THE INCIDENCE AND MANAGEMENT OF TYPHOID FEVER IN NIGERIA

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ABSTRACT

Typhoid or enteric fever is caused by Salmonella typhi. It is largely a disease of developing nations due to their poor standard of hygiene and unavailability of potable water. It is transmitted faeco-orally through contaminated food and water. The most prominent feature of the infection is fever which gradually rises to a high plateau. Symptoms such as diarrhoea, constipation, abdominal pain and encephalopathy may occur. Complications like intestinal perforation and gastrointestinal haemorrhage may occur in severe disease. The gold standard of diagnosis is by isolation of the organism from culture of blood, bone marrow aspirate, stool, bile, rose spots or urine. The Widal test which is commonly used here is not a reliable diagnostic modality. Treatment is by use of antibiotics and drugs of choice are the fluoroquinolones and third generation cephalosporins.

BACKGROUND

Typhoid or enteric fever is a systemic infection caused by *Salmonella typhi* or by related but less virulent *Salmonella paratyphi*. Today typhoid fever is rare in industrialized nation. But remains a serious health threat in the developing nations where the level of hygiene is poor and potable water not readily available. In Nigeria however typhoid fever appears to be over diagnosed due to over reliance on the Widal test which can be affected by other infections including malaria which is prevalent here.

EPIDEMIOLOGY

Typhoid fever is endemic in Africa, Asia, Latin America, the Caribbean and Oceania. World-wide more than 13-17 million people are affected annually with 600,000 deaths.[1] Recent epidemiologic studies showed incidence rates of >100/100,000 population per year in south east and south central Asia which have the highest endemicity; the rest of Asia, Africa, Latin America, Caribbean and Oceania had the next highest rates of 10 – 100/100,000 population per year.[2] Incidence in travellers was estimated to be 3-30 /100,000 travellers to developing countries.[3] Ogunleye *et al*[4] in a 1 year review done in children at Ibadan found an incidence of 12.5% for *S.typhi* and 3.9% for *S. paratyphi*. There is no racial or sex predilection. Children 1-5 years are at highest risk of infection, morbidity and mortality.

AETIOLOGY

Salmonellae belong to the family of Enterobacteriacae. They are gram negative, non-sporing, flagellate, facultative anaerobic bacilli. They are glucose fermenting and synthesize peritrichous flagellae when motile and all but *S.typhi* produce gas upon sugar fermentation. It possesses a flagella (H) antigen, a cell wall (O) lipopolysaccharide antigen, and a polysaccharide virulence (Vi) antigen located in the cell capsule. The polysaccharide side chain of the O antigen confers serologic specificity to the organism and is essential in virulence.

TRANSMISSION

Transmission is by the fecal-oral route through contaminated water or food. The main sources of infection in the community are asymptomatic carriers and cases during either disease or convalescence. *S. typhi* survive prolonged periods in dried sewage, water, food and ice because they are resistant to drying and cooling, direct fecal–oral transmission occurs occasionally. Shell fish taken from sewage polluted beds are an important source of infection. Infection may also occur through eating raw fruit and vegetables fertilized with human faeces and from milk and milk products. Flies may transfer infection to foods.

PATHOGENESIS AND PATHOLOGY

After ingestion of *S. typhi*, the part of the innoculum that survives the stomach acid enters the small intestine, where they penetrate the mucosa and enter mononuclear phagocytes of ileal Peyer's patches and mesenteric lymph nodes. About 10^5-10^7 bacteria or more are required to cause disease. The bacteria proliferate in the mononuclear phagocytes and spread via the blood to the spleen, liver, gall bladder and bone marrow where they further proliferate in macrophages. Inflammatory reactions occur in the spleen, liver, bone marrow, Peyer's patches in the terminal ileum

mainly and skin, and consists of mononuclear cell infiltration, hyperplasia and focal necrosis. Gall bladder inflammation may lead to cholecystitis and patients with pre- existing gall bladder disease have a penchant for becoming carriers as the bacilli may become incorporated into gall stones. Focal collections of mononuculear leukocytes are called "typhoid nodules". Fever and other constitutional symptoms are probably due to release of cytokines including tumor necrosis factor and interleukin 1 from infected phagocytes. Intestinal symptoms are caused by hyperplasia of Peyer's patches with ulceration of overlying mucosa, resulting in pain, diarrhoea, bleeding if it erodes into a blood vessel or perforation[5].

RISK FACTORS

Salmonellae are usually killed at a pH of <1.5. Thus patients who continually ingest antacids. H_2 receptor antagonists or proton pump inhibitors; who have had gastrectomy or have achlorhydria due to aging or other factors require fewer bacilli to produce disease. Also acquired immune deficiencies or hereditary deficiencies increase the risk of infection, complications and death[1].

CLINICAL FEATURES

The incubation period for *S.typhi* is 3-21days[7]. The variability may be due to the size of the inoculum, the health and immune status of the host. Transient diarrhoea (enterocolitis) may occur during the incubation period.

Prolonged fever (38.8 to 40.5°C) which gradually rises to a high plateau (step ladder pattern) is a prominent feature of this infection. A prodrome of non-specific symptoms like chills, headache, anorexia, dry cough, weakness, sore throat, dizziness and myalgias may precede fever. Gastrointestinal symptoms include diarrhoea or constipation; diarrhoea being commoner in AIDS patients and children <1year of age. Abdominal pain occurs in 20-40% of patients[7]. Towards the end of the first week, an evanescent rash (rose spots) may appear on the chest, shoulders and abdomen in light skinned patients (difficult to detect in dark skin). The rash blanches on pressure and fades after a few days. Splenomegaly and hepatomegaly may occur. There may be temperature-pulse dissociation (relative bradycardia).

In the second week the fever may become more continuous and the patient more sick and withdrawn. In the third week the patient's illness evolves into the 'typhoidal state' with disordered mentation including psychosis, and in some cases extreme toxaemia and weight loss and unarousable stupor ('coma vigil'). During this period intestinal involvement often occurs and is manifested clinically by greenish 'pea soup' diarrhoea and the dire complications of intestinal perforation and hemorrhage may occur[6].

In the fourth week the fever reduces and there is usually improvement in the clinical status. The symptoms and signs may however return after about 2 weeks.

Paratyphoid fever causes similar symptoms and signs, but is usually milder and recovery quicker.

About a quarter of untreated patients become chronic carriers. The presence of *Schistosoma haematobium* infection predisposes to urinary carriage while gall bladder disease predisposes to stool carriage.

DIAGNOSIS

Culture: This is the 'gold standard'[7]. Also makes it possible to test antibiotics susceptibility. Blood culture is positive in about 90% of patient's during the first week and in 50% by the third week. Bone marrow culture also has a high yield even after 5 days of antibiotic treatment. Stool cultures become positive in the second and third weeks while urine culture is positive in about 25% of patients in the third week. Bile culture obtained from an over-night duodenal string capsule has a high yield. Rose spots, rectal swab and CSF cultures may also be positive. Cultures are unfortunately not readily available in our environment.

Widal test: This test which is an agglutination test that detects the O and H antigens is simpler and cheaper than culture. But it has many pitfalls and so may not be a reliable index for making a diagnosis of typhoid fever[8,9]. The antibody level in the normal population in a locality needs to be established so as to determine a threshold above which the antibody titre is considered significant. This is particularly important of a simple acute sample is available for testing. If paired sera are available, a 4-fold rise in the titre between the convalescence and acute sera of 7-10days interval is diagnostic. False positive Widal results can occur in malaria[10], typhus, bacteraemia from other organisms and cirrhosis[11]. Thus it is important to screen for malaria in an environment like ours when making a diagnosis of typhoid fever[12].

IDL Tubex^R Test: This detects antibodies to a single *S.typhi* antigen i.e 09 antigen. It is very specific and the antigen is only found in serogroup D salmonellae. This test has however not been evaluated extensively. But several trials are on the way[11].

Typhidot R test: This makes use of the 50KD antigen to detect specific IgM and IgG antibodies to S.typhi. This test offers simplicity, speed, specificity (75%), economy, early diagnosis, sensitivity (95%) and high negative and positive predictive values. IgM indicates acute infection in early phase, while detection of IgM and IgG shows acute typhoid in middle phase of infection. IgG may persist for up to 2 years after infection. A modification of this test: Typhidot-M inactivates the total IgG in the serum sample, thus making only IgM available for binding.

Typhidot-M has been found to be superior to the Widal test and culture methods with sensitivity of >93%[11].

IgM dipstick test: This detects *S.typhi* specific IgM in serum or whole blood. The assay is based on the binding of *S.typhi* specific IgM antibodies to LPS antigen and the staining of bound antibodies by an antihuman antibody conjugated to colloidal dye particles. Studies showed sensitivities of 95-100% for samples collected at time of first consultation. The dipstick test provides a rapid and simple alternative for diagnosis, particularly where culture facilities are not available.

DNA testing: Polymerase chain reaction assays for identifying *S.typhi* are available in some areas. However this is used mostly for research since the test is generally too expensive for patients in developing countries.

Other laboratory findings may include mild normochromic anaemia, mild thrombocytopenia, and increased erythrocyte sedimentation rate. The white cell count may be normal or decreased. Leukocytosis suggests either perforation or another diagnosis[13]. A liver function test may show elevated levels of transaminases and bilirubin. Renal failure is an infrequent complication. In patients with diarrhea, the stool shows fecal leukocytes.

Imaging studies may be necessary if perforation is suspected.

TREATMENT

The health care workers caring for typhoid patients should pay strict attention to hand washing and safe disposal of faeces and urine. Antibiotic treatment is the only effective treatment for typhoid fever and should be commenced empirically while confirmatory tests are pending if clinical evidence is strong. Antibiotic resistance however remains an important problem in Africa and Asia because of the possibility to by antibiotics over the counter in the open market. Susceptibility patterns of *S.typhi* in Africa and Asia have shown high rates of multidrug resistance.[14]

Chloramphenicol was the first antibiotic found to be effective against typhoid fever, but is no longer used in many areas because of the emergence of multidrug resistant strains and also its potential for bone marrow toxicity.

Ampicillin, Amoxycillin, Trimethoprim- Sulfamethoxazole was also effective. But again a high rate of resistance to them has developed.

The drugs of choice currently for the empirical treatment of typhoid fever are the quinolones and third generation cephalosporins. Azithromycin is also effective in treatment of MDR *S. typhi*.

The fluoroquinolones are generally well tolerated and can be given orally or intravenously. Examples are ciprofloxacin 500mg bid, ofloxacin 200-400mg bid, perfloxacin 400mg bid, levofloxacin 500mg qd. Duration of treatment is 5-7 days in uncomplicated disease and 10-14 days in severe disease. Recent reports from a study in Lagos by Akinyemi *et al* [15] shows reduced susceptibility to fluoroquinolones. This is worrisome, but fluoroquinolones still remain the drugs of choice.

Ceftriaxone 1-2g q12h, cefixime or Azithromycin 500mg-1g q.d are recommended in quinolone resistant uncomplicated disease, while Ceftriaxone or Cefotaxime are recommended in severe disease also. Duration of therapy with cephalosporin is 10-14 days, while it is 7 days for Azithromycin.

In cases with mental state changes, high dose dexamethasone 3mg/kg stat, followed by 6hrly dose of 1mg/kg for 8 doses has been found effective. High dose prednisolone may also be used.

In complicated cases, surgical therapy may be required. Chronic carriers may be treated with ciprofloxacin 750mg twice daily or norfloxacin 400mg for 28days. This leads to 80% clearance rate. Alternatively, Amoxycillin or Ampicillin (100mg/kg/day) plus probenecid (1g orally or 23mg /kg in children) for six weeks achieves 60% clearance rate. Cholecystectomy may be necessary in patients with cholelithiasis and antiparasitic treatment in those with schistosomiasis.

PREVENTION

- Provision of safe water
- Food safety
- Proper sanitation
- Health education

- Vaccination: In practice vaccines are given mainly to travellers to endemic areas, though the greatest need is among children in endemic areas and laboratory workers handling *S.typhi*. The rate of typhoid vaccination in Nigeria is low. Available vaccines include the killed whole cell vaccine which is given parenterally (no longer used due to side effects), the Vi vaccine (Typhim Vi) given as a single intramuscular injection with 70-80% protection for 3 years, and the live attenuated oral Ty21a vaccine given in 3doses with 2 days between doses and gives protection for 3-7 years. Mefloquine and antibiotics may affect the effectiveness of the oral vaccine. Typhoid vaccines do not protect against paratyphoid infection and large inocular of bacteria may overcome their protection. Booster doses are required every 3 years. Newer vaccines include Vi conjugate vaccine, TAB vaccine, S. paratyphoid A vaccine, Live attenuated vaccines using CVD 909 and *S. typhi* Ty 2[11].

COMPLICATIONS

Common complications include development of encephalopathy, intestinal perforation and gastrointestinal haemorrhage.

Rarer complications include pancreatitis, hepatic and splenic abscesses, endocarditis, pericarditis, hepatitis, orchitis, meningitis, nephritis, myocarditis, pneumonia, arthritis, osteomyelitis and parotitis[7].

PROGNOSIS

It depends on geographical location and its demographics. Case fatality rates of <1% in developed countries and up to 10% in developing countries have been reported. About 5% of patients present with complications. One to 3 percent of patients become chronic carriers.

CONCLUSION

Typhoid fever remains a major cause of death and disease in the developing world. Its eradication awaits the provision of sanitary water supplies and proper disposal of human sewage. Mass immunization in endemic areas would help accelerate the eradication. The provision of appropriate diagnostic facilities would aid the diagnosis and treatment. There should be less reliance on the Widal test for the diagnosis of typhoid fever.

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