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Research Article

Information about Pathogenesis, Diagnosis and Prognosis of Typhoid Fever

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Abstract

Typhoid fever, caused primarily by Salmonella enterica serovar Typhi, is a systemic illness with significant global health implications, especially in resource-limited regions. The pathogenesis involves ingestion of contaminated food or water, followed by intestinal invasion and dissemination through the lymphatic and circulatory systems. S. Typhi exhibits intracellular survival within macrophages, leading to sustained bacteremia and systemic manifestations such as fever, abdominal pain, and malaise. Diagnosis relies mainly on blood culture, the gold standard during early infection, although its sensitivity is limited by prior antibiotic use. Other methods include stool culture, serologic testing, and emerging molecular techniques. Prognosis is generally favorable with prompt and appropriate antibiotic therapy, reducing mortality to less than 1%. However, delayed diagnosis or inadequate treatment may result in severe complications, including intestinal perforation, hemorrhage, and chronic carriage. Continued investment in diagnostic capacity, early case detection, and effective treatment protocols is essential to improve clinical outcomes and reduce the global burden of typhoid fever.

Keywords: *Pathogenesis, Diagnosis, Prognosis Typhoidal Salmonellosis, Typhoid Fever, Enteric Fever, Infection, Diagnosis Test.*

Introduction:

Pathogenesis

The estimated number of bacteria that must be ingested to cause symptomatic disease in healthyadultsis 106 -108 Salmonella organisms. The gastric acidity inhibits multiplication of salmonellae, and most organisms are rapidly killed at gastric pH ≤2.0. Achlorhydria, buffering medications, rapid gastric emptying after gastrectomy or gastroenterostomy, and a large inoculum enable viable organisms to reach the small intestine. Figure 1 shows the Salmonella organisms.

Figure 1: Salmonella organisms

The typical intestinal mucosal response to NTS infection is an enterocolitis with diffuse mucosal inflammation and edema, sometimes with erosions and micro abscesses. Salmonella organisms are capable of penetrating the intestinal mucosa, although destruction of epithelial cells and ulcers are usually not found. Intestinal inflammation with PMNs and macrophages usually involves the lamina propria.

Underlying intestinal lymphoid tissue and mesenteric lymph nodes enlarge and may demonstrate small areas of necrosis. Such lymphoid hypertrophy may cause interference with the blood supply to the gut mucosa**.**

Hyperplasia of the RES is also found within the liver and spleen. If bacteremia develops, it may lead to localized infection and suppuration in almost any organ. Both S. Typhi and NTS possess overlapping and distinct virulence systems.

Intestinal infection usually results in a localized enteritis that is associated with a secretory response in the intestinal epithelium. Intestinal infection also induces secretion of interleukin (IL)-8 from the basolateral surface and other chemo-attractants from the apical surface, directing recruitment and transmigration of neutrophils into the gut lumen and thus preventing the systemic spread of the bacteria.

SPI-1 and SPI-2, which are responsible for the secretion and translocation of a set of bacterial proteins termed effectors into host cells; effectors are able to alter host cell physiology to facilitate bacterial entry and survival. Once delivered by the type III secretion systems, the secreted effectors play critical roles in manipulating the host cell to allow bacterial invasion, induction of inflammatory responses, and assembly of an intracellular protective niche conducive to bacterial survival and replication. The type III secretion system encoded on SPI-1 mediates invasion of the intestinal epithelium, whereas the type III secretion system encoded on SPI-2 is required for survival within macrophages.

In addition, the expression of strong agonists of innate pattern recognition receptors (lipopolysaccharide and flagellin) is important for triggering a Toll-like receptor (TLR) – mediated inflammatory response. Salmonella spp. Invade epithelial cells in vitro by a process of bacteria mediated endocytosis involving cytoskeletal rearrangement, disruption of the epithelial cell brush-border, and subsequent formation of membrane ruffles. Figure 2 shows Pathogenesis of Typhoid Fever.

The invasive phenotype is mediated in part by SPI-1, a 40-kb region that encodes regulator proteins such as Hil A and a variety of other products.

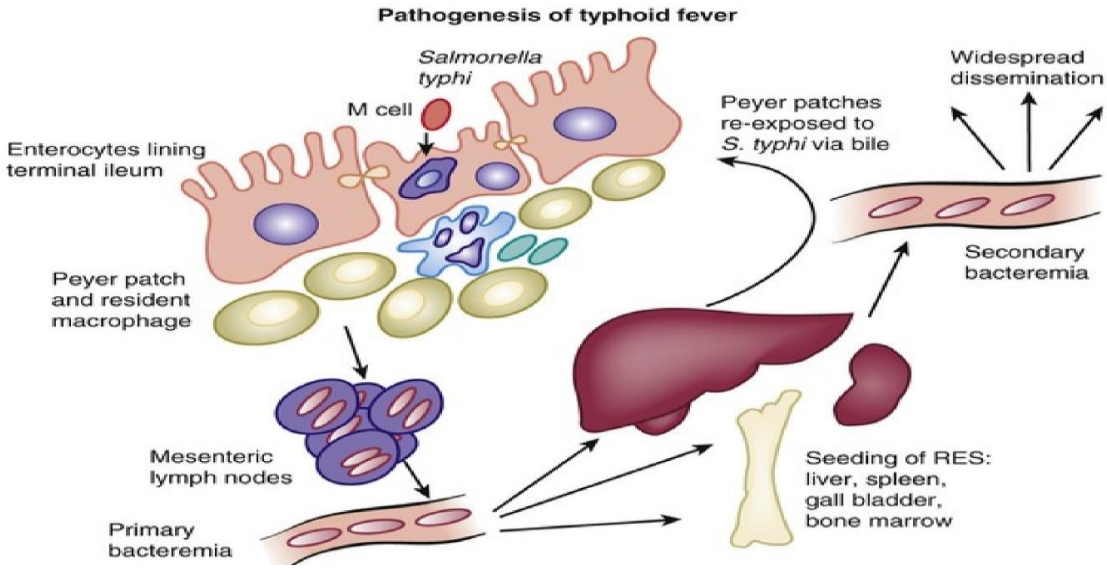

Figure 2: Pathogenesis of Typhoid Fever

Method, Material, Findings and Discusssion:

Enteric fever occurs through the ingestion of the organism, and a variety of sources of fecal contamination have been reported, including street foods and contamination of water reservoirs Human volunteer experiments established an infecting dose of about 105-109 organisms, with an incubation period ranging from 4-14 days, depending on the inoculating dose of viable bacteria.

After ingestion, S. Typhi organisms are thought to invade the body through the gut mucosa in the terminal ileum, possibly through specialized antigen-sampling cells known as M cells that overlie GALT, through enterocytes, or via a paracellular

route. S. Typhi crosses the intestinal mucosal barrier after attachment to the microvilli by an intricate mechanism involving membrane ruffling, actin rearrangement, and internalization in an intracellular vacuole.

In contrast to NTS, S. Typhi expresses virulence factors that allow it to downregulate the pathogen recognition receptor–mediated host inflammatory response. Within the Peyer patches in the terminal ileum, S. Typhi can traverse the intestinal barrier through several mechanisms, including the M cells in the follicle-associated epithelium, epithelial cells, and dendritic cells.) Figure 3 shows Faeco-Oral Transmission

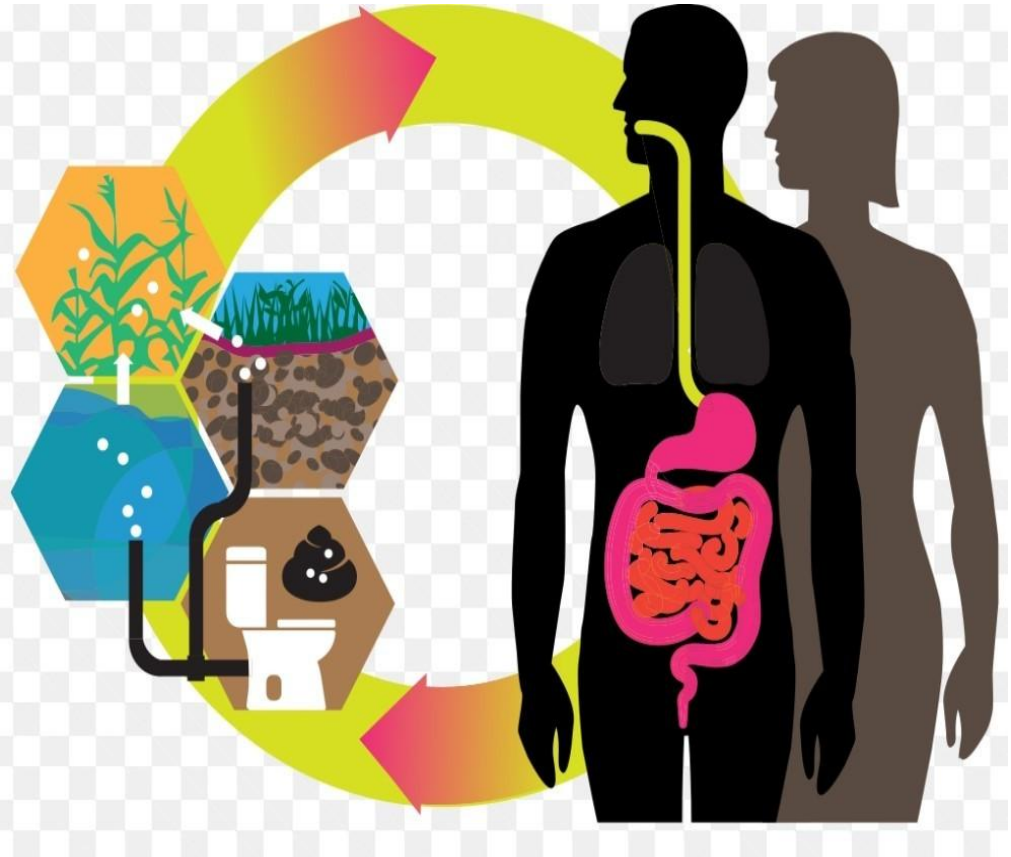

Figure 3: Faeco-Oral Transmission

At the villi, Salmonella can enter through the M cells or by passage through or between compromised epithelial cells. On contact with the epithelial cell, S. Typhi assembles type III secretion system encodes SPI-1 and translocate effectors into the cytoplasm.

These effectors activate host Rho guanosine triphosphatases, resulting in the rearrangement of the actin cytoskeleton into membrane ruffles, induction of mitogen-activated protein kinase (MAPK) pathways, and destabilization of tight junctions. Changes in the actin cytoskeleton is further modulated by the actin binding proteins Sip A and Sip C and lead to bacterial uptake. Figure 4 shows Pathogenesis of Enteric Fever.

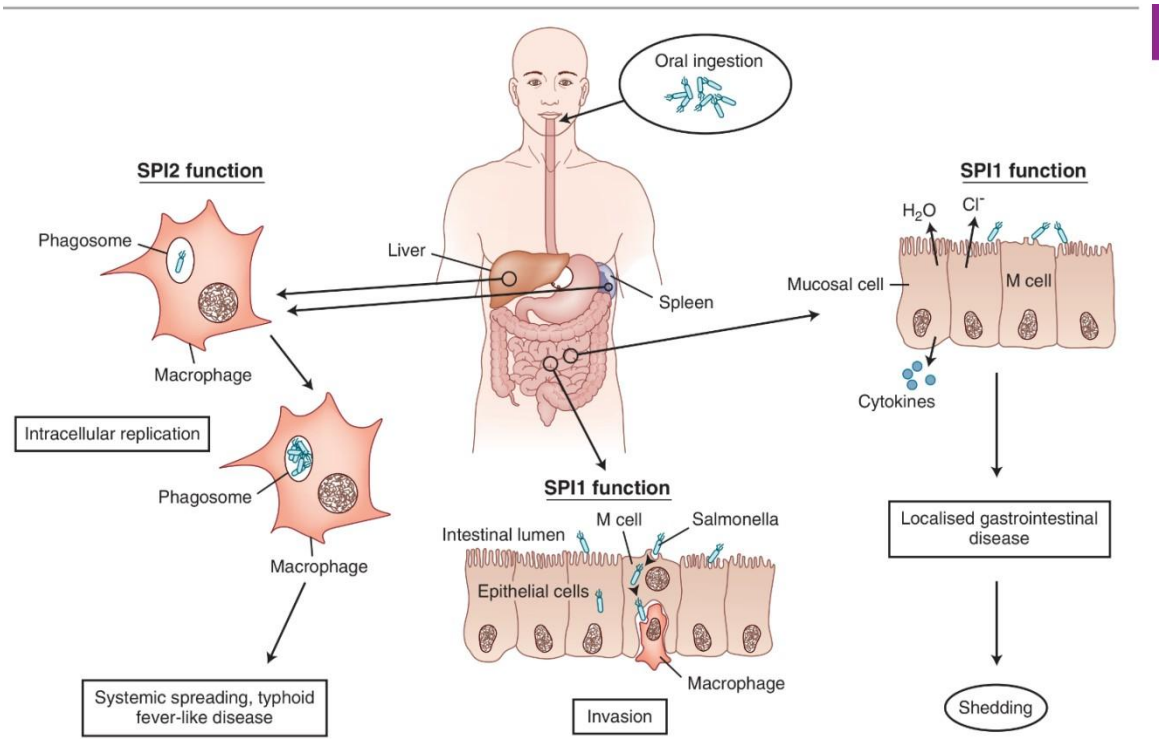

Figure 4: Pathogenesis of Enteric Fever

MAPK signaling activates the transcription factors activator protein (AP)-1 and nuclear factor (NF)-κB, which turn on production of IL-8. The destabilization of tight junctions allows the transmigration of PMNs from the basolateral surface to the apical surface, paracellular fluid leakage, and access of bacteria to the basolateral surface. Shortly after internalization of S. Typhi by micropinocytosis, salmonellae are enclosed in a spacious phagosome formed by membrane ruffles. Later, the phagosome fuses with lysosomes, acidifies, and shrinks to become adherent around the bacterium, forming the Salmonella -containing vacuole. Figure 5 shows Pathogenesis of Typhoid Fever.

A 2nd type II secretion system encoded on SPI-2 is induced within the Salmonella -containing vacuole and translocate effector proteins Sifa and PipB2, which contribute to Salmonella -induced filament formation along microtubules. After passing through the intestinal mucosa, S. Typhi organisms enter the mesenteric lymphoid system and then pass into the bloodstream via the lymphatics.

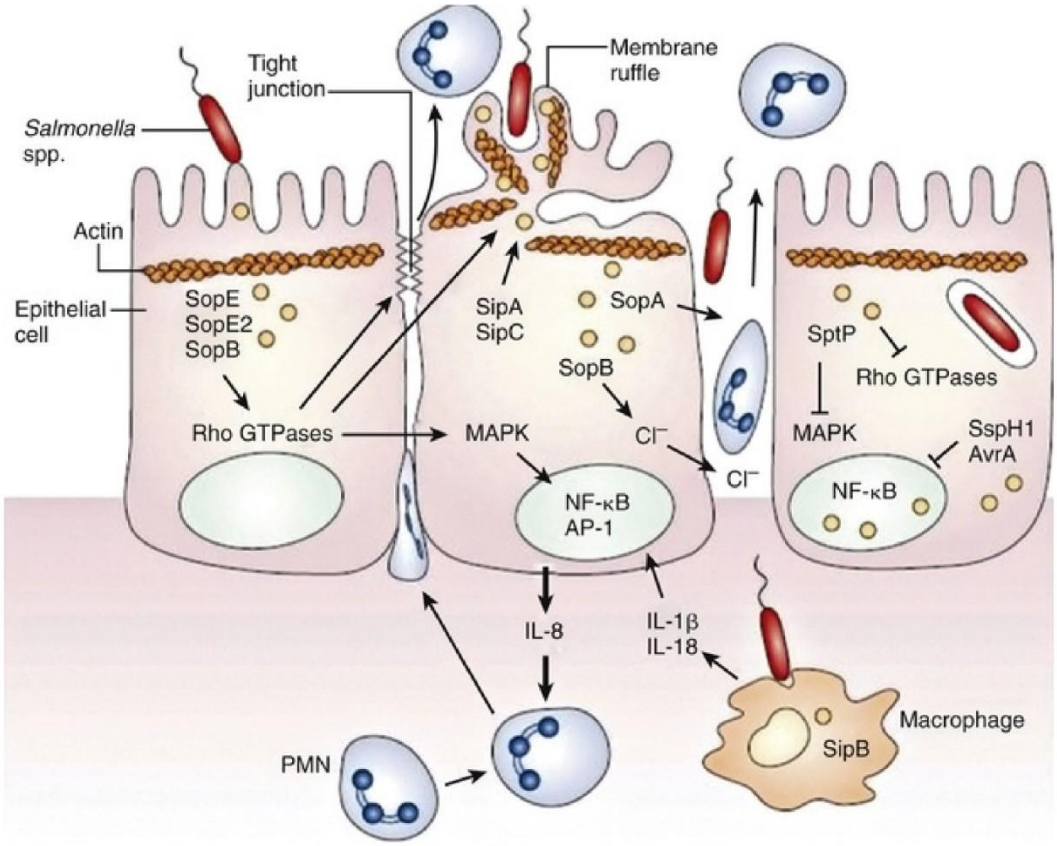

Figure 5: Pathogenesis of Typhoid Fever

This primary bacteremia is usually asymptomatic, and blood culture results are frequently negative at this stage of the disease. The bloodborne bacteria are disseminated throughout the body and are thought to colonize the organs of the RES, where they may replicate within macrophages. After a period of bacterial replication, S. Typhi organisms are shed back into the blood, causing a secondary bacteremia that coincides with the onset of clinical symptoms and marks the end of the incubation

period. In vitro studies with human cell lines have shown qualitative and quantitative differences in the epithelial cell response to S. Typhi and S. Typhimurium with regard to cytokine and chemokine secretion. Thus, perhaps by avoiding the triggering of an early inflammatory response in the gut, S. Typhi can instead colonize deeper tissues and organ systems. Infection with S. Typhi produces an inflammatory response in the deeper mucosal layers and underlying lymphoid tissue, with hyperplasia of Peyer patches and subsequent necrosis and sloughing of overlying epithelium. The resulting ulcers can bleed but usually heal without scarring or stricture formation.

The inflammatory lesion may occasionally penetrate the muscularis and serosa of the intestine and produce perforation. The mesenteric lymph nodes, liver, and spleen are hyperemic and generally have areas of focal necrosis as well.

The occasional occurrence of diarrhea may be explained by the presence of a toxin related to cholera toxin and E. coli heat-labile enterotoxin the clinical syndrome of fever and systemic symptoms is produced by a release of proinflammatory cytokines (IL-6, IL-1β and TNF-α) from the infected cells.

Figure 6 shows Mechanism of Action and Table 1 shows: Disease Manifestation.
Patients who are infected with HIV are at significantly higher risk for clinical infection with S. Typhi and S. Paratyphi. Similarly, patients with Helicobacter pylori infection have an increased risk of acquiring typhoid fever.

Disease Manifestation	Mechanisms and Bacterial Genes
Bloody diarrhea	*sip* A-D–mediated invasion and interleukin-8–mediated inflammation
Watery diarrhea	*stn* enterotoxin (cholera-like toxin) *SopB*-mediated intestinal inflammation and fluid secretion Serotypes that induce transepithelial polymorphonuclear leukocyte migration (e.g., *S.* ser. Typhimurium) are more likely to cause diarrhea than are serotypes that do not (e.g., *S.* ser. Typhi)
Bacteremia	*viaB* (Vi synthesis) capsular antigen interferes with C3 binding (*S.* ser. Typhi, *S.* ser. Dublin, *S.* ser. Paratyphi C) *rck* resistance to serum complement (virulence plasmid encoded) *rfb* encodes lipopolysaccharide synthesis; lipopolysaccharide contributes to persistence of bacteremia
Relapses, prolonged fever, failure of certain antibiotics	Survival in macrophages (*sseABC*, *spiC*, *mgtCB*, cytotoxin and virulence plasmid genes *spvRABCD*)

Table 1: Disease Manifestation

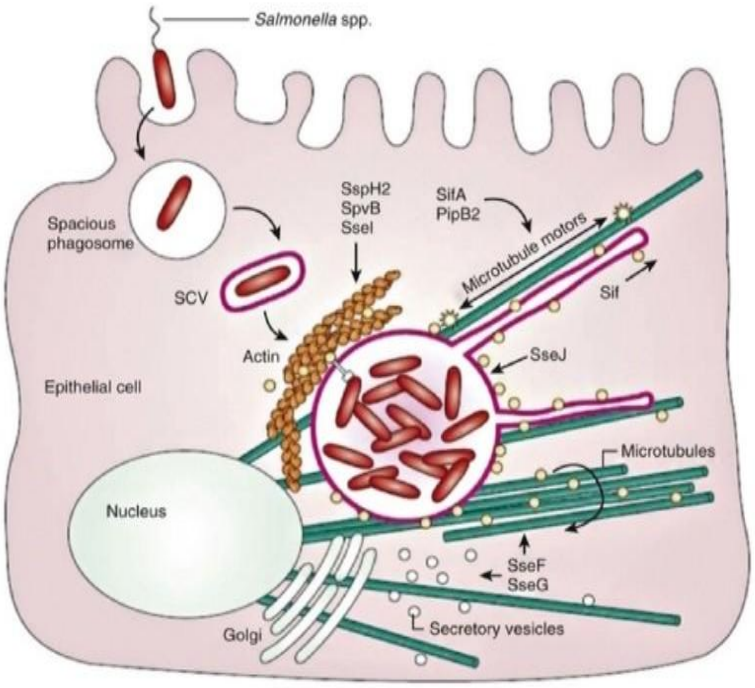

Figure 6: Mechanism of Action

Clinical Manifestation of Typhoid (Enteric) Fever

Fever, headache, vomiting, abdominal pain, malaise, drowsiness, confusion, rash, diarrhoea, constipation, pallor, anorexia,

Acute enteritis is most common clinical presentation of salmonellosis is acute enteritis. After an incubation period of 6-72 hrs. (mean: 24hr), there is an abrupt onset of nausea, vomiting, and crampy abdominal pain, located primarily in the

periumbilical area and right lower quadrant, followed by mild to severe watery diarrhea and sometimes by diarrhea containing blood and mucus. Table 2 shows common clinical features of typhoid fever in children.

NTS GI infections typically cause bacteremia in developing countries.

Furthermore, 60% of children have an apparent lower respiratory tract infection focus.

Hepatomegaly and Splenomegaly, coated tongue, jaundice, Abdominal distention, ileus, intestinal perforation.

Following bacteremia, salmonellae have the propensity to seed and cause focal suppurative infection of many organs. The most common Local infections involve the skeletal system, meninges, intravascular sites, and sites of preexisting abnormalities.

Common Clinical Features of Typhoid Fever in Children*

FEATURE	RATE (%)
High-grade fever	95
Coated tongue	76
Anorexia	70
Vomiting	39
Hepatomegaly	37
Diarrhea	36
Toxicity	29
Abdominal pain	21
Pallor	20
Splenomegaly	17
Constipation	7
Headache	4
Jaundice	2
Obtundation	2
Ileus	1
Intestinal perforation	0.5

Table 2 Common clinical features of typhoid fever in children.

Localized infection: Intraabdominal infections due to NTS are rare and usually manifest as hepatic or splenic abscesses or as **cholecystitis.** Risk factors include hepatobiliary anatomic abnormalities (e.g., gallstones), abdominal malignancy, and sickle cell disease (especially with splenic abscesses. Figure 7 shows Coated Tongue.

Central nervous system infections NTS meningitis most commonly develops in infants 1–4 months of age. It often results in severe sequelae (including seizures, hydrocephalus, brain infarction, and mental retardation), with death in up to 60% of cases.

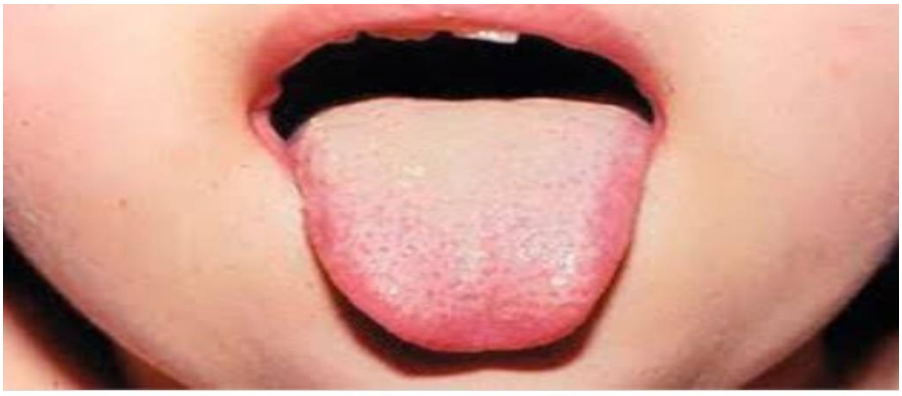

Figure 7: Coated Tongue

Other rare central nervous system infections include ventriculitis, subdural empyema, and brain abscesses, menengism, seizures, encephalopathy.

Pulmonary infections NTS pulmonary infections usually present as lobar pneumonia, and complications include lung abscess, empyema, and bronchopleural fistula formation.

Figure 8 shows Stepladder Fever in Enteric Fever. Figure 9 shows Rose Spots in Enteric Fever. Urinary and genital tract infections. Urinary tract infections caused by NTS present as either cystitis or pyelonephritis. Like other focal infections, both genital and urinary tract infections can be complicated by abscess formation.
Salmonella osteomyelitis most commonly affects the femur, tibia, humerus, or lumbar vertebrae and is most often seen in association with sickle cell disease, hemoglobinopathies, or preexisting bone disease (e.g., fractures). Septic arthritis occurs in the same patient population as osteomyelitis and usually involves the knee, hip, or shoulder joints

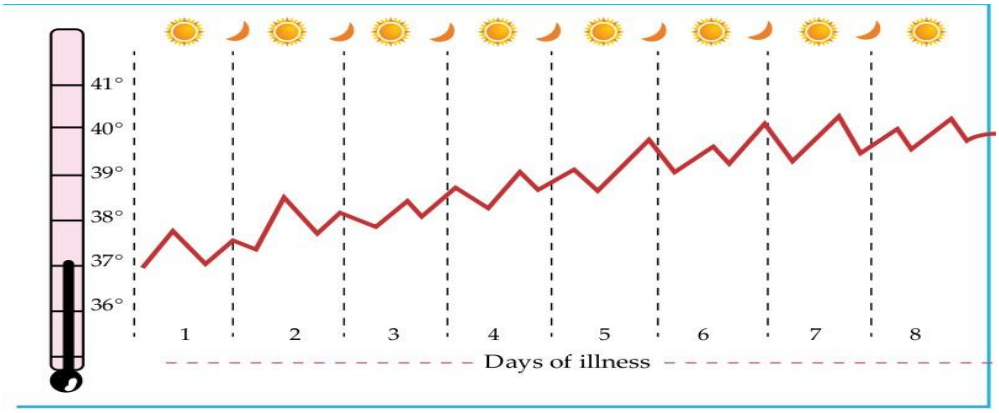

Figure 8: Stepladder Fever in Enteric Fever

In approximately 25% of cases, a macular or maculopapular rash ("rosespots") may be visible around the 7th-10th day of the illness, and lesions may appear in crops of 10-15 on the lower chest and abdomen and last 2-3 days.

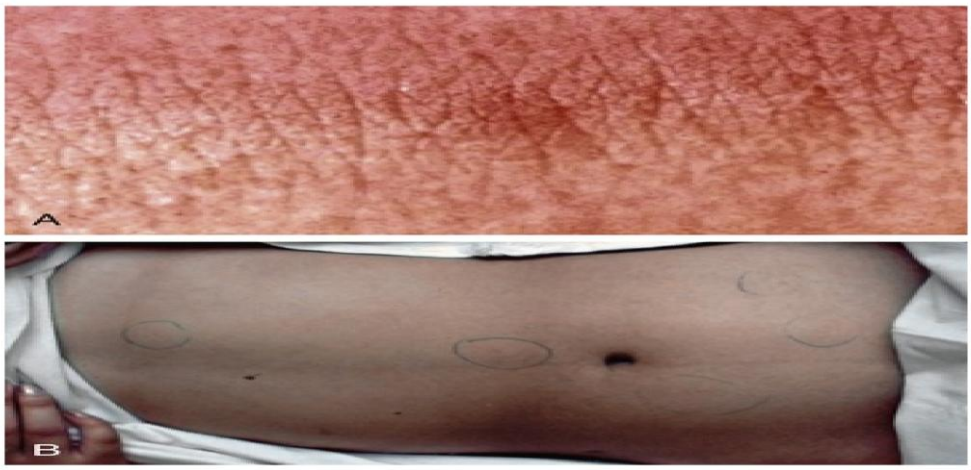

Figure 9: Rose Spots in Enteric Fever

Clinical Manifestation of Non Typhoidal Salmonellosis

Gastroenteritis:

Nausea, vomiting, and diarrhea occur 6–48 hours of ingestion of contaminated food or water. Patients often experience abdominal cramping and fever (38–39°C; 100.5–102.2°F). Diarrheal stools are usually loose, non-bloody, and of moderate volume. However, large-volume watery stools, bloody stools, or symptoms of dysentery may occur. Rarely, NTS causes pseudo appendicitis or an illness that mimics inflammatory bowel disease. Gastroenteritis caused by NTS is usually self-limited. Diarrhea resolves within 3–7 days and fever within 72 h. Stool cultures remain positive for 4–5 weeks of infection and—in rare cases of chronic carriage (<1%)—for >1 year. For acute NTS gastroenteritis, antibiotic treatment usually is not recommended and may prolong fecal carriage.

Bacteremia And Endovascular Infection:

Up to 8% of patients with NTS gastroenteritis develop bacteremia; of these, 5–10% develop localized infections. Bacteremia and metastatic infection are most common with Salmonella Choleraesuis and Salmonella Dublin and among infants, the elderly, and immunocompromised patients, especially those with HIV infection. NTS endovascular infection should be suspected in high-grade or persistent bacteremia, especially with preexisting valvular heart disease,

atherosclerotic vascular disease, prosthetic valves, or aortic aneurysm. Arteritis should be suspected in elderly patients with prolonged fever and back, chest, or abdominal pain developing in an episode of gastroenteritis. Endocarditis and arteritis.

Localised Infection:

INTRAABDOMINAL INFECTION: Intraabdominal infections due to NTS are rare and usually manifest as hepatic or splenic abscesses or as cholecystitis. Risk factors include hepatobiliary anatomic abnormalities (e.g., gallstones), abdominal malignancy, and sickle cell disease (especially with splenic abscesses).

CNS Infections:

Meningitis most commonly develops in infants 1–4 months of age and in adults with HIV infection. It results in severe sequelae (including seizures, hydrocephalus, brain infarction, and mental retardation), with death in up to 60% of cases.

Pulmonary Infections:

NTS pulmonary infections usually present as lobar pneumonia, and complications include lung abscess, empyema, and bronchopleural fistula formation. The majority of cases occur in patients with lung cancer, structural lung disease, sickle cell disease, or glucocorticoid use.

Urinary Tract Infection:

Urinary tract infections caused by NTS present as either cystitis or pyelonephritis. Risk factors include malignancy, urolithiasis, structural abnormalities, HIV infection, and renal transplantation. NTS genital infections are rare and include ovarian and testicular abscesses, prostatitis, and epididymitis. Like other focal infections, both genital and urinary tract infections can be complicated by abscess formation. Figure 10 shows Salmonella Osteomyelitis.

Bone, Joint, Soft Tissue Infections:

Salmonella osteomyelitis most commonly affects the femur, tibia, humerus, or lumbar vertebrae and is most often seen in association with sickle cell disease, hemoglobinopathies, or preexisting bone disease (e.g., fractures). Prolonged antibiotic treatment is recommended to decrease the risk of relapse and chronic osteomyelitis. Septic arthritis occurs in the same patient population as osteomyelitis and usually involves the knee, hip, or shoulder joints. Reactive arthritis can follow NTS gastroenteritis and is seen most frequently in persons with the HLA-B27 histocompatibility antigen.

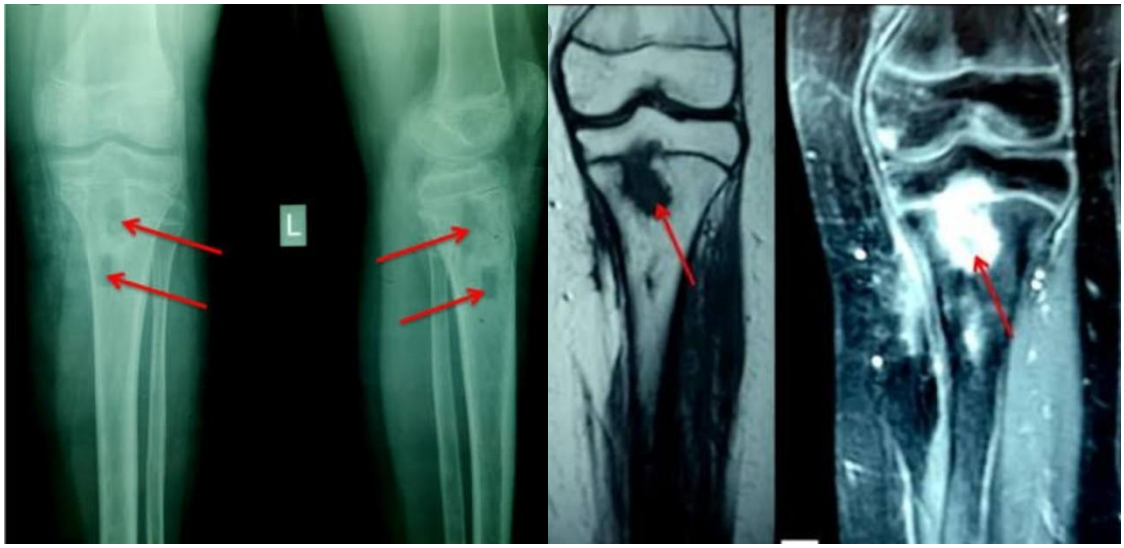

Figure 10: Salmonella Osteomyelitis

COMPLICATIONS

1) Although altered liver function is found in many patients with enteric fever, clinically significant hepatitis, jaundice, And cholecystitis is relatively rare and may be associated with higher rates of adverse outcome.

Table 3 shows Focal Infection in Non Typhoidal Salmonellosis, Table 4 shows Complications of Enteric Fever, Figure 11shows Perforation of Colon, Figure 12 shows Typhoid Ulcer, Figure 13 shows Typhoid Myocarditis.

Brain
- Meningitis
- Brain abscess and empyema

Osteoarticular
- Arthritis
- Osteomyelitis
- Pyomyositis and psoas abscess
- Prosthetic osteoarthritis
- Subcutaneous abscess

Cardiovascular
- Endocarditis
- Pericarditis
- Mycotic aneurysm
- Myocardial abscess
- Septic thrombophlebitis

Respiratory Tract
- Retropharyngeal and pharyngeal abscess
- Pneumonia and empyema

Other
- Urinary tract infection
- Epididymitis and orchitis
- Reiter syndrome
- Endophthalmitis
- Suppurative lymphadenitis

Table 3: Focal Infection in Non Typhoidal Salmonellosis

Intestinal hemorrhage (<1%) and perforation (0.5–1%) are infrequent among children. Intestinal perforation may be preceded by a marked increase in abdominal pain (usually in the right lower quadrant), tenderness, vomiting, and features of peritonitis. Intestinal perforation and peritonitis maybe accompanied by a sudden rise in pulse rate, hypotension, marked abdominal tenderness and guarding, and subsequent abdominal rigidity.

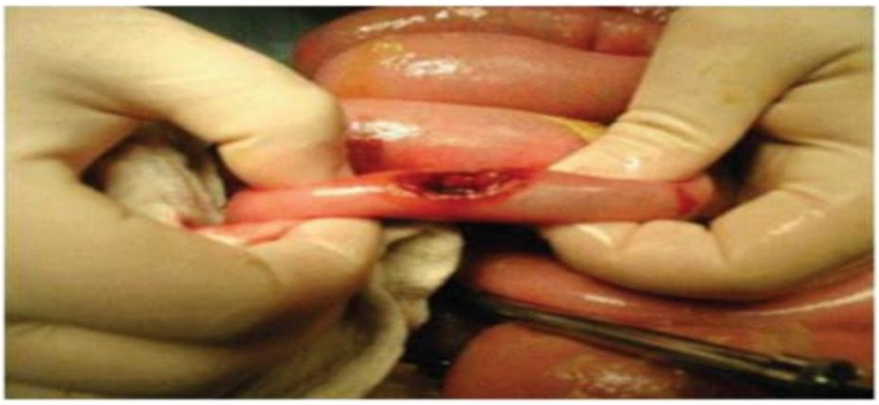

Figure 11: Perforation Of Colon

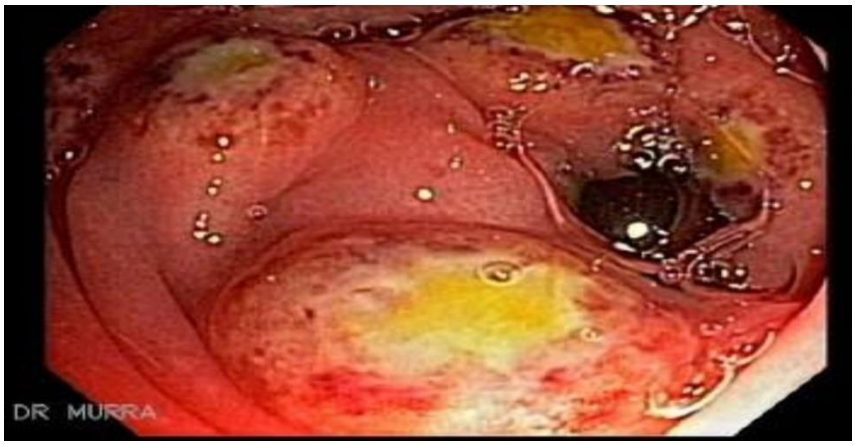

Figure 12: Typhoid Ulcer

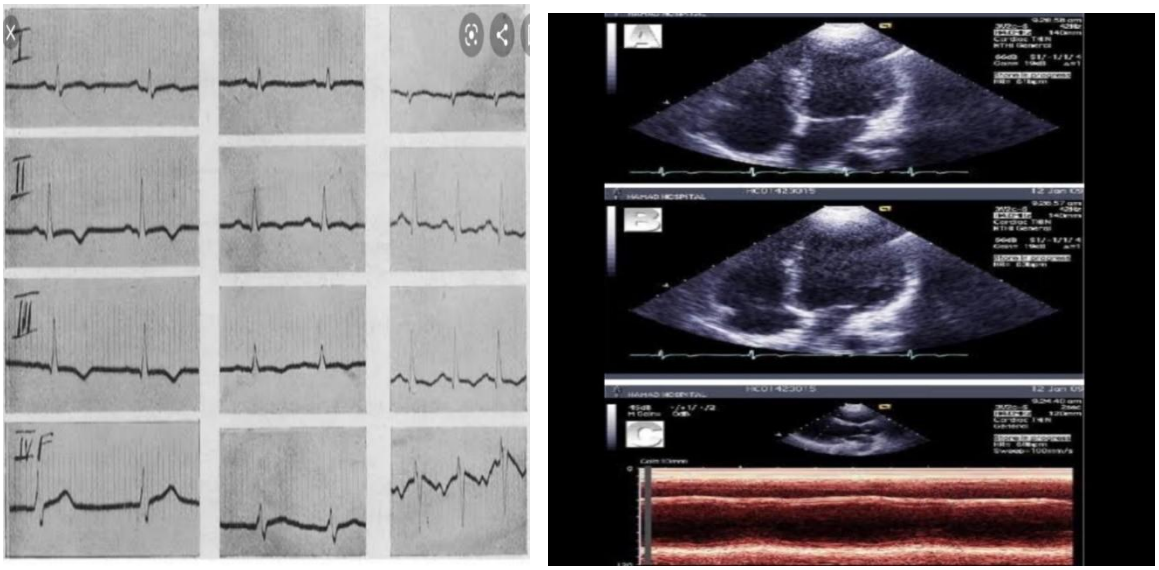

Figure 13: Typhoid Myocarditis

Abdominal
- Gastrointestinal hemorrhage
- Intestinal perforation
- Hepatitis
- Cholecystitis
- Pancreatitis
- Neuropsychiatric
- Encephalopathy
- Delirium
- Psychosis
- Meningitis
- Impairment of coordination

Cardiovascular
- Asymptomatic electrocardiographic changes
- Myocarditis
- Infected prosthetic valve
- Shock
- Respiratory
- Bronchitis
- Pneumonia

Hematologic
- Anemia
- Disseminated intravascular coagulation

Other
- Focal abscess
- Suppurative lymphadenitis
- Mesenteric lymphadenitis
- Pharyngitis
- Tonsillitis
- Osteomyelitis
- Arthritis
- Parotiditis
- Orchitis
- Pyelonephritis
- Miscarriage
- Relapse
- Chronic carriage

Table 4: Complications of Enteric Fever

Diagnosis of Salmonellosis

1) The mainstay of the diagnosis of typhoid fever is a positive result of culture from the blood or another anatomic site. Results of blood cultures are positive in 40– 60% of the patients seen early in the course of the disease, and serial blood cultures may be required to identify Salmonella bacteremia.

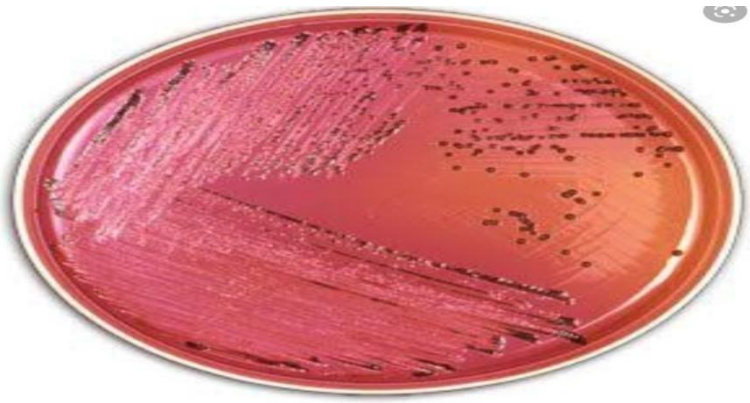

Figure 14: Culture Medium of Salmonella Typhi

2) Stool and urine culture result may become positive after the 1st wk. The stool culture result is also occasionally positive during the incubation period. The sensitivity of blood cultures in diagnosing typhoid fever in many parts of the developing world is limited. Widespread liberal antibiotic use may render bacteriologic confirmation even more difficult.

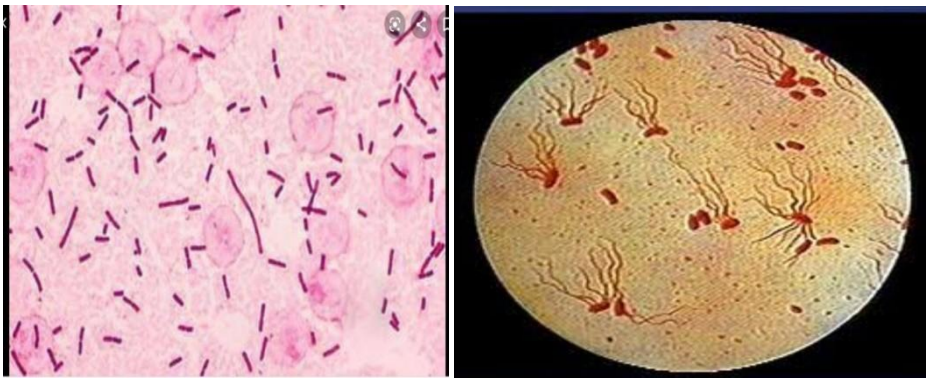

Figure 15: Microscopic Picture of Salmonella

3) Bone marrow cultures may increase the likelihood of bacteriologic confirmation of typhoid and may provide a diagnosis for patients with classic fever of unknown origin caused by Salmonella. Still, collection of bone marrow specimens is difficult and relatively invasive.
4) Leukocytosis is common and may reach 20,000-25,000 cells/µ Thrombocytopenia may be a marker of severe illness and may accompany DIC.
5) Liver function test results may be deranged, but significant hepatic dysfunction is rare.
6) The classic Widal test measures antibodies against O and H antigens of S. Typhi but lacks sensitivity and specificity in endemic areas. Because many false positive and false-negative results occur, Other relatively newer diagnostic tests using monoclonal antibodies have been developed that directly detect S. Typhi– specific antigens in the serum or S. Typhi Vi antigen in the urine. However, few have proved sufficiently robust in large-scale evaluations.

Figure 16: Felix -Widal Kit

7) Polymerase chain reaction (PCR) analysis using H1-d primers has been used to amplify specific genes of S. Typhi in the blood of patients; it is a promising means of making a rapid diagnosis, especially given the low level of bacteremia in enteric fever.

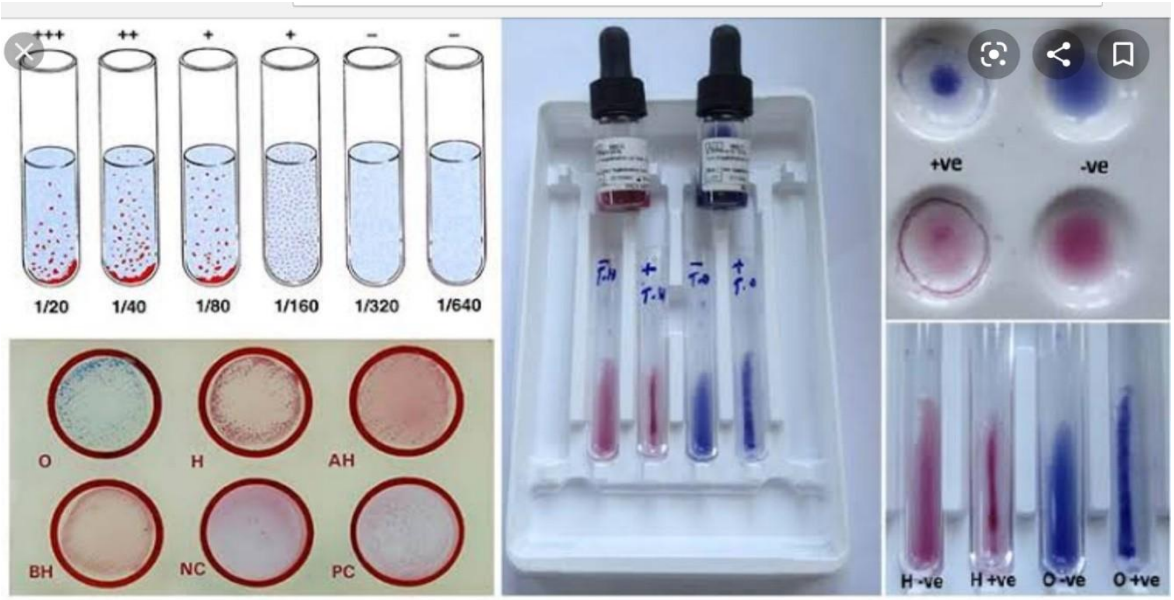

Figure 17: Widal Test

Diagnosis of Non Typhoidal Salmonellosis

- The diagnosis of NTS infection is based on isolation of the organism from freshly passed stool or from blood or another ordinarily sterile body fluid. All salmonellae isolated in clinical laboratories should be sent to local public health departments for serotyping.
- Blood cultures should be done whenever a patient has prolonged or recurrent fever. Endovascular infection should be suspected if there is high-grade bacteremia (>50% of three or more blood cultures positive).
- Echocardiography, CT, and indium-labeled white cell scanning are used to identify localized infection.
- When another localized infection is suspected, joint fluid, abscess drainage, or cerebrospinal fluid should be cultured, as clinically indicated.

Figure 14 shows Culture Medium of Salmonella Typhi, Figure 15 shows Microscopic Picture of Salmonella, Figure 16 Felix -Widal Kit, Figure 17 shows Widal Test.

Newer Diagnosis Tests:

1) **IDL TUBEX test for typhoid fever:** it is rapid test taking approximately 2 minutes. the o9 antigen is used in this test.
2) **Typhidot Test:** This test makes use of 50Kd antigen to detect IGM and IG-G antibodies to s typhi.
3) **IGM dipstick test:** this assay is based on binding of s typhi specific IG-M antibody to LPS antigen. (Figure 18)

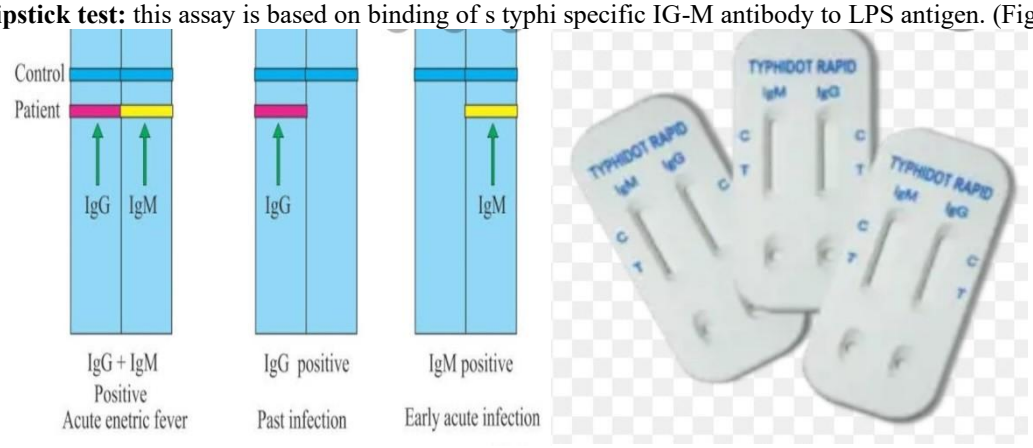

Figure 18: Typhidot Test

Conclusion:

Chronic carriers:

Individuals who excrete S. Typhi for ≥3 months after infection are regarded as chronic carriers. The risk for becoming a carrier is low in most children (<2% for all infected children) and increases with age.

Generally, patients who are not food handlers probably should not be cultured or given special treatment after having a bout of gastroenteritis caused by a NTS strain. Carriers of S. ser. typhi should be decolonized to decrease the risk to close contacts. Figure 19 shows Salmonella and Table 5 shows Risk Factors.

Carriers who have a normal gallbladder can be treated with oral ciprofloxacin or norfloxacin for 4 weeks; these drugs concentrate highly in bile. If oral fluoroquinolone therapy is not tolerated, then high-dose intravenous ampicillin for 4 weeks could be indicated.

Other options are oral ampicillin or amoxicillin combined with probenecid for 6 weeks. Chronic carriers who cannot be decolonized are treated with cholecystectomy if cholelithiasis or cholecystitis is present; these patients should receive ampicillin intravenously for 7 to 10 days before and 30 days after cholecystectomy.

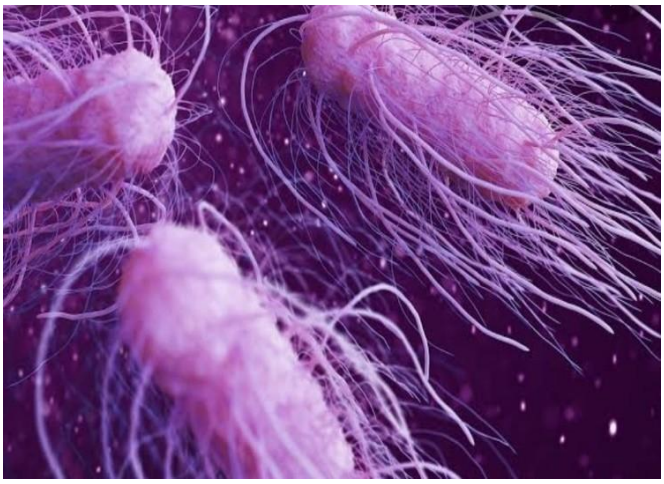

Figure 19: Salmonella

Chronic carriers excrete Salmonella organisms in stools for longer than 1 year after having gastroenteritis-enterocolitis or enteric fever. Approximately 1% to 4% of patients who recover from enteric fever caused by S. ser. Typhi chronically excrete the organism265; fewer than 1% of patients with NTS excrete for a prolonged period. Twenty-five percent of prolonged carriers have no history of typhoid. Nontyphoidal infection is associated with excretion for a mean of 5 weeks, although children younger than 5 years,59 female patients, elderly patients, and patients with biliary tract disease are more likely to become carriers.

The biliary tract is infected in almost all chronic carriers of S. ser. Typhi. As many as 106 organisms per 1 g of feces may be excreted.265 Chronic excretion in such patients serves as the source of infection to their contacts. Chronic carriers represent an epidemiologically important reservoir of S. ser. Typhi; they often are the source of outbreaks of typhoid fever.

Prognosis

The prognosis for a patient with enteric fever depends on the rapidity of diagnosis and institution of appropriate antibiotic therapy. Other factors are the patient/s, age, general state of health, and nutrition; the causative Salmonella serotype; and the appearance of complications.

Patient Group at Risk	Mechanism
Newborn	Achlorhydria, rapid gastric emptying Poorly developed cell-mediated immunity Complement deficiency Immunoglobulin deficiency in premature infants
Sickle-cell anemia	Reticuloendothelial system overload owing to hemolysis Functional asplenia Tissue infarcts Defective opsonization
Neutropenia (congenital or acquired)	Polymorphonuclear neutrophils needed for killing
Chronic granulomatous disease	Defective killing by polymorphonuclear neutrophils
Defects of immune system IL-12/interferon-γ axis	Defective signaling resulting in failure to activate macrophages and recurrent/ persistent infection by nontyphoid *Salmonella*
Acquired immunodeficiency syndrome	Low CD4 Effects of malnutrition on cell-mediated immunity Survival of organisms in macrophages (owing to *Salmonella* genes *PhoP/PhoQ, spvA-D, R*)
Organ transplantation, immunosuppression	Defective cell-mediated immunity
Gastrectomy	Loss of stomach acid barrier
Malaria	Reticuloendothelial overload during hemolysis Abnormal complement levels Abnormal macrophage function
Bartonellosis (verruga peruana)	Reticuloendothelial overload during hemolysis
Schistosomiasis	*Salmonella* sequestered in schistosomes protected from host defenses and antibiotics

Table 5: Risk Factors

Infants and children with underlying malnutrition and patients infected with MDR isolates are at higher risk for adverse outcomes.

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