Enteric fever

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ABSTRACT

Enteric fever is a major public health problem especially for India due to poor sanitation, lack of clean drinking water and poor food hygiene. It can affect all age groups, but recent shift towards infants and young children is worrisome. The majority of patients improve with ambulatory treatment, supportive care, and administration of appropriate antibiotics early during course of the disease. Hospitalization is indicated in patients with persistent vomiting, poor oral intake or severe diarrhea or any of the serious complications. Patients with shock, encephalopathy, intestinal perforation or hemorrhage and toxemia should be managed in the intensive care unit. Diagnosis is often based on serological tests but blood culture remains the gold standard. Ceftriaxone is the drug of choice for complicated enteric fever. A short course of dexamethasone for 2 days may decrease the mortality in children with serious complications. Early surgical intervention is warranted in intestinal perforation. The emergence of multidrug-resistant strains, is a serious concern thus necessitating more focus on preventive measures. Integrated preventive approach like improvement in sanitation, hygienic food practices and mass vaccination will go a long way in decreasing the incidence of these infections.

Key Words: Children, Enteric fever,
Introduction

Enteric fever is a common public health problem in India and is becoming a challenge in the face of increasing antimicrobial resistance. Children below the age of 5 years are the most affected age group.\(^1\) Few of serious complications may require intensive care management in these children.

Epidemiology

Enteric fever is widely prevalent worldwide, especially so in the Indian subcontinent with a reported incidence of 6.3 million cases per year.\(^2\) The disease is mostly endemic with sporadic cases occurring in persons who travel to endemic areas. South-central, South East Asia, and southern Africa have the highest prevalence of disease of which Indian subcontinent having the highest incidence of typhoid among travelers.\(^3\) Hospital-based studies from India analyzing fevers presenting to hospitals, have reported a prevalence of 9.7% (95% CI 5.7 – 16%) for enteric fever.\(^4\) The incidence among children has been reported to be 340/100000 and 493/100000 population-year among under five and 5-15 years of age respectively. Though the prevalence over time has shown an overall decreasing trend, the shift towards increased incidence in younger children is worrisome.\(^4,5\) The risk factors identified for transmission of the disease include poor sanitation, overcrowding, ingestion of unhygienic street foods, contaminated water, and history of contact with a patient. The epidemics in India have been caused mostly by fecal contamination of drinking water by the typhoid carriers.

Pathogenesis

The causative organism of enteric fever is *Salmonella typhi* (called as *S. enterica* serotype Typhi), *S. paratyphi A, B or C* which are gram-negative bacilli of the Enterobacteriaceae family. Humans are the only reservoir of infection. The transmission of the disease occurs through direct contact or indirectly via contact with fecal contaminated food or water.

The ingested organisms survive the acidic pH of the stomach and pass down to infect the small bowel mucosa. This is responsible for producing intestinal symptoms following which the organism enters the circulation through lymphatics, to cause the systemic manifestations. Chronic use of proton pump inhibitors, primary immunodeficiency disorders like chronic granulomatous disease, neutropenia’s, organ transplant recipients are some factors that predispose to severe infection. The incubation period ranges from 6 to 21 days (typically 2 weeks).

Clinical presentation

Children typically present with fever, anorexia, non-localized abdominal pain and a dry cough. Fever is the presenting complaint in the majority (90%) of patients. Fever is usually of remittent nature, without touching baseline, characteristically called “step ladder” pattern and the spikes often reach 40°C by the end of first week of the illness. Vomiting, diarrhea and occasionally constipation can occur during the first week of illness If untreated fever becomes unremitting and the illness may progress with appearance of CNS symptoms like a headache, irritability and meningeal signs. Clinical examination reveals a coated tongue, few scattered blanching erythematous skin lesion (rose spots), hepatomegaly and a soft splenomegaly. Occasionally, children may present as acute abdomen with hypotension pointing to intestinal perforation. Neuropsychiatric manifestations like severe agitation, delirium or obtundation can also be seen.
Paratyphoid fever usually presents with similar clinical features, but with shorter incubation period and milder manifestations. During the convalescent phase, the general well-being, appetite improves and the systemic signs resolve. This may sometimes be followed by a prolonged asymptomatic carrier state in about 10 – 15% of patients.

**Multiorgan involvement /Complications**

Ten to 15% of children may land up with serious complications usually in the second week of illness; important among them being intestinal perforation or hemorrhage and typhoid encephalopathy. Factors that determine the occurrence of complications and overall outcome are duration of illness before seeking appropriate antibiotic therapy, age of the child, vaccination status, virulence of the strain and the host nutritional and immune status. Infants and younger children are at higher risk of systemic toxicity; the initial illness tends to be very nonspecific in this age group and progresses to systemic manifestations like anasarca, hepatomegaly, seizures, thrombocytopenia, and bleeding making clinical suspicion difficult. The multidrug resistant strains are highly virulent and result in intense bacteremia and a higher rate of complications.

**Intestinal complications**

Intestinal perforation occurs in about 1-3% of hospitalized patients with enteric fever. Though the published data on incidence of typhoid intestinal perforation is highly variable among the community based and hospital based Indian studies, higher rates of perforation have been reported from western Africa (10% to 33%). The presence of abdominal tenderness in a child with suspected enteric fever should always alert the physician towards this complication though younger children may manifest with milder symptoms like fever and vomiting at presentation. Immunologically mediated release of cytokines like TNFα from the sensitized macrophages causes necrosis of the bowel wall resulting in intestinal perforation. Perforation is common in older children (>5 years) as the immune mechanisms are mature. The common site affected is the terminal ileum (70-80%) followed by less commonly involved sites like jejunum, cecum, colon or gall bladder. Unusual complications like appendicitis, appendicular perforation and toxic megacolon have also been reported.

**Neurological complications**

Children may present with neurological manifestations like headache, photophobia, vomiting, and neck stiffness. Encephalopathy is a common presentation. In a cohort of 129 children from single center observational study, about 30 children (23%) had neurological manifestations at admission. Complications like meningitis, encephalomyelitis, and seizures are also described. Benign intracranial hypertension, Guillain-Barre syndrome, acute cerebellar ataxia, cranial nerve palsies and peripheral neuritis have been rarely reported.

Renal involvement including cystitis, pyelitis, pyelonephritis and mild proteinuria have been reported. Rare but serious manifestations like myocarditis, glomerulonephritis, acute respiratory distress syndrome (ARDS) and hepatic manifestations like jaundice, hepatitis may occur with highly virulent *S. Typhi* infection. Hematological complications include bone marrow suppression, hemophagocytic lymphohistiocytosis (HLH) and disseminated intravascular coagulation (DIC). Osteomyelitis, soft tissue abscesses, mycotic aneurysms have also been reported commonly as a complication of paratyphoid infections. Case fatality has been reported to be higher in young children and infants.
Emergency Management

A comprehensive history and thorough clinical examination is needed to identify the manifestations of enteric fever. Early clinical diagnosis is often difficult to establish as the findings are nonspecific and may mimic other febrile illnesses like malaria, scrub typhus, Epstein-Barr virus and brucellosis. For patients in non-endemic regions, the history of recent travel to the endemic area is important.

Children with persistent vomiting, abdominal distention, and poor oral acceptance or severe diarrhea or any complications must be hospitalized. Stabilization of airway, breathing and circulation take precedence over other therapy in all critically ill children. Children presenting with shock may require fluid resuscitation followed by vasoactive support and those presenting with altered sensorium and a Glasgow Coma Scale of less than 8 may require airway stabilization during emergency management.

The point of care tests like TUBEX TF (IDL, Sweden) and Typhidot (Malaysian Biodiagnostic Research, Malaysia) may be useful in an emergency setting for diagnosis. The former is an antibody-based test on the principle of inhibition reaction between host and in vitro antibodies that compete for S. Typhi-specific lipopolysaccharide. A visible decolorization of serum in the test reagent indicates a positive test. The latter is based on a qualitative Enzyme-Linked Immunosorbent Assay (ELISA) that detects the presence of IgG and IgM antibodies against S. Typhi outer membrane protein. These tests have been reported to have a sensitivity of 55 – 70% and a specificity of more than 85%. 23

Specific therapy

The important factor correlated with poor outcome is the delay in initiating an effective antibiotic therapy. Most patients with uncomplicated disease improve with home-based treatment comprising appropriate oral antibiotics, hydration, and supportive care. Parenteral antibiotics are indicated in children with persistent gastrointestinal symptoms, poor oral acceptance and those with neurological manifestations. Most Salmonella spp are resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole. This antibiotic resistance is transferable through plasmids between organisms thus posing a significant risk factor for the development of multidrug resistant Salmonella infection (resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole). Fluoroquinolones resistant strains have been reported from various countries. Currently, third generation cephalosporins are being widely used; though few sporadic reports of resistance having been documented.24 Reassuringly there have been some reports of increased susceptibility to previously used drugs like co-trimoxazole and chloramphenicol.25

Therefore, while deciding empiric therapy local data on resistance pattern, should help in making the right antibiotic choice. For uncomplicated quinolone sensitive strains, cefixime or fluoroquinolones are the initial antibiotics of choice. In areas of prevalent fluoroquinolone resistance, third-generation cephalosporins should be used as the first line of choice for hospitalized patients and oral cefixime (20 mg/kg/d) for ambulatory patients.21,26 Parenteral antibiotics should be given for a period of at least 5 days after defervescence or for a total duration of 14 days. It has been observed that a total treatment duration of 14 days is associated with zero relapse rate.27 Alternatively, azithromycin can be used in cases of strains resistant to cephalosporins. Multidrug-resistant strains should be suspected in children presenting with short
duration of illness, serious complications, failure to respond to first-line antibiotics or a known household contact or during an epidemic of MDR typhoid fever. Children with enteric fever have severe anorexia along with spiking fever, necessitating adequate hydration, liberal use of antipyretics and early resumption of nutrition.

**Intensive Care Needs**

Depending on the clinical condition and complications a hospitalized patient may need admission to PICU for the following:

1. Hemodynamic monitoring for shock
2. Neurological monitoring for encephalopathy
3. Monitoring for abdominal complications
4. Fluid and electrolyte balance
5. Bleeding diathesis due to thrombocytopenia
6. Disseminated intravascular coagulation and multiorgan failure

**Organ supportive therapies**

Children presenting with shock or enteric encephalopathy should be treated with steroids preferably dexamethasone as an initial dose of 3 mg/kg followed by 1mg/kg every 6 hours for total 8 doses. In the Indonesian cohort, treatment with dexamethasone in patients with severe typhoid decreased the mortality from 50% to 10%. Thus, high dose dexamethasone has been recommended for children with severe complications like shock, delirium, and encephalopathy. Acute transverse myelitis due to enteric fever may be treated with high-dose methylprednisolone followed by oral steroids for one week along with specific antimicrobial therapy.

Intestinal hemorrhage requires intensive monitoring, volume resuscitation, and blood transfusion. Patients with suspected intestinal perforation should be stabilized first followed by urgent surgical intervention. Secondary peritonitis with gram-negative organisms like *E. coli* and *Klebsiella* is common after perforation and may lead to secondary organ dysfunction. Radiological evidence of perforation, pneumoperitoneum has been reported in 54 to 70% of children suspected of perforation. Though pneumoperitoneum is a definitive radiological sign of perforation, its absence should not delay surgical intervention as surgery is the only definitive option. There is no role for conservative management; a delay in surgical intervention has been associated with poor outcomes. The overall case fatality rate due to typhoid intestinal perforation varies between 15% to 25% and the mean duration of hospital stay is about 18 to 23 days. The common postoperative complications are entero-cutaneous fistula and wound infection. Majority of the children die with overwhelming sepsis rather than as a complication of surgery. Delayed presentation to the hospital, presence of shock, fecal peritonitis, prolonged duration of perforation, younger age at presentation are identified risk factors for mortality in enteric fever.

Acute respiratory distress syndrome requires mechanical ventilatory support. Myocarditis presenting as cardiogenic pulmonary edema and/or shock with ST segment, and T wave changes requires supportive care which includes ventilation, fluid restriction and inotropic support while cardiac function takes few days to improve. Other complications like hepatitis, cystitis, cerebellar ataxia, cranial nerve palsies require only conservative management. As a rare complication progressive thrombocytopenia and pancytopenia, can occur secondary to infection
induced hemophagocytic lymphohistiocytosis (HLH). Patients usually improve with conservative management with appropriate antibiotics as in any other case of infection induced HLH.

**Diagnostic tests**

Positive blood culture confirms the diagnosis. The yield of culture positivity in first week of illness has been shown to be up to 90% but it decreases as time elapses. The blood culture yield increases if amount of blood sample taken is as per recommendations of World Health Organization --10 to 15mL from school children and 2 to 4 mL and from preschool children and toddlers (WHO). Bone marrow culture has the highest yield, especially in partially treated patients. In a systematic review of 529 patients with proven *S. Typhi* infection, 61% were detected by blood culture and 96% were detected by bone marrow culture. Though the culture positive yield from the stool and urine samples increase after the second week of illness, the overall yield is low (about 10% and 35% respectively). Nonspecific laboratory findings like normocytic, normochromic anemia, leukopenia, and a mild increase in transaminase levels may occur frequently.

**Serological tests**

The widely used serological test in a community setting for diagnosis of enteric fever is Widal Test. It detects the antibodies against the O and H antigens of *S. Typhi* the predictive value of which is variable among geographic areas. A titer of 1:160 is considered positive if done during the second week of illness and a fourfold rise in titers of paired sera is considered more specific. False negative test occurs due to inadequate antibody response while a false positive test occurs due to antigenic cross-reactivity with non-typhoid salmonella and vaccine strains.

**Outcomes**

The overall mortality rate has decreased over the period of time to about 1% irrespective of emergence of resistant strains. Children with serious complications like intestinal perforation, encephalopathy and those requiring intensive care admission have a higher mortality. The overall risk of becoming a chronic carrier is less than 2% in children.

**Preventive strategies**

Provision of safe drinking water and hygienic sanitary practices are the most effective public health preventive strategies. Currently, two vaccines have been recommended by WHO, the oral (Ty21a vaccine) and the injectable Vi capsular polysaccharide vaccine. The Vi capsular polysaccharide vaccine is to be administered at 2 years and should be repeated every three years. Ty21a is available as enteric-coated capsules to be administered on days 1, 3 and 5 and to be repeated every three years for individuals living in or traveling to endemic regions. Those children treated for enteric fever should be vaccinated after 4 weeks of recovery.

**Conclusions**

With the advent of effective antibiotics, vaccines and availability of intensive care the mortality due to enteric fever is on the decreasing trend. The emerging threat of multidrug resistant strains mandate a rational use of antibiotics, effective utilization of the available preventive strategies like provision of safe drinking water, improving hygiene and sanitation, administration of mass vaccination.
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