Update in
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Typhoid enteric fever – part 1

Falan Mouton, Esohe I Ohuoba, Faye M Evans and Ibironke Desalu

Correspondence: bruce.mccormick@nhs.net

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Summary

Typhoid enteric fever is a bacterial infection transmitted by faecal–oral route exclusively through human hosts.

Gut perforation is a potentially lethal complication associated with an inflammatory response at Peyer's patches

Definitive diagnosis requires successful culture from blood, stool, skin, or other infected site. Prompt antibiotic therapy reduces mortality.

Typhoid intestinal perforation is a surgical emergency that is potentially fatal, with children accounting for more than half of cases.

INTRODUCTION

Typhoid fever, otherwise known as enteric fever, is a bacterial infection of the gastrointestinal system that has long plagued humanity. The causative agent is in the family of Enterobacteria, and the genus *Salmonella*. These Gram-negative, facultative anaerobic bacilli are also flagellated, motile and non-spore forming. Although the organism lacks an exotoxin to promote illness, it is strongly antigenic and causes an intense inflammatory response in tissues. Typhoid fever is associated with the *Salmonella* serotypes typhimurium (*S. typhi*) and paratyphimurium (*S. paratyphi*).[1]

While a wide variety of animals can be infected with *Salmonella*, only humans carry the *S. typhi* and *S. paratyphi* serotypes associated with typhoid fever. Thus, livestock, household pets and other animals are neither carriers nor vectors of typhoid fever.[2] Humans acquire the disease from other humans through faecal–oral transmission, most commonly in the setting of contaminated water or food. It is not surprising that the greatest disease burden is found among the world's poorest countries where water and sanitation services are the least robust. Non-typhoidal salmonellosis (NTS) can be spread by animals other than humans and presents as a milder gastroenteritis. NTS is beyond the scope of our discussion of typhoid fever and will not be elaborated on.[1]

EPIDEMIOLOGY

Typhoid is more common in urban than in rural areas. Worldwide there are over 22 million cases with over 200 000 deaths each year, representing a 1–4% mortality rate.[3,4] The disease burden of typhoid fever is lowest in the developed world and highest in resource-limited settings. North America and Europe have fewer than 10 cases per 100 000 people per year, while Central and Southeast Asia have 10 times that number, achieving the highest rates in the world. The burden of the disease is difficult to estimate in African countries owing to limitations in laboratory testing capacities.[4,5] Outbreaks are more frequent in low-resource countries because they are associated with contaminated food and water and with fields fertilised by sewage, street vendors, uncooked fruits and vegetables, sick contacts, limited toilet access, and limited ability to wash the hands.

PATHOPHYSIOLOGY

Once consumed, typhoid bacteria cross the epithelial layer of the intestinal wall. They are then quickly consumed by macrophages and transported to the aggregates of lymphoid tissue in the small intestine (Peyer's patches), where the immune function of the gut is most concentrated. The typhoid bacteria alter host cell signalling and function in such a way that host cells ultimately promote the survival and replication of *S. typhi* and *S. paratyphi*.

The incubation stage of a typhoid infection is characterised by the replication and transfer of *S. typhi* and *S. paratyphi* from the Peyer's patches in the gastrointestinal system, through the lymphatics, to the organs of the reticuloendothelial system including the

Falan Mouton
Paediatric Anaesthesia Fellow
Lagos University Teaching Hospital
Lagos
Nigeria

Esohe I Ohuoba
Consultant anaesthetist
Lagos University Teaching Hospital
Lagos
Nigeria

Faye M Evans
Anaesthesiologist
Boston Children's Hospital
Boston, MA
USA

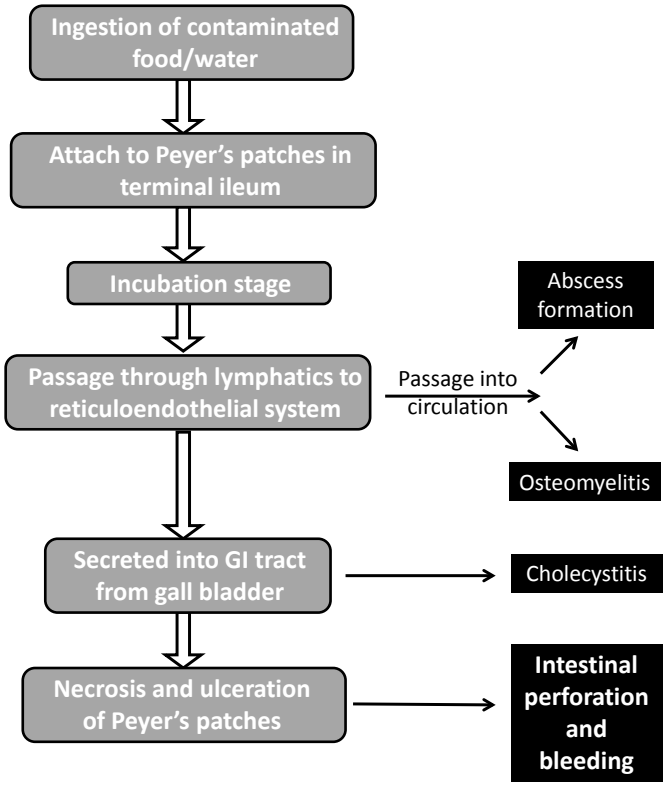

Figure 1. *Aetiopathogenesis of typhoid intestinal perforation and other complications*

lymph nodes, spleen, bone marrow and liver. Once in the gallbladder, *S. typhi* and *S. paratyphi* are secreted back into the gastrointestinal tract. Having been previously exposed to the organism, the Peyer's patches respond with an intense inflammatory reaction, leading to congestion and clogging of the microcirculation and capillaries with release of lytic lysosomal enzymes and other inflammatory mediators.[1,3] This results in varying degrees of necrosis and ulceration of Peyer's patches, of which the clinical manifestation is bleeding and perforation. The terminal ileum is the most common site of perforation, but perforation has also been reported to occur anywhere from the duodenum to the colon including the gall bladder and appendix (Figure 1).[3]

Depending on the strength of the host's immune system and the size of the inoculum, the incubation phase may last 3 days to 3 weeks.[1] During this interval, a patient may have no symptoms or vague complaints of fever and abdominal pain. Once the bacterial load reaches a critical mass, an individual is said to have an active typhoid infection.

SIGNS AND SYMPTOMS

Although *S. typhi* is four times more common than *S. paratyphi*, in general, the clinical appearances of *S. typhi* and *S. paratyphi* infections are virtually indistinguishable. Signs and symptoms of the infection consist mostly of abdominal complaints including fever associated with frontal throbbing headache, nausea, vomiting, abdominal pain, anorexia, diarrhoea, constipation, gastrointestinal bleeding and hepatosplenomegaly. Systemic complaints are also common, and more than 75% of patients report having flu-like symptoms. Neurological problems include meningitis, Guillain–Barré syndrome and a delirium that features muttering and picking at clothes and imaginary objects. Disseminated intravascular coagulation, haemolytic–uraemic syndrome, renal failure, cardiac failure and respiratory failure have all been reported as a consequence of severe infection. While no specific constellation of symptoms is pathognomonic of the disease, a transient skin rash, described as rose spots, can be biopsied to confirm the diagnosis.[1]

The severity and duration of typhoid fever depends on several host factors including age, integrity of the immune system and gastrointestinal tract, and alkalinisation of the stomach. It has been found that a more acidotic environment in the stomach is bactericidal, while a concomitant *Helicobacter pylori* infection, which increases gastric pH, promotes the disease.[1] Up to 4% of patients with untreated disease that resolves spontaneously will become asymptomatic carriers and continue to shed the bacteria in urine and stool.

COMPLICATIONS

S. typhi has the capacity to affect virtually every organ system; as a result patients are vulnerable to a wide variety of complications. Intestinal perforation, occurring in 1–3% of cases, is associated with the highest mortality.[1,3,4] Even when aggressively treated, mortality with perforation can be as high as 40%. In contrast, in unperforated cases treatment reduces the mortality rate to only 1%. Perforations can occur anywhere from the duodenum to the colon, though the ileum is the most common site. Gall bladder perforation has also been reported. In children, multiple perforations are frequently present.[3] Anaesthesia in a child with typhoid intestinal perforation will be discussed later in this article.

Additional complications include heart failure from myocarditis or endocarditis, liver failure from hepatitis or pancreatitis, renal failure from pyelonephritis or glomerulonephritis and respiratory failure from pneumonia, as well as disseminated intravascular coagulation, arthritis and orchitis.[1]

Although both sexes are infected equally, some evidence suggests that males suffer significantly more intestinal perforations than females.[5] Typhoid fever can affect people of all ages, but the burden is heaviest among children aged 5–10 years. In endemic regions, children account for greater than 50% of intestinal perforation cases.[5]

In one published report of an outbreak in Uganda from 2007–2009 there were 577 cases with 249 intestinal perforations and 47 deaths. resulting in an incidence rate of 8092 cases per 100 000 people.[4] Although this is unlikely to represent the incidence rate of the

population as a whole, it does emphasise that during an outbreak the burden of the disease can be tremendous.

DIAGNOSIS

The diagnosis of typhoid cannot be confirmed based on clinical presentation alone. Because the symptoms of typhoid fever are so variable, the differential diagnosis can be quite broad. Other diseases such as malaria, HIV infection, hepatitis, gastrointestinal viral infections and bacterial infections such as *Clostridium difficile* or *Escherichia coli* must be excluded. Suspicion of more common causes of fever such as malaria frequently delays diagnosis of typhoid. Malignancy, rheumatic processes and inflammatory bowel diseases should also be considered.

Definitive diagnosis requires isolation of the causative organism from tissues. Punch biopsies from rose spots on skin, or cultures from blood, urine, bone marrow or stool are often adequate for diagnosis. Bone marrow cultures are the most sensitive, at 55–90%, and can grow *S. typhi* even in the setting of 5 days of antibiotic treatment. Unfortunately, even samples from patient with active typhoid can sometimes fail to grow the bacteria in culture.[1]

In such settings, Widal's test has some efficacy and remains the most commonly used serological test. It evaluates agglutination between antibodies in the patient's blood to the H (flagella) and O (somatic) antigens of *S. typhi*. The test is plagued by a high false-positive rate as antibodies from other infectious disease such as dengue, malaria and non-typhoidal salmonella also cross-react with the *S. typhi* antigens. Previous immunisation or exposure to the disease can also cause false-positives in acute disease. Poor commercial antigen preparation is responsible for both false-positives and false-negatives. Additionally, *S. typhi* carriers and others with low antibody production can have false-negative results in the setting of acute infection.[6,7]

In regions of the world where typhoid is endemic, laboratory resources are also very limited. PCR identification of *S. typhi* solves many of the shortcomings of cultures and Widal's test, but these studies are expensive and require some of the most advanced technologies available. As a result of the laboratory limitations, practitioners must have a high index of suspicion for the disease and rely on the familiar constellation of symptoms previously described.

MEDICAL MANAGEMENT

Medical management is the preferred treatment for typhoid fever. Prompt diagnosis and initiation of appropriate antibiotic therapy is critical to treatment success and mortality reduction. The majority of uncomplicated cases do not require hospitalisation. When possible, typhoid should be cultured and susceptibilities noted to help guide antibiotic therapy. If laboratory testing is not available, antibiotics should be selected based on regional susceptibilities.

Fluoroquniolones, such as ciprofloxacin and ofloxacin, are the first-line antibiotic treatment for *S. typhi* and *S. paratyphi*. Chloramphenicol, amoxicillin, and TMP-SMX (trimethoprim–sulfamethoxazole (Bactrim)) are all known to be efficacious against susceptible strains of typhoid. For drug resistant strains or empirical treatment, antibiotic coverage is broadened to include ceftriaxone and azithromycin.[1,5]

Antibiotics can be administered orally (PO) or intravenously (IV) depending on the drug, and treatment courses rarely exceed 21 days. Steroid therapy with dexamethasone in conjunction with antibiotics has been shown to reduce mortality and is considered standard therapy for management of the disease. Chronic carriers of typhoid require a longer, 4- to 6-week, course of antibiotics with amoxicillin, TMP-SMX or ciprofloxacin.[1]

Surgical intervention is recommended only in the case of intestinal perforation. If no perforation has been identified, surgery is not indicated as it could spread infection. In addition, it is difficult to identify which areas to resect, as the disease can be ubiquitous in the bowel.[3]

Surviving sepsis

The recently revised Surviving Sepsis guidelines provide an excellent framework for managing cases of typhoid fever that have been complicated by intestinal perforation.[8] The child or adult presenting for laparotomy because of typhoid perforation will almost always have concomitant septic shock. The definition of sepsis is a documented or suspected source of infection as well as symptoms of the systemic inflammatory response syndrome. These symptoms include altered mental status, tachypnoea, fever or hypothermia, leucocytosis or leucopenia, tachycardia (possibly bradycardia if the child is less than 1 year old) and systemic hypotension. There is also evidence of end-organ dysfunction including an elevated lactate or creatinine or a new coagulopathy.

Mortality in sepsis in minimised when the condition is promptly diagnosed and treated. The current Surviving Sepsis guidelines for adults recommend that within 3 hours of diagnosis cultures are drawn, empiric antibiotics are administered, a lactate level is measured, and a fluid bolus is given of 30 mL kg^{-1}. Within 6 hours the objective is to address hypotension and end-organ perfusion by measuring a central venous pressure (CVP) and mixed venous saturation if available. Vasopressors can then be added to maintain a mean arterial pressure (MAP) of 55–65 mmHg with a goal of a CVP > 8 mmHg or a venous oxygen saturation (SvO_2) > 70%.

Haemodynamic goals are similar in paediatric patients, but there are some management differences in the Surviving Sepsis guidelines. A child in respiratory distress should initially be managed with high-flow nasal cannula or continuous positive airway pressure (CPAP). Fluid resuscitation should start with 20 mL kg^{-1}crystalloid or an albumin equivalent with a goal of maintaining a capillary refill time of < 2 seconds, normal blood pressures, baseline mental status,

urine output of 1 mL kg^{-1} h^{-1} and ultimately SvO_2 of 70%. Empiric antibiotics should be administered within 1 hour of diagnosis. American College of Critical Care Medicine-Pediatric Life Support (ACCM-PALS) guidelines should be followed if the child is in shock and blood should be given to an initial goal of haemoglobin concentration of 10 g dL^{-1}. Once stable, haemoglobin of 7 g dL^{-1} can be allowed.

In both paediatric and adult patients, vasopressors should be added to maintain haemodynamic goals if shock is refractory to fluid boluses. Lung-protective ventilation strategies should be employed. These typically involve low tidal volumes of 6–7 mL kg^{-1}, higher respiratory rates, application of positive end-expiratory pressure (PEEP) and permissive hypercapnia. In children, if hypotension does not respond to fluid boluses and vasopressors, adrenal insufficiency should be considered and managed with steroids.[8]

PREVENTION

Prevention is the preferred method of management of typhoid. Strategies include improved sanitation services, sewage disposal, water treatment services and early identification and minimisation of outbreaks.

Vaccinations are available for several of the typhoid serotypes, but their effectiveness is limited. Additionally, there is no vaccine for *S. paratyphi*, which accounts for up to 25% of cases of typhoid fever. The potential of vaccinations is limited because they are ineffective at preventing disease in the event of a large inoculum. Discretion is advised when food choices are made while travelling in a typhoid-endemic area. Despite this limitation, vaccinations are still warranted as they will behave as an adjunct to treatment and limit the extent and duration of the disease.

There are two forms of the *S. typhi* vaccine that are currently commercially available; however, neither form is available for children below 2 years of age. The live attenuated oral vaccine, Ty21a, is administered every other day for three doses. It has an efficacy of 67–80% and provides some cross-protection against *S. paratyphi*. It requires a booster vaccination every 5 years, and is not generally given until the age of 6 years. The Vi CPS vaccine is an alternative parenteral form featuring the Vi polysaccharide of the *S. typhi* bacterial capsule. It can be administered to children as young as 2 years old but requires a booster every 2 years and it has an efficacy of 55–72%. Typhoid vaccination is recommended for persons visiting endemic or high-risk areas, but not for those who reside in them, and not for those with an acute infection.[9]

CONCLUSION

Typhoid fever is an infectious disease that exclusively affects humans and is transmitted by faecal–oral routes. Though it typically results in gastrointestinal symptoms, typhoid enteric fever may present as a multisystemic disease when infection is severe. Management strategies involve prompt diagnosis or a high index of suspicion, appropriate antibiotic therapy and early initiation of sepsis management. Typhoid intestinal perforation is a serious complication if prompt surgical intervention is not available.

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