid may not give 100% protection but it does lower the incidence and morbidity of the disease. TAb vaccine has been in use since long and has a short lived effect on individual resistance. It does not protect an individual from Typhoid completely and severe form of Typhoid may occur even in vaccinated individuals. VI Capsular polysaccharide (Vicps) is a single parenteral vaccine and provides protection against the disease for 3 years and dthis ranges between 67-75%. Reactions include pain, swelling or erythema at the site, fever and nausea. It is useful for prevention of Typhoid fever in adults and children over two years of age.

Live attenuated oral vaccine (Ty21a strain) is another vaccine. It is a plasmid containing enzyme deficient and genetically crippled strain and its capacity to survive in the intestinal tract gives a protection rate of 90-95%. Three doses of the vaccine (one capsule on days 1,3, and 5), one hour before a meal with a cold or lukewarm drink e.g. milk is advocate). Protection commences 2 weeks after taking the last capsule and lasts for at least 3 years. Live oral typhoid vaccine is indicated for immunization of adults and children above 5 years of age. Booster dose of the vaccine which consists of same three doses is recommended once every three years. Side effects include mild gastrointestinal disturbances and a transitory exanthema. Results with oral vaccine are encouraging as has been shown by the field trails.

To sum up Typhoid despite the introduction of newer antimicrobial agents still remains a major health problem in our country. Its clinical profile is changing and none comes across a more serious profile of the disease. Emergence of drug resistant strains has further complicated the picture. Because of its bizarre presentation its early and correct recognition is important to prevent the morbidity of the disease.
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