Typhoid fever: yesterday, today and unfortunately still tomorrow

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Enteric fever is caused by *Salmonella typhi* and *Salmonella paratyphi A, B* and *C*. Typhoid fever refers to the illness caused by *S. typhi*, whereas enteric fever refers to the disease caused by all four organisms. In this article the author describes the history of our understanding of typhoid fever and its current prevention and management.

Typhoid was one of the most common causes of fever in European and North American cities during the 19th century. It was very common in armies during wartime; notably, more soldiers died from typhoid fever during the Boer War than from wounds.

During the 17th century, Sir Thomas Willis described the ulceration of Peyer's patches in the small intestine, a characteristic feature of typhoid fever. Pierre Louis, a French physician, coined the word typhoid in 1829. The suffix 'oid' comes from the Greek eidos, meaning 'like.' At that time, doctors were unable to distinguish between typhus and typhoid fever, hence 'typhoid' means 'like typhus.' Apathy and confusion are features of both infections.

In 1880, Karl Eberth described an organism in sections of the mesenteric lymph nodes and spleen of a patient who had died from typhoid fever, naming it *Bacillus typhosus*. In 1884, Georg Gaffky cultured the typhoid bacillus for the first time and stated that typhoid fever was a waterborne infection.

Although Georges-Fernand Widal usually receives the credit for discovering the serological test that bears his name, most of the work on the sero-diagnosis of typhoid fever was undertaken by Albert Grünbaum at the end of the 19th century.

Sir Almroth Wright, Professor of Bacteriology at St Mary's Hospital, London, introduced a successful vaccine against typhoid in 1897. In spite of strong opposition from the military, the majority of soldiers in the British Army were inoculated against typhoid fever, a measure
promoted by Wright. Consequently, the incidence of typhoid fever among British troops was much lower than it was in other armies during the First World War.

There was no effective treatment for typhoid fever until the introduction of chloramphenicol in 1948.

**EPIDEMIOLOGY**
Salmonellae are Gram-negative, facultative anaerobic motile organisms that do not form spores. S. typhi can survive for several weeks in food, water and dried sewage.

Typhoid fever occurs throughout the world. It is estimated that there are at least 12.5 million cases per annum, of which around 500,000 will prove fatal. This is almost certainly an underestimate, as many cases in the developing world will be either misdiagnosed due to lack of laboratory facilities or not reported to the relevant authority.

Today, most cases of typhoid fever occur in Asia and Africa. In European countries, patients seen with typhoid fever will usually have acquired it outside of Europe.

Most salmonellae, other than than S. typhi and S. paratyphi, cause an illness in which the symptoms of gastroenteritis predominate. This is not the case with typhoid and paratyphoid fevers, which are really systemic illnesses, sometimes with few (if any) gastrointestinal symptoms.

Multidrug-resistant (MDR) strains of S. typhi have become common in Asia since the mid-1980s. An MDR strain is one that is resistant to chloramphenicol, ampicillin and clotrimoxazole. Resistance to ciprofloxacin is now also reported.

**TRANSMISSION**
Enteric fever is spread by the oral-faecal route, either through food or water, another case or from an asymptomatic carrier. Patients infected with HIV do not seem to be more susceptible to infection with S. typhi or S. paratyphi, but are more susceptible to infection by non-typhoidal salmonellae.

**PATHOGENESIS**
Studies with human volunteers have shown that 100,000 organisms will cause disease in about 50% of volunteers, whereas one million organisms will cause infection in 95% of volunteers. Increasing the number of organisms ingested reduces the incubation period. The infective dose is increased if the patient has a full stomach, and is reduced in conditions such as achlorhydria.

After ingestion, the organisms multiply in the small bowel before penetrating the mucosa of the small intestine, through which they are transported to lymphoid tissue, where they multiply within cells of the macrophage-monocytic system. From there, the organisms spread in lymphatic vessels to other organs where there are abundant macrophage-monocytic cells, in particular the liver, spleen and bone marrow. After multiplication within these cells, organisms are released into the bloodstream. This heralds the onset of clinical symptoms.

CLINICAL SYMPTOMS
It is important to remember that the clinical presentation of typhoid fever in Britain is usually different from that of a patient living in the tropics. Patients seen in the UK are usually young, well-nourished and previously well adults who present during the early stage of their illness, whereas those in the tropics present later and with complications.

Though the symptoms and signs of typhoid fever vary from one patient to another, 10–20% of patients will have a transient episode of diarrhoea after ingesting typhoid bacilli. They will then be asymptomatic during the usual incubation period of 7–14 days. The incubation period can vary between 3 and 60 days, depending on the number of organisms ingested. The onset of symptoms coincides with the development of the secondary bacteraemia.

Patients are invariably febrile and have a headache. Relative bradycardia (Faget’s sign) may be present. Tachycardia >120, associated with a fall in blood pressure, suggests a complication such as perforation.
haemorrhage from the small intestine or both. However, features of 'Gram-negative shock' are unusual.

Patients may look apathetic — I can describe the facial appearance in no other way. Their hearing may also be impaired, and some may have features suggestive of acute myocarditis.

Although the patient may complain of diarrhoea, up to 30% will have constipation, a sign not usually associated with salmonella infections.

Hepatosplenomegaly will be detectable in about 50% of patients. The massive splenomegaly associated with conditions such as malaria and systemic leishmaniasis does not occur. Jaundice is uncommon.

Rose spots, mentioned in all textbooks, are seen in <30% of patients. They are pale pink, indistinct spots, which are difficult to see, especially if the skin is dark. There are usually less than two dozen.

Some patients look well and have few symptoms apart from pyrexia. A few years ago I treated a young man who had recently returned from Pakistan who was pyrexial but had no gastrointestinal symptoms. On physical examination I could find no abnormalities, yet _S. typhi_ was isolated from blood cultures.

**COMPLICATIONS**

Perforation of the small intestine, with or without haemorrhage, occurs in around 3% of patients admitted to hospital. In such incidences, the patient complains of severe abdominal pain, often in the lower right quadrant of the abdomen. A surgical opinion should be sought.

Though fewer than 5% of patients develop myocarditis, the electrocardiogram will show non-specific changes in at least three times that number. Myocarditis is a serious complication when it occurs in young children.

Focal infection can occur, eg osteomyelitis. Osteomyelitis is more likely to be seen in patients with sickle cell disease, perhaps due to their having small infarcts in their bones that provide a nidus for the growth of _S. typhi_. Cholecystitis may occur months after the patient has recovered from the acute infection. I observed a tubo-ovarian abscess in a 37-year-old woman who contracted the infection in Greece, which developed weeks after she had been treated successfully with co-trimoxazole.

**CARRIERS**

A chronic carrier is defined as a person who continues to excrete _S. typhi_ one year after being treated successfully for the infection. Although most carriers excrete _S. typhi_ in their stools, urinary carriage is common in countries such as Egypt where schistosomal infestation of the urinary tract is common. Such carriers cannot be treated successfully until the schistosomiasis has been cured. Females and patients with abnormalities of the gallbladder are most likely to become carriers. Carriers have a high titre of antibodies to the Vi antigen. Treatment can eradicate _S. typhi_ in chronic carriers.

The danger of asymptomatic carriers can be dangerous in that they can cause secondary cases, especially if they are food handlers and their personal hygiene is poor.

**DIAGNOSIS**

Although a clinician may suspect that a patient has typhoid or paratyphoid fever, a definite diagnosis can be made only if _S. typhi_ is isolated from blood cultures, stools or urine. A combination of blood and stool cultures is likely to establish the diagnosis in around 90% of cases. It is important to remember that a negative stool culture does not exclude the diagnosis. In one case I experienced when working in a London teaching hospital, over a dozen stool cultures were made from a patient thought to have typhoid before the organism was isolated. _S. typhi_ is most likely to be isolated from blood cultures during the first week of the illness.

The Widal test is of no diagnostic value and is now performed in few, if any, laboratories in the UK. Patients with typhoid fever may have titres to the H and O antigens <1/20, which is the ‘cut-off point’ of the test. Other salmonellae can produce raised titres. The organism can be isolated from the small intestine using a duodenal string cap.

**TREATMENT**

Typhoid and malaria must be excluded in any patient who develops a fever after having visited an endemic area. Viral haemorrhagic fever, of which infection with the Ebola virus has recently dominated in the news, can be excluded if the patient becomes febrile more than three weeks after returning to Britain.

Antibiotic therapy is the mainstay of treatment, in addition to standard fever management. Chloramphenicol was originally the antibiotic of choice, and continued to be used in Europe until the mid-1980s. It is no longer used for two reasons: firstly, resistance is common; secondly, there is a risk of aplastic anaemia, which occurs in 1:10 000–1:15 000 of patients.

Ciprofloxacin is the drug of choice in the UK. However, resistance to ciprofloxacin is increasing, especially in Asia, resulting in an increase in the use of ceftriaxone or azithromycin. If treatment is started promptly, the mortality rate should be <1%.

**IMMUNISATION AGAINST TYPHOID FEVER**

Sir Almroth Wright introduced the first vaccine against typhoid fever using killed _S. typhi_. In 1916, as paratyphoid fever was causing problems in some theatres of war, _S. paratyphi_ A and _B_ were also included in the vaccine. This vaccine, known as ‘TAB’ remained the standard vaccine against typhoid fever until late in the 20th century.
It provided moderate protection, but the side-effects were unpleasant (I speak from personal experience).

TAB is no longer available in the UK. Of the two vaccines currently available, one is based on the Vi antigen and the other uses a live, attenuated strain of \(S.\) \textit{typhi}.

The Vi vaccine (Typhim Vi) is given in a single parenteral dose, which has to be repeated every three years. It provides up to 70\% protection against typhoid fever, but none against paratyphoid fever.

The Ty21A vaccine (Vivotif) is given as three doses by mouth. Some patients become febrile after receiving this vaccine. Although it is less effective than the Vi vaccine, it provides protection against \(S.\) \textit{paratyphi} \textit{A} and \textit{B}. It can be made inactive by some antimalarials.

**THE FUTURE**

It should, in theory, be possible to eradicate enteric fever since there are no animal reservoirs. However, this will only be possible if there is a marked improvement in hygiene in countries in which enteric fever is endemic, together with vaccines that are more effective than those currently available.

Tests based on the polymerase chain reaction (PCR) are likely to become available. Although they will provide a more sensitive and rapid method for diagnosing enteric fever, the cost is likely to preclude their use in those countries where the infection is endemic.

**FURTHER READING**

• Cox FEG, ed. \textit{An illustrated history of tropical diseases}. London: Wellcome Trust, 1996.
• Rolleston JD. \textit{Acute infectious diseases}. London: Heinemann, 1929.