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0521835046 - Salmonella Infections: Clinical, Immunological and Molecular Aspects
Edited by Pietro Mastroeni and Duncan Maskell
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CHAPTER 1

Epidemiological and clinical aspects of human typhoid fever

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1.1 INTRODUCTION

Typhoid fever is an acute systemic infection caused by the bacterium *Salmonella enterica* serovar Typhi. *Salmonella enterica* serovars Paratyphi A, B, and C cause the clinically similar condition, paratyphoid fever. Typhoid and paratyphoid fevers are collectively referred to as enteric fevers. In most endemic areas, approximately 90% of enteric fever is typhoid. Typhoid is transmitted by the fecal-oral route via contaminated food and water and is therefore common where sanitary conditions are inadequate and access to clean water is limited. Although typhoid fever was common in the United States and Europe in the 19th century, it is now encountered mostly throughout the developing world. In the last fifteen years, the emergence of resistance to the antibiotics used for treatment has led to large epidemics, and complicated the management of this serious disease.

Before the 19th century, typhoid fever was commonly confused with other prolonged febrile syndromes, particularly typhus fever. Following the observations of Huxham, Louis, Bretonneau, Gerhard and William Jenner, by the middle of the 19th century the two conditions were clearly differentiated (Richens, 1996). In 1873, William Budd described the contagious nature of the disease and incriminated fecally contaminated water sources in transmission. The causative organism was visualized in tissue sections from Peyer's patches and spleens of infected patients by Eberth in 1880 and was grown in pure culture by Gaffky in 1884. The organism has been variously known as *Bacillus typhosus*, *Erbethella typhosa*, *Salmonella typhosa* and *Salmonella typhi*.

'Salmonella' Infections: Clinical, Immunological and Molecular Aspects, ed. Pietro Mastroeni and Duncan Maskell. Published by Cambridge University Press. © Cambridge University Press, 2005.

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1.2 *SALMONELLA ENTERICA* SEROVAR TYPHI

Salmonella enterica serovar Typhi is a member of the genus *Salmonella* in the family Enterobacteriaceae. The *Salmonella* genus contains two species, *enterica* and *bongori* (Brenner *et al.*, 2000). *S. enterica* is further divided into six subspecies (*enterica*, *salamae*, *arizonae*, *diarizonae*, *houtenae* and *indica*) containing 2443 serovars. Most of the salmonellae that cause disease, with some important exceptions, are in the subspecies *Salmonella enterica* subspecies *enterica*. The agents that cause enteric fever are therefore *Salmonella enterica* subspecies *enterica* serovar Typhi (commonly referred to as *S. enterica* serovar Typhi) and serovars Paratyphi A, B and C.

When isolated from clinical specimens, colonies of *S. enterica* serovar Typhi are non-lactose fermenting and produce a characteristic biochemical pattern in Kligler iron agar (acid but without gas, an alkaline slant and a moderate amount of H_2S production). Identification is confirmed by serological demonstration of the lipopolysaccharide antigen O9, 12 (group D), protein flagellar antigen Hd and Vi polysaccharide capsular antigen. Unique flagella types, Hj and H_{z66} are present in some *S. enterica* serovar Typhi from Indonesia. *S. enterica* serovar Typhi exhibits a remarkable degree of biochemical and serological homogeneity. Vi phage typing and molecular typing by pulse field gel electrophoresis and ribotyping, differentiate strains from different geographical areas and have shown a relative diversity of strains circulating in endemic areas, but comparative uniformity in outbreak strains (Thong *et al.*, 1994).

1.3 EPIDEMIOLOGY OF TYPHOID FEVER

Typhoid fever is endemic throughout Africa and Asia and persists in the Middle East, a few southern and eastern European countries and central and South America. In the US and most of Europe, apart from occasional point source epidemics, typhoid is predominantly a disease of the returning traveler (Ackers *et al.*, 2000). A recent study estimated there to be approximately 22 million cases of typhoid each year with at least 200 000 deaths (Crump *et al.*, 2004). However, the true magnitude is difficult to quantify because the clinical picture is confused with many other febrile illnesses and most typhoid endemic areas lack facilities to confirm the diagnosis. Data from placebo groups in large-scale field trials of typhoid vaccines and population-based epidemiology studies show annual incidence rates ranging from 10 to 1000 cases per 100 000 people (Table 1.1).

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Table 1.1. *Mean annual incidence of blood culture confirmed cases of typhoid fever recorded in the control groups of vaccine field trials and in population based epidemiology studies*

Country	Year	Study type	Age range (years)	Rate per 100 000 person years	Reference
Egypt	1982	Ty21a vaccine	6–7	46	Wahdan *et al.*, 1982
Chile	1983–1986	Ty21a vaccine	6–21	104	Levine *et al.*, 1987
Indonesia	1986–1989	Ty21a vaccine	3–44	810	Simanjuntak *et al.*, 1991
Nepal	1985–1987	Vi vaccine	5–44	655	Acharya *et al.*, 1987
South Africa	1985–1987	Vi vaccine	5–16	387	Klugman *et al.*, 1987
China	1995–1996	Vi vaccine	3–50	22	Yang *et al.*, 2001
Vietnam	1997–2000	Vi conjugate vaccine	2–5	414	Lin *et al.*, 2001
India	1995–1996	Epidemiology study	All	980	Sinha *et al.*, 1999
Vietnam	1995–1996	Epidemiology study	All	198	Lin *et al.*, 2000
Egypt	2001	Epidemiology study	All	13	Crump *et al.*, 2003

The incidence of typhoid in endemic areas is typically considered to be low in the first few years of life, peaking in school-aged children and young adults and then falling in middle age. Older adults are presumably relatively resistant due to frequent boosting of immunity, but the apparent low incidence in pre-school children contrasts with the high incidence of most other enteric infections at this age in these countries (Mahle and Levine, 1993). Some hospital and community-based studies have found a significant incidence of typhoid in pre-school children (Table 1.2). The character of the diseases in these studies has varied from a non-specific febrile illness or mild infection through to one that is severe and life-threatening (Bhutta, 1996a;

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Table 1.2. *Mean annual age-specific incidence of typhoid fever per 100 000 population in three studies. Santiago represents an urban centre with reasonably good sanitation and clean water. Most infection is probably related to contaminated food (Ferreccio* et al.*, 1984). Dong Thap province in the Mekong river delta has poor sanitation and most people use river water for all their daily needs (Lin* et al.*, 2000). Kalkaji in New Dehli is an overcrowded urban slum with very poor levels of sanitation (Sinha* et al.*, 1999)*

Age group (years)	Santiago, Chile 1977–1981 (Ferreccio *et al.*, 1984)	Dong Thap Province, Vietnam 1995–1996 (Lin *et al.*, 2000)	Kalkaji, New Dehli India 1995–1996 (Sinha *et al.*, 1999)
0–4	89	358[1]	2730
5–9	272	531	1390[2]
10–14	333	429	860[3]
15–19	283	153	860[3]
20–24	247	149	110[4]
25–29	153	149	110[4]
All ages	166	198	980

[1] Figure is for the age range 2–4 years. No typhoid was observed in children < 2 years.
[2] Figure is the mean value for the age range ≥ 5 to 12 years.
[3] Figure is the mean value for the age range > 12 to 19 years
[4] Figure is the mean value for the age range > 19 to 40 years

Butler *et al.*, 1991; Duggan and Beyer, 1975; Ferreccio *et al.*, 1984; Topley, 1986).

Although this variation in part relates to the patchy distribution of health care facilities capable of diagnosing and treating typhoid, there do appear to be different epidemiological patterns of *S. enterica* serovar Typhi (Ashcroft, 1964). Ashcroft suggested that where hygiene and sanitation is non-existent, *S. enterica* serovar Typhi is prevalent but classical clinical typhoid fever is uncommon. Immunity is acquired in infancy or very early childhood when infection is either asymptomatic or unrecognized. Where hygiene and sanitation are poor, *S. enterica* serovar Typhi infection is common and typhoid fever is particularly frequent in school-aged children. Most infections occur in childhood and are recognizable although often mild. This is the situation

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in endemic typhoid regions such as the Mekong Delta region of Vietnam. Where sanitation and hygiene are a mixture of poor and good, as is the case in many of the rapidly expanding conurbations of Asia, outbreaks of typhoid fever may involve all age groups. Where hygiene is excellent, as is the situation in developed countries, *S. enterica* serovar Typhi and typhoid fever are rare.

Typhoid is usually contracted by ingestion of food or water contaminated by fecal or urinary carriers excreting *S. enterica* serovar Typhi. In addition, these bacteria can survive for prolonged periods in water, ice, dust and dried sewage and these may become sources of infection. In endemic areas, peaks of transmission occur in dry weather or at the onset of rains. Risk factors for disease include eating food prepared outside the home, such as ice creams or flavoured iced drinks from street vendors, drinking contaminated water and eating vegetables and salads that have been grown with human waste as fertilizer (Black *et al.*, 1985; Morris *et al.*, 1984; Velema *et al.*, 1997). A close contact or relative with recent typhoid fever, poor housing with inadequate food and personal hygiene and recent consumption of antimicrobials are further risk factors (Gasem *et al.*, 2001; Luby *et al.*, 1998; Luxemburger *et al.*, 2001). Transmission of typhoid has also been attributed to flies, laboratory mishaps, unsterile instruments and anal intercourse.

Chloramphenicol was introduced for the treatment of typhoid fever in 1948 (Woodward *et al.*, 1948) but resistance did not emerge as a problem until 1972. At that time outbreaks occurred in Mexico, India, Vietnam, Thailand, Korea and Peru (Rowe *et al.*, 1997). Curiously, after a few years these antibiotic resistant isolates disappeared from Mexico and Peru but persisted at low levels in Asia. Towards the end of the 1980s and 1990s, *S. enterica* serovar Typhi developed resistance simultaneously to all the first line drugs (chloramphenicol, trimethoprim, sulphamethoxazole and ampicillin) (Rowe *et al.*, 1997). Outbreaks with these strains have occurred in India, Pakistan, Bangladesh, Vietnam, the Middle East and Africa (Kariuki *et al.*, 2000). Multidrug resistant (MDR) *S. enterica* serovar Typhi are still common in many areas, although in some regions fully sensitive strains have re-emerged and in other regions *S. enterica* serovar Typhi has been overtaken by MDR *S. enterica* serovar Paratyphi A (Rodrigues *et al.*, 2003; Threlfall *et al.*, 2001; Wasfy *et al.*, 2002).

The appearance of MDR *S. enterica* serovar Typhi in Asia led to the widespread use of fluoroquinolones and extended spectrum cephalosporins for treatment. Isolates with low-level resistance to fluoroquinolones appeared within a few years of this change and have become common in Asia (Brown *et al.*, 1996; Dutta *et al.*, 2001). Large outbreaks of typhoid with such strains have occurred in Tajikistan, Vietnam and Nepal (Mermin *et al.*, 1999; Parry,

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2004) and these resistant strains are causing an increasing number of infections in returning travelers (Ackers *et al.*, 2000; Threlfall *et al.*, 2001). Although reported as susceptible by disc testing using recommended breakpoints to fluoroquinolones, these isolates have smaller zones of inhibition to fluoroquinolones by disc testing and fluoroquinolone minimum inhibitory concentrations 10-fold higher than fully susceptible strains (Crump *et al.*, 2003). They are invariably resistant to nalidixic acid and this is an important laboratory marker. Infection with these isolates leads to a poor clinical response to fluoroquinolone treatment (Rupali *et al.*, 2004; Wain *et al.*, 1997). Fully fluoroquinolone resistant and fully ceftriaxone resistant isolates in Asia appear to be uncommon, although systematic data are lacking (Mehta *et al.*, 2001; Saha *et al.*, 1999).

1.4 PATHOPHYSIOLOGY OF TYPHOID FEVER

Humans are the only natural host and reservoir of infection for *S. enterica* serovar Typhi. The infectious dose in volunteers varies between 10^3–10^9 organisms (Hornick *et al.*, 1970). Vi negative strains of *S. enterica* serovar Typhi are less infectious and less virulent than Vi positive strains. *S. enterica* serovar Typhi must survive the gastric acid barrier en route to the small intestine. Achlorhydria, due to ageing, previous gastrectomy, treatment with H_2 receptor antagonists, proton-pump inhibitors, large amounts of antacids or *Helicobacter pylori* infection increase susceptibility to typhoid fever (Bhan *et al.*, 2002). In the small intestine, the bacteria adhere to mucosal cells and then invade, translocate to the intestinal lymphoid follicles and the draining mesenteric lymph nodes and some pass on to the reticuloendothelial cells of the liver and spleen (House *et al.*, 2001a). Salmonellae are able to survive and multiply within the mononuclear phagocytic cells of the lymphoid follicles, liver and spleen. After a 7- to 14-day incubation period, the onset of a sustained secondary bacteraemia results in clinical disease.

The bacteraemia of typhoid fever persists for several weeks if antibiotic therapy is not given. In this phase, the organism disseminates widely to the liver, spleen, bone marrow, gall bladder and the Peyer's patches of the terminal ileum. The symptoms and signs of typhoid fever are not thought to be entirely due to circulating endotoxin (Butler *et al.*, 1978; Hornick *et al.*, 1970). Increased levels of circulating pro- and anti-inflammatory cytokines have been demonstrated in typhoid fever as well as a reduced capacity of whole blood to produce pro-inflammatory cytokines in severe disease. Ulceration of Peyer's patches is seen where the inflammatory process has resulted in ischaemia and necrosis (Everest *et al.*, 2001). Relapse probably occurs because

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of persisting organisms within the reticuloendothelial system. Gall bladder infection may become chronic, particularly in those individuals who have gall bladder pathology. Carriers may shed as many as 10^9 organisms/g feces.

Typhoid fever induces systemic and local humoral and cellular immune responses but these confer incomplete protection against relapse and reinfection (Marmion *et al.*, 1953).

1.5 CLINICAL FEATURES OF TYPHOID FEVER

S. enterica serovar Typhi infections result in a clinical syndrome that varies widely in severity (Huckstep, 1962; Osler and McCrae, 1926; Stuart and Pullen, 1946). After ingestion of the bacteria, an incubation period follows usually lasting 8 to 14 days (range 3–60 days). Fever and malaise mark the onset of bacteraemia but patients do not usually present to hospital until towards the end of the first week of symptoms. Fever, flu-like symptoms with chills (although rigors are rare) and a dull frontal headache are common. The fever, initially low grade, rises progressively, and by the second week is often high and sustained (39–40 °C). Other symptoms include malaise, anorexia, poorly localized abdominal discomfort, a dry cough and myalgia. Physical signs are few, but a coated tongue, tender abdomen, hepatomegaly and/or splenomegaly may be found. The abdominal pain is usually diffuse and poorly localized, but occasionally sufficiently intense in the right iliac fossa to suggest appendicitis. Dilated loops of bowel may be palpated indicating an ileus. Nausea and vomiting are infrequent in uncomplicated typhoid but are seen with abdominal distension in severe cases. Relative bradycardia is not a consistent feature. Rose spots are reported in 5–30% of cases but are easily missed in dark-skinned patients. These rose spots are small blanching erythematous maculopapular lesions typically on the abdomen and chest. Melanesian typhoid patients may develop purpuric macules that do not blanch. Constipation is generally more common in adults, but in young children and adults with HIV infection diarrhoea predominates. *S. enterica* serovar Paratyphi causes a similar, although less severe, syndrome.

Untreated, the fever persists for two weeks or more and defervescence occurs slowly over the following 2–3 weeks. Convalescence may last for 3–4 months. If an appropriate antibiotic is given the fever gradually falls over 3–4 days. The duration of untreated illness prior to the initiation of therapy influences the severity of the disease. Those individuals infected with multi-drug-resistant (MDR) isolates of *S. enterica* serovar Typhi may also suffer more severe disease. Patients with typhoid fever in the second to fourth

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Table 1.3. *Principle complications of typhoid fever*

Abdominal	*Neuropsychiatric*
Intestinal perforation	Obtundation
Intestinal haemorrhage	Delirium
Hepatitis	Coma
Cholecystitis (usually subclinical)	Psychotic states
Genitourinary	Depression
Retention of urine	Deafness
Glomerulonephritis	Meningitis
	Seizures (children)
Cardiovascular	Cerebellar ataxia
Asymptomatic ECG changes	Encephalomyelitis
Myocarditis	*Haematological*
Shock	Disseminated intravascular coagulation (usually subclinical)
Sudden death	Anaemia
Respiratory	Haemolysis
Bronchitis	*Other*
Pneumonia (Rarely due to *S.enterica* serotype Typhi, more commonly a secondary infection due to *Streptococcus pneumoniae*)	Focal abscesses of brain, liver, spleen, breast, thyroid, muscles, lymph nodes
	Metabolic acidosis
	Relapse

week present with accelerating weight loss, weakness, an alteration of mental state and the development of complications that occur in 10–15% of hospitalized patients and occasionally dominate the clinical picture deflecting attention from the underlying diagnosis of typhoid. Although many complications have been described (Table 1.3), gastrointestinal bleeding, intestinal perforation and typhoid encephalopathy are the most important.

Gastrointestinal bleeding occurs in up to 10% of patients and results from erosion of a necrotic Peyer's patch through the wall of an enteric vessel. Usually the bleeding is slight and resolves without the need for blood transfusion. In 1–2% of cases, bleeding is significant, and can be rapidly fatal if a large vessel is involved. Intestinal (usually ileal) perforation is the most serious complication occurring in 1–3% of hospitalized patients. Perforation may present with an acute abdomen or more covertly with simple worsening of abdominal pain, rising pulse and falling blood pressure in an already sick

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patient. Typhoid encephalopathy, often accompanied by shock, is associated with a high mortality. Patients may display the "typhoid" facies, a thin, flushed face with a staring, apathetic expression. Mental apathy may progress to an agitated delirium, frequently accompanied by tremor of the hands, tremulous speech and gait ataxia, and then muttering delirium, twitchings of the fingers and wrists (subsultus tendinum), agitated plucking at the bedclothes (carphology), and a staring, unrousable stupor (coma vigil) (Osler and McCrae, 1926).

Typhoid fever in pregnancy may be complicated by miscarriage, although antimicrobial treatment has made this less common (Seoud *et al.*, 1988). Vertical intra-uterine transmission from a typhoid-infected mother may lead to neonatal typhoid, a rare but severe and life-threatening complication (Reed and Klugman, 1994). Relapse occurs in 5–10% of patients, usually 2 to 3 weeks after defervescence. The illness is usually, but not invariably, milder than the original attack and the relapse *S. enterica* serovar Typhi isolate has the same susceptibility pattern as in the original episode. Reinfection may also occur (Marmion *et al.*, 1953). Up to 10% of untreated convalescent typhoid cases will excrete *S. enterica* serovar Typhi in feces for 1–3 months and between 1 and 4% become chronic carriers excreting the organism for more than one year. Chronic carriers give no prior history of typhoid fever in up to 25% of cases. Fecal carriage is more frequent in individuals with gallbladder disease and is most common in women over 40; in the Far East there is an association with opisthorchiasis. Chronic carriage carries an increased risk of carcinoma of the gallbladder, pancreas and large bowel (Caygill *et al.*, 1994). Urinary carriage is associated with schistosomiasis and nephrolithiasis.

1.6 DIAGNOSIS OF TYPHOID FEVER

The lack of specific clinical signs complicates the diagnosis of typhoid fever, which must be distinguished from other endemic acute and subacute febrile illnesses. These can include malaria, deep abscesses, tuberculosis, amoebic liver abscesses, encephalitis, influenza, dengue fever, infectious mononucleosis, infectious hepatitis, leptospirosis, endocarditis, brucellosis, typhus, visceral leishmaniasis, toxoplasmosis, lymphoproliferative disease and connective tissue diseases. A fever lasting more than one week without evident cause should be considered typhoid until proven otherwise and typhoid should always be considered when suspected malaria has not been confirmed or has not responded to antimalarial therapy. It is unusual for a patient hospitalized with typhoid fever to have no abdominal symptoms

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and normal bowel habit. In non-endemic countries, a travel history is crucial.

The haemoglobin, white cell and platelet count are usually within the normal range or reduced. Leucocytosis suggests either intestinal perforation or an incorrect diagnosis. Laboratory evidence of disseminated intravascular coagulation may be present but is very rarely of clinical significance. Liver transaminases are characteristically two to three times above normal. The urine may contain protein and leukocytes.

Blood cultures are the standard diagnostic method and can be positive in 60–80% of cases. In mild typhoid the number of bacteria may be as low as one colony-forming unit per ml of blood (Butler *et al.*, 1978; Wain *et al.*, 1998). The number of bacteria in the blood of children is higher than in adults and declines with increasing duration of illness. Recovery of the organism from blood cultures depends on several factors including the volume of blood cultured, the ratio of the volume of blood to the volume of culture broth in which it is inoculated (the ratio should be at least 1:8) and inclusion of anticomplementary substances in the medium (such as sodium polyethol sulfonate or bile). Culture of bone marrow is more sensitive regardless of the illness duration and is positive in 80–95% of patients despite prior antibiotic therapy (Gilman *et al.*, 1975, Hoffman *et al.*, 1986). The higher sensitivity of bone marrow cultures compared to blood in part relates to the higher concentration of organisms in bone marrow (Wain *et al.*, 2001).

Other diagnostic approaches have included culturing the organisms from the buffy coats of blood, from streptokinase-treated blood clots, from intestinal secretions using a duodenal string capsule and from skin snips of rose spots (Gilman *et al.*, 1975; Hoffman *et al.*, 1984b; Hoffman *et al.*, 1986). On average stool cultures are positive in 30% of patients with acute typhoid fever although the results should be interpreted with caution in areas with many carriers. For the detection of carriers, several samples should be examined because of irregular shedding. Isolation from urine is more common in areas with schistosomiasis.

Serological tests for typhoid fever have been used since the late 19th century. Widal and Sicard in 1896 showed that the serum of patients with typhoid fever agglutinated typhoid bacilli. The Widal test, in which O and H agglutinins are demonstrated in serum, may be performed with appropriate antigens in tubes or on slides. Typically antibodies to the O and H antigens appear during the end of the first week of disease and peak at the end of the third week but there is much variability (Levine *et al.*, 1978). The use of a single measurement of antibody titres is useful if the background levels of antibodies in the population are known (Clegg *et al.*, 1994; Parry *et al.*, 1999).

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