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Typhoid

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CHAPTER 1

Epidemiology

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INTRODUCTION

Typhoid fever is endemic in many developing countries due to poor sanitation and contaminated water supply. It is caused due to infection by the genus *Salmonella* which comprises of *Salmonella typhi*, *S. paratyphi A*, *S. paratyphi B* and *S. paratyphi C*. All these organisms can cause a bacteremic illness known as enteric fever. Among all these, *S. typhi* causes typhoid fever and the rest causes paratyphoid fever. Human is the only reservoir in the form of either cases or carriers. Infected patients excrete these organisms for varying periods of times. Those patients who excrete *S. typhi* bacilli for more than 1 year after clinical or subclinical typhoid infection are classified as chronic carriers. Nearly 3–5% of the typhoid fever cases become chronic carriers.

EPIDEMIOLOGY

The regional typhoid fever rates are classified as high (>100 cases/100,000/year), medium (10–100 cases/100,000/year), and low (<10 cases/100,000/year) incidence settings. India including South Central Asia has an incidence setting of roughly 622 cases/100,000/year suggesting to be in high incidence setting group.[1] Community-based studies show

consistently higher levels of typhoid than public health figure. Annual incidence rate of 980/100,000 in Delhi has been reported from our country.[2]

Typhoid fever may occur at any age but it is more prevalent in children and young adults, the peak incidence is in children aged 5–15 years. As the person grows older he becomes relatively immune because of the acquired immunity due to subclinical exposure to typhoid bacilli. Cases occur throughout the year but increase during the summers, the peak months being July to September.

CAUSATIVE ORGANISM

Salmonella is a gram negative bacillus. The organism survives intracellularly, grows rapidly on ordinary media under aerobic as well as anaerobic conditions. It is rapidly killed by drying, pasteurization and common disinfectants. *S. typhi*, *S. paratyphi A, S. paratyphi B* and *S. paratyphi C* organisms have three main antigens O, H and Vi. *S. typhi* has more than 80 phage types. Phage typing is a useful epidemiological tool in tracing the source of epidemics. *S. typhi* and *paratyphi* together form a group of fever referred to as enteric fever. Typhoid contributes 90% in this group.

Salmonella survive refrigeration and also heating. They may remain viable at ambient temperatures and also in various foods for weeks. It may remain viable in foods after low heat cooking (less than 140°C) cooked for less than 12 minutes. *Salmonella* may survive for hours in the hand of food handlers.[3]

INCUBATION PERIOD

Incubation period of *Salmonella* is 10–14 days. It may be as short as 3 days and as long as 3 weeks. It depends on the load of the bacillus ingested. The incubation period is inversely

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proportional to the size of inoculum. *S. typhi* divides rapidly in less than half hour. So that, after 1–2 weeks, the amount of bacilli that results from even a single bacillus are tremendous. Thus, the total bacilli load is usually huge. However, normal intestinal flora is an important defense against invasion by typhoid bacillus and not all persons who get infected would get the disease eventually.

SOURCE OF INFECTION

The primary source of infection is the feces and urine of cases and carriers. The secondary sources are contaminated water, food, and dissemination by hands and flies. *S. typhi* does not multiply in water but can survive for about a week. In soil irrigated with water from sewage, *S. typhi* may survive for nearly 2 months. It can survive for more than a month in ice and ice-creams. *S. typhi* can also grow rapidly in milk without altering its taste or appearance. Milk products like cream, ice-cream and cheese have also been known to have caused *Salmonella* epidemics. Vegetables grown on sewage irrigated farms may be infected with typhoid bacilli and can be a source of infection if taken raw without being washed properly or disinfecting them by using chlorine and potassium permanganate. Other food sources which can commonly lead to infection are meat products (when not cooked well) and untreated shellfish. The organism remains viable on external surface of houseflies for as long as 20 days. These flies carry the bacillus from the feces to food and are thus an important source of infection.[4]

Various personal and social factors or practices which are conducive for the spread of infection are improper hand washing after toilets, low standard of food and kitchen hygiene, washing infected material near kitchen, defecation and urination in open spaces, illiteracy and lack of health

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education. Inadequate facilities for processing human waste further contaminates water supply. Patients with parasitic infections such as roundworms or schistosomiasis are also readily infected with *S. typhi* as the organism gets adhered to the surface of the parasites.

EPIDEMIOLOGY OF MULTIDRUG RESISTANT TYPHOID FEVER

Multiple drug resistant *S. typhi* (MDRST) denotes those strains of typhoid fever which have resistance to all the three first line antibiotics (chloramphenicol, ampicillin and trimethoprim/sulfamethoxazole). It has assumed a massive proportion not only in many developing countries but is also being increasingly seen in the developed countries.[3]

Initially in 1948 chloramphenicol was the treatment of choice for typhoid. It was in 1972 that major resistance to this drug developed and outbreaks occurred in many countries including India. Toward the end of 1990s typhoid was resistant to all the first-line drugs and infections with these strains were reported from India also.[5]

Fluoroquinolones was the next drug to be introduced in the treatment of typhoid but resistance to this drug was also reported. So, there are two categories of drug resistance—resistance to first-line antibiotics and resistance to the fluoroquinolone drugs. Resistance to fluoroquinolone may again be total or partial. The so called nalidixic acid resistant *S. typhi* (NARST) is a marker of reduced susceptibility to fluoroquinolones compared to nalidixic acid sensitive strains. Nalidixic acid is not used for the treatment of typhoid. NARST isolates are susceptible to fluoroquinolones in current disk sensitivity test. But the clinical response to treatment with fluoroquinolones of NARST is worse than with

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nalidixic acid sensitive strains.[6,7] This reduced susceptibility to fluoroquinolones has become a major problem in Asia.

Third generation cephalosporins including oral cefixime and parenteral ceftriaxone were found to be effective in children.[3] Sporadic reports of high level resistance to ceftriaxone followed though rare. Recently, azithromycin is used in children for the treatment of uncomplicated typhoid fever.

KEY MESSAGES

- Poor sanitation and contaminated water supply are the main causes of endemicity of typhoid in developing countries
- Human is the only reservoir of typhoid
- India including South Central Asia falls into the high incidence setting group of typhoid
- *Salmonella* survive refrigeration, heating including low heat cooking, stored food for weeks and also for hours in the hand of food handlers
- The source of infection primarily is feces and urine of cases and carriers and secondarily by contaminated water, food and dissemination by hands and flies.

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CHAPTER 2

Pathogenesis

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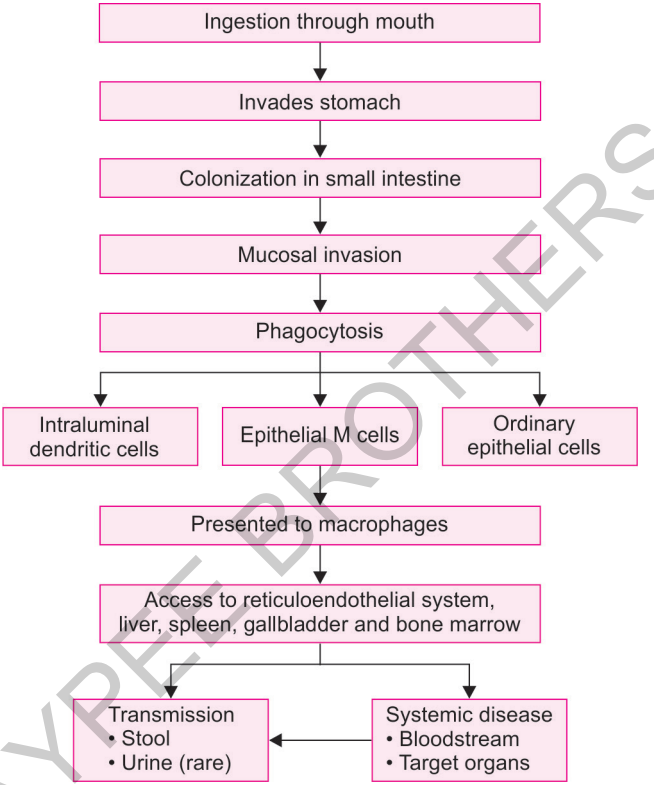
INTRODUCTION

The invasiveness of *Salmonella* is regulated by growth state, high osmolarity, low oxygen tension and pH. *Salmonella typhi* must survive the gastric acid barrier to reach the small intestine and a low gastric pH is an important defense mechanism. The infectious dose of *S. typhi* in volunteers varies between 1,000 and 1 million organisms. Vi-negative strains of *S. typhi* are less infectious and less virulent than Vi-positive strains.[1]

Increased susceptibility to *Salmonella* is seen in conditions that decrease stomach acidity (children below 1 year age, antacid ingestion and achlorhydria) and in conditions that decrease intestinal integrity (inflammatory bowel disease, gastrointestinal surgery, alteration of intestinal flora by antibiotic administration). Flowchart 1 shows the pathogenic mechanism of typhoid.

IN THE SMALL INTESTINE

The bacteria reach the small intestine where they colonize. It then adheres to the intestinal epithelia via five different fimbrial operons (fim, lpf, agf, sef and pef). lpf are important in the initial attachment to Peyer's patches. These are lymphoid follicles similar in many ways to lymph nodes, located in



FLOWCHART 1: Pathogenetic mechanism for typhoid.

the mucosa and extending into the submucosa of small intestine. It is usually found in the lowest portion of the small intestine, mainly in the distal jejunum and the ileum. It could also be detected in the duodenum. In adults, B lymphocytes predominate in Peyer's patches.

Salmonella enter the intestines through phagocytic microfold or M cells overlying the Peyer's patches in small intestine.

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These M Cells, specialized epithelial cells overlying Peyer's patches, are probably the site of the internalization of *S. typhi*.

Salmonella also enter nonphagocytic epithelial cells by a process known as bacteria-mediated endocytosis. This is thought to be facilitated by direct translocation of *Salmonella* proteins into the host cell cytoplasm by a specialized secretion apparatus (type III secretion). This mechanism promotes survival of bacteria within the phagocytes. The easy access through the bowel may be explained by the bacteria's ability to invade the gut without stimulating an acute inflammatory response or recruitment of neutrophils.

IN THE BLOOD STREAM

After passing through the intestinal epithelial cells, they reach the lamina propria where they are phagocytosed by macrophages. The bacteria are conveyed to the draining mesenteric lymph nodes and from there reach the blood stream via the thoracic duct. This transient primary bacteremia is followed by seeding of the reticuloendothelial cells of different organs like liver, spleen and bone morrow.

BACTEREMIA

During the incubation period, the organisms multiply silently within sites to which they have been seeded by the primary bacteremia. The onset of symptoms correlates with the secondary persistent bacteremia into the blood of large number of organisms from primarily infected sites. The gallbladder is particularly susceptible to being infected and constantly delivers more bacilli to the intestine via the bile.

The surface Vi capsular antigen interferes with phagocytosis by preventing the binding of C3 to the surface of bacterium. The ability of bacteria to survive within macrophages after

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phagocytosis is an important virulence trait encoded by the PhoP regulon.

Circulating endotoxin, a lipopolysaccharide component of bacterial cell wall is thought to cause the prolonged fever and toxic symptoms of enteric fever, although its levels in symptomatic patients are often low. Alternatively, endotoxin-induced cytokine production by macrophages when a critical number of organisms have replicated may cause systemic symptoms. At a critical point that is probably determined by the number of bacteria, their virulence, and the host response, bacteria are released from this sequestered intracellular habitat into the bloodstream.[1]

ORGAN INVOLVEMENT

In the bacteremic phase, the organism is widely disseminated throughout the body. The most common sites of secondary infection are the liver, spleen, bone marrow, gallbladder and Peyer's patches of the terminal ileum.[2] Gallbladder invasion occurs either directly from the blood or by retrograde spread from the bile. Organisms excreted in the bile either reinvade the intestinal wall or are excreted in the feces. Proliferation of bacilli, which is enhanced by bile, continues in the bile ducts and especially in the gallbladder, from where large numbers of bacteria pass into the gut and may be cultured from a duodenal aspirate.

After the macrophages have been activated by sensitized lymphocytes, an inflammatory reaction takes place and results in swelling, necrosis and ulceration of Peyer's patches, which in most cases, heals uneventfully.[3]

The hepatosplenomegaly is due to recruitment of mononuclear cells and the development of a cell-mediated immune response to *S. typhi* colonization. The recruitment of additional

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mononuclear cells and lymphocytes Peyer's patches afterwards can result in marked enlargement of Peyer's patches, with right lower quadrant abdominal pain. However, erosion of blood vessels may cause intestinal hemorrhage and extension of necrosis through the bowel wall may result in perforation.

Many tissues of the body can be affected, including liver, spleen, kidney, heart and lungs.

Typhoid nodules, which are foci of macrophages and lymphocytes, can be detected in a large number of internal organs.

NEUROPSYCHIATRIC COMPLICATIONS

Various neuropsychiatric complications are common in typhoid fever. The exact pathogenesis is not known. However, various mechanisms have been postulated.[3]

- Endotoxin as well as bacteria (*Salmonella*) per se may produce myelitis
- Nonspecific allergic demyelinating form of encephalomyelitis which may occur as a reaction to a number of bacterial and viral illnesses
- An "endarteritis obliterans" producing thrombosis and ultimate paraplegia.

Pathological changes in patients with neuropsychiatric complications reveals varying lesions such as diffuse neuronal damage, nonspecific vascular changes with thrombosis and hemorrhages, perivascular softening, and disseminated granuloma formation.

MECHANISMS OF IMMUNITY

Cell-mediated immunity is probably the key factor in production of immunity and recovery from infection. Humoral

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antibody production appears to play minimal role in recovery from acute infection, as the patient continues to deteriorate despite the appearance of O, H and Vi antibodies.[4]

Local gut immunity, both innate and acquired is also important in preventing infection and re-infection.

In endemic countries, typhoid fever has highest prevalence in children and adolescents.[1] Adults are protected after having acquired substantial immunity to previous subclinical exposures.

KEY MESSAGES

- Invasiveness of *Salmonella* is regulated by growth state of the bacteria, high osmolarity, low oxygen tension, high pH, inflammatory bowel disease, gastrointestinal surgery and alteration of intestinal flora by antibiotic use
- The bacteria adhere to the epithelium of small intestine then they are conveyed to the draining mesenteric lymph nodes and reach the blood stream via the thoracic duct. Finally seed the reticuloendothelial cells of liver, spleen and bone morrow
- Onset of symptoms correlates with the secondary persistent bacteremia from primarily infected sites
- The organism is widely disseminated in liver, spleen, bone marrow, gallbladder and Peyer's patches of the terminal ileum
- Gallbladder is invaded either directly from the blood or by retrograde spread from the bile.

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- The subject is presented in a brief, to the point ready-to-read format for handy reference
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- The chapters in this book cover various aspects of typhoid in a concise presentation
- Focus has been given to recommended diagnostic modalities and treatment including drug-resistant typhoid fever
- Latest recommendation of vaccines against typhoid fever has been discussed
- This book will be helpful for all the undergraduate, postgraduate medical students and the medical practitioners who treat children suffering from typhoid fever.

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