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A COMPREHENSIVE REVIEW ON *SALMONELLA TYPHI*: PATHOGENESIS, CLINICAL FEATURES AND ANTIBIOTIC RESISTANCE PATTERNS

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Abstract

Salmonellosis is a worldwide disease caused by bacteria of the genus Salmonella. The hospitalization for Salmonella is costly in most countries. An average procedure costs around $7400 USD, according to the data observed in USA, between 1990 and 1999. At present, there are over 2,5oo identified serovar of Salmonella. A reduced number of these serovar, about eighty, are implicated in most animals and human diseases. Most cases of salmonellosis in humans are associated with the consumption of contaminated food products such as beef, pork, poultry meat, eggs, vegetables, juices and other kind of foods. Human infections with Salmonella enterica results in two major groups of diseases: gastroenteritis and typhoid fever. Salmonella infections that involve invasive serotypes are often life threatening, necessitating appropriate and effective antibiotic therapy. The emergence of multi-drug resistant (MDR) Salmonella serotypes have great impact on the efficacy of antibiotic treatment, and an increasing prevalence of MDR strains may lead to a surge in mortality rates of Salmonella infections. Epidemiological studies specify that MDR Salmonella serotypes are more virulent than susceptible strains, as reflected by increased severity and more prolonged disease in patients infected by MDR strains. Zoonotic serotypes, including Salmonella Enteritidis, Salmonella Virchow, Salmonella Typhimurium, and Salmonella Hadar have come up with developing various drug-resistance patterns. Preventive measures have been suggested to eliminate the spread of Salmonella infection. While the maintenance of effective food hygiene and water sanitation remains the cornerstone. Additional measures such as restriction of indiscriminate use of antibiotics in food animals are important. This review provides a comprehensive overview of Salmonella infection, exploring the nomenclature, pathogenesis, clinical manifestations, epidemiology and antibiotic resistance of Salmonella. It will provide a gateway to the researchers for further research extensions in this field. The article is further divided into data that show clear understanding of pathogenesis facts and stages, including implantation of virus, local replication, spread to target organs, and spread through close environmental scenarios. In other words, exposure, adhesion, invasion, infection, and transmission are the ingredients of this article.

Keywords: *Antibiotics, Bacteremia, Gastrointestinal infections, Salmonella, Salmonella paratyphi*

INTRODUCTION

HISTORICAL BACKGROUND

Salmonella are Gram-negative motile bacilli. The genus *Salmonella*, which belongs to the family Enterobacteriaceae, was named after Daniel E. Salmon, an American veterinarian who first isolated *Salmonella* choleraesuis from pigs with hog cholera in 1884 (1). *Salmonella typhimurium* and almost all other serotypes of *Salmonella* which causes human gastroenteritis produce hydrogen sulfide from both thiosulfate and sulfite (2). The germ-nagative bacteria, Salmonella enteric typhi, often cause typhoid fever in humans and have been causing human race defamation. Despite taking treatment of typhoid fever serious, the health stats are still showing this as a major concern that needs immediate attention.

INCUBATION PERIOD

After ingestion of *Salmonella* serovar *typhi* or *Paratyphi* A, an asymptomatic period follows that usually lasts 7 to 14 days (range, 3 to 60 days). Human challenge models, both in the 1950s to 1970s (3). The

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temperature rises gradually during the first week of the illness and reaches a high plateau of 39 to 40°C the following week. There is slight diurnal variation, although the pattern maybe modified by anti-pyretic medications.

SIGNS & SYMPTOMS

Patients can have influenza like symptoms, a dull frontal headache, malaise, anorexia, a dry cough, sore throat, and occasionally epistaxis. Constipation is a recurrent early symptom although many patients will experience diarrhea at some point. Enteric fever can present as a diarrheal illness and occasionally with bloody diarrhea. Most patients have abdominal pain that is diffuse and poorly localized. Nausea is common, and vomiting occurs in more severe cases. (4) Other frequent symptoms include chills, hepatosplenomegaly, rash (rose spots) (5). Serotype analysis is the most common method that used for identification and classification of *Salmonella* (6). The genus *Salmonella* includes 2000 serotypes of clinical standing which are reported to be associated with human infection. Depending on the common clinical symptoms, they have been divided into two groups (Enteric fever and food poisoning) as shown in Table I.

Table I. Clinically important *Salmonella* groups

Enteric fever group		**Food Poisoning group**	
Species	**Key features**	**Species**	**Key features**
S. typhi	Typhoid	*S. typhimurium*	Gastroenteritis, Septicemia
S. paratyphi A, B, C	Paratyphoid	*S. enetriditis*	Gastroenteritis, Septicemia
		S. heidlberg	Gastroenteritis
		S. agona	Gastroenteritis
		S. indiana	Gastroenteritis
		S. newport	Gastroenteritis
		S. anatum	Gastroenteritis, Septicemia

*Data taken from Slideshare.com (60)

SOURCES AND MODES OF TRANSMISSION

Typhoidal *Salmonella* is transmitted predominantly through water or food contaminated with human feces. The risk for infection is high in low- and middle-income countries where typhoidal *Salmonella* is endemic and that have poor sanitation and lack of access to safe food and water (7). Enteric fever in high-income countries is usually acquired abroad and is associated with travel to areas of endemicity (8), although clusters may be associated with food preparers who are chronic carriers of Salmonella serovar typhi (9).

CHRONIC CARRIER STATE

The status of chronic carrier is defined as the shedding of bacteria in stools for more than a year after the acute stage of *Salmonella* infection. Since humans are the only reservoir of typhoid *Salmonella*, carriers of *S. typhi* and *S. paratyphi* are responsible for the spreading of enteric fever in endemic regions, as the common transmission route is the ingestion of water or food contaminated with the feces of chronic carriers (10). About 4% of patients with enteric fever, predominantly infants, elderly people and women, may become chronic carriers (11). Interestingly, up to 10% of convalescing, untreated patients continue to shed *S. typhi* in their stool for up to three months after infection (12). One to four percent of individuals infected with *S.typhi* become asymptomatic, chronic carriers that continue to excrete 106–1010 *S. typhi* bacteria per gram of feces for more than 12 months. The role of such chronic carriers in disease transmission was notoriously demonstrated by the case of Mary Mallon (Typhoid Mary). During her work at different households as a cok in the New York City area in the early 20th century, Mary Mallon infected between 26 and 54 people (13).

Another example of an asymptomatic *S. typhi* carrier was "Mr. N" who worked as a cowman and milker in South–East England and was responsible for a 207 case outbreak of typhoid fever, which peaked in 1899 but continued until 1909 (14). The suspected site of persistence of *S. typhi* in carriers is the gallbladder and gallstones are thought to be an important risk factor for developing chronic carriage (15) as they are conducive for biofilm formation which protects bacteria from antimicrobial compounds and the host

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immune system. However, even though symptoms usually last only for a few days, adults excrete Salmonella on average for 1 month after infection and children under the age of 5 years shed bacteria in their feces for an average of 7 weeks (16, 17). Interestingly, several studies have shown that treatments with antibiotics can prolong shedding of NTS bacteria (18), although these findings are controversial (19).

TRANSMISSION OF INFECTION

The ingestion of contaminated food, these bacteria will colonize the intestines by invading dendritic cells and enterocytes of the intestinal epithelium barrier. *Salmonella* species, which are successful in passing this barrier, are confronted by proximal macrophages and may be phagocytosed, or actively, invade the macrophages, using T3SS-1 and fimbriae, among other bacterial surface adhesions (20). After being internalized by macrophages, *Salmonella* then reside within a membrane bound compartment distinct from the phagosome and lysosome known as the SCV. In this cellular compartment, *Salmonella* can survive and replicate in the absence of host antimicrobial defense mechanisms, thereby evading endosomal fusion with the NADPH oxidase complex (21) From within the SCVs, SPI-2 genes are expressed encoding T3SS-2, which enables Salmonella to translocate a range of effector proteins into the cytoplasm of the host cell including SigD/SopB, SipA, SipC, SodC-1, SopE2, and Spt Pleading to their arrangement of the actin cytoskeleton. T3SS-2 has been described as necessary for systemic virulence in murine models and survival within macrophages (22).

THE INTERACTION OF *SALMONELLA* WITH HOST

Salmonella invades both phagocytic and non-phagocytic cells including mononuclear phagocytic cells present in the lymphoid follicles, liver, and spleen. Epithelial cells and phagocytic cells such as dendritic cells, neutrophils, and macrophages identify specific pathogen-associated molecular pattern (PAMP) motifs and endogenous danger-associated molecular pattern molecules (DAMPs) present in the bacteria. Pattern-recognition receptors (PRRs), which include NOD-like receptors (NLRs) and TLRs, comprise the early components of the immune system that function to detect invading pathogens through PAMPs and DAMPs and signal to recruit and activate phagocytic cells such as neutrophils and macrophages (23, 24). These receptors trigger an immune response and are key to establishing an important network between the innate and adaptive immune systems. Bacterial DNA, flagella, and LPS are examples of PAMPs, which activate TLR4, TLR5, and TLR9 signaling in the host. LPS-induced TLR4 activation is important for triggering the inflammatory responses of the host. It also plays an important role in mounting an inflammatory response to intravenously administered LPS. Mice with mutations in TLR4- encoding genes exhibit an increased susceptibility to *Salmonella* infection irrespective of other Salmonella resistance loci (25). Additionally, LPS plays an important role in the onset of sepsis during systemic infection as observed by its role in inducing inflammation in macrophages (26). The immune system can be divided into two main parts: the innate or non-specific and the adaptive or specific components. The innate immune system is the first host challenge presented to invading pathogens whereas the adaptive immune system provides further protection in addition to an immunological memory, which enables a faster response upon repeat exposure to the same pathogen or antigen. In addition to cellular components such as phagocytic cells, there are humoral elements such as the complement system that make up the innate immune system. Additionally, anatomical features like the mammalian skin layer act as physical barriers to infection. The interplay between the innate and adaptive immune systems, including different types of cells and molecules such as cytokines and antibodies form the totality of the host immunity. Leukocytes of the innate immune system include phagocytic cells, namely dendritic cells, macrophages, and neutrophils, which can engulf foreign antigens, particles, or pathogens. These phagocytic cells are recruited following the release of specific cytokinesignals.

These cells serve an important role in the activation of the adaptive immunity, which usually assumes the presence of lymphocytes (27). Other cells, such as basophils, eosinophil and mast cells are also part of the host innate immune system that contributes to the innate immunity. During the initial stages of an inflammatory response, neutrophils and macrophages are recruited to the site of infection. Neutrophils

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phagocytose the invading pathogens and kill them intracellular. Similarly, macrophages and newly recruited monocytes, which will differentiate into macrophages following signaling or chemical stimulation, also function by phagocytizing and killing the pathogens at the intracellular level. Furthermore, macrophages are capable of killing infected or self-target cells and can also induce further downstream immune responses through the presentation of surface antigens to signal and recruit other cells and cell types (28). A common feature of Salmonellosis is the notable inflammatory response elicited by the host innate immune system. Both the host and pathogen have evolved defense mechanisms that result in a complex cross-talk that culminates with the induction of the host immune response. Salmonella species can cross the epithelial barrier by passive transport facilitated by dendritic cells, which extend pseudopods between local epithelial cells, or by active invasion. Upon reaching the lower intestine, the bacteria will adhere to the mucosal membranes and invade epithelial cells (29). One such site where this occurs is the microfold (M) cells of Payer's patches that are located in the small intestine where the bacteria will translocate across the epithelial barrier to the underlying follicles and mesenteric lymph nodes of the lymphoid tissue (30). During sustained bacteremia, secondary infections can occur due to the dissemination of the bacteria to other organs such as the gallbladder, liver, and spleen. The gallbladder serves as a reservoir in chronic cases of S. Typhi and *S. Typhimurium* infection (31). Infection by invading bacteria can originate from both the blood and/or retrograde bile.

Biofilm formation on gallstones is a reported avenue through which chronic carriage and shedding of Salmonella species can be established. These events set in motion a cycle of infection where in bacteria basolaterally reinvade epithelial cells of the intestinal wall or are shed in feces. In time, the symptoms of salmonellosis will resolve. However, asymptomatic carriage of the bacteria can occur in patients for months or years with the potential to relapse in the future (32).

ENVIRONMENT ADAPTATION

Salmonella adapt to the intracellular environment of phagocytic cells during infection. The transition from extracellular to intravascular environments involves global modulation of bacterial gene expression. The complete transcriptional landscape of intracellular *S. typhimurium* following macrophage infection has been previously reported (33). Similarly, the subsequent ingestion of the bacterium by the host presents an array of challenges to the organism including acid, cold, osmotic, and peroxide stress (34).

CLINICAL MANIFESTATIONS ENTERIC FEVER

Salmonella typhi is the etiological agent of typhoid fever. Since the clinical symptoms of Paratyphoid fever are indistinguishable from typhoid fever, the term "enteric fever" is used collectively for both fevers, and both *S. typhi* and *S. paratyphi* are referred as typhoid Salmonella (35). Humans are the sole reservoir for the two strains of typhoid Salmonella. Diarrhea is more commonly observed in children, whereas patients with immunosuppression are more likely to develop constipation (36). During the illness, enteric fever displays a specific fever pattern with an initial low-grade fever (> 37.5°C to 38.2°C) which slowly develops to high-grade fever (> 38.2°C to 41.5°C) in the second week.

Besides fever, infected patients may also develop myalgia, bradycardia, hepatomegaly (enlarged liver), splenomegaly (enlarged spleen), and rose spots on their chest and abdomen (37). In endemic regions, approximately 15% of the infected patients develop gastrointestinal complications which include pancreatitis, hepatitis and cholecystitis. Haemorrhage is one of the most severe gastrointestinal complications that occur as a result of perforation of Payer's patches, lymphatic nodules located at the terminal ileum, resulting in bloody diarrhea. On top of that, the ability of typhoid Salmonella to survive and persist in the RES results in relapse in approximately 10% of the infected patients.

BACTEREMIA AND OTHER EXTRA INTESTINAL COMPLICATIONS

Salmonella bacteremia is a condition whereby the bacteria enter the blodstream after invading the intestinal barrier. Almost all the serotypes of *Salmonella* can cause bacteremia, while *S. dublin* and *S. cholearaesuis* are two invasive strains that are highly associated with the manifestations of bacteremia (38).

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Similar to enteric fever, high fever is the characteristic symptom of bacteremia, but without the formation of rose spots as observed in patients with enteric fever. In severe conditions, the immune response triggered by bacteremia can lead to septic shock, with a high mortality rate. Other extra intestinal complications include cellulites, urinary tract infections, pneumonia, endocarditis and meningitis (39, 40).

MISCARRIAGE

A 34-year old multi gravid woman presented at 16 weeks of gestation with a Six-hour history of abdominal pain, Similar to uterine contractions, and mild vaginal bleeding or 24 h prior to the onset of abdominal pain she had felt generally unwell, with flu-Like symptoms, a headache, and mild pyrexia. She had no gastrointestinal disturbance. The pregnancy had otherwise been un-eventful that had undergone an ultrasound scan at seven weeks of gestation for reassurance, as she had a history of a previous miscarriage at 11 weeks of gestation. Her obstetric history also included a normal delivery at term and two early termination of pregnancy. On examination she was distressed, requiring opiate analgesia. She was pyrexia, with a temperature of 37.6 °C. She had a tense, tender uterus on palpation, and proceeded to deliver a 16-week male fetus, but failed to deliver the placenta, and required an evacuation of retained products of conception. Postoperatively, her temperature set to 38.2 °C, and antibiotic therapy was started. Twenty-four hours later she was pyrexia with no abdominal pain and minimal vaginal blood loss and was discharged home on oral antibiotics. A full count taken on admission had initially shown a raised white cell count with neutrophilia and a high monocyte count, which returned to normal 24 h post-miscarriage. A high vaginal swab was taken at the time of the evacuation of the placenta. This grew *Salmonella* group C, which was Later further identified as being *Salmonella virchow*. As part of the investigation into the cause of the mid-trimester miscarriage, the fetus and placenta were histologically examined. Histology of the fetus confirmed a male fetus weighing 85 g, equivalent to 16 weeks of gestation. There were no fetal malformations. However, the histologic assessment of the placenta revealed the presence of intervillous thrombi with focal perivillous and villous inflammatory changes. This was a true villitis associated with a hematogenous infection. The placental tissue was then Gramstained, and this revealed numerous colonies of Gram-negative bacilli within the fibrin between the villas. There was no significant inflammation or colonization of the membranes and placental bed, as would be expected if this had been an ascending infection. Two weeks prior to the miscarriage, the woman had been on holiday in Turkey and had eaten an omelet, which she felt was undercooked. Twenty-four hours after this she had symptoms of loose stools and a temperature for one day, but these symptoms were mild and no medical attention had been sought. There were no other dietary or animal exposures to *Salmonella*. Based on this history, it was suggested that she had contracted a *salmonella* infection from eating undercooked eggs while on a holiday but had remained well until the time of the miscarriage. Even the evidence of swabs taken from the posterior fornix growing *Salmonella*, the placenta, histology showing hematogenous infection with a Gram-negative bacillus, and the woman's pyrexia and neutrophilia, it appears that the miscarriage was caused by a *Salmonella* sepsis, with crossing of the infection to the placenta itself and subsequent choric ammonites (41).

SALMONELLA TYPHI AND GALLBLADDER CANCER

Global annual incidence of gallbladder cancer (GC) is 17 million cases with high incidence rates in certain populations. The malignancy is usually associated with gallstone disease, late diagnosis, unsatisfactory treatment, and poor prognosis. The five-year survival rate is approximately 32 percent for lesions confined to the gallbladder mucosa and one-year survival rate of 10 percent for more advanced stages Involving gallstones in 78% – 85% of cases (42). Over 90 percent of gallbladder carcinomas are adeno carcinoma (43).

There are several risk factors for gallbladder cancer. The main associated risk factors include cholelithiasis (especially untreated chronic symptomatic gallstones), obesity, reproductive factors, and environmental exposure to certain chemicals, congenital developmental abnormalities of the pancreatic bile-duct junction and chronic infections of the gallbladder (44). The interplay of genetic susceptibility, lifestyle factors and infections in gallbladder carcinogenesis is still poorly understood (45). However, a link has been

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specifically proposed between chronic bacterial infections of the gallbladder and *Salmonella typhi* the strongest epidemiological evidence of bacterial oncogenic potential, aside of *Helicobacter pylori*, concerns *S. typhi*. Infection with this bacterium of typhoid, can lead to chronic bacterial carriage in the gallbladder (46). Recent epidemiological studies have shown that those who become carriers of *S. typhi* have several times the increased risk of developing carcinoma of the gallbladder compared with people who have had acute typhoid and have cleared the infection. These findings agreed with earlier investigations by (46, 47).

ANTIBIOTIC RESISTANCE

Prior to the mid-1970s, chloramphenicol was the mainstay of treatment of enteric fever (48). Antibiotic resistance of *S. paratyphi A* appears to be an emerging problem. Recent studies, research, and data show that, in the most common type of Salmonella in humans, the Salmonella Enteritidis, the facts of resistance to the fluoroquinolone class of antibiotics were found and observed. The 1996 outbreak of paratyphoid fever in India demonstrated that isolates were sensitive to all antibiotics including chloramphenicol, amoxicillin, cotrimoxazole, gentamicin ciprofloxacin, and ceftriaxone (49, 50). Two years later, there was a report from New Delhi, India, concerning drug-resistant *S.paratyphi A*. The incidence of resistance to ciprofloxacin increased to 24%, and 32% of isolates had decreased susceptibility to ciprofloxacin minimum inhibitory concentrations (MIC"s) >2 mg/mL, the drug of choice for EF in India (51). There were also reports of an increasing incidence of drug-resistant *S paratyphi A* from endemic regions. Reports from a north Indian tertiary care hospital showed increasing multidrug-resistant *S. paratyphi A* strain (52). In an outbreak of paratyphoid fever in 2001 in Nepal, 84% of the isolated strains were reported as resistant to nalidixic acid, which is considered the best predictor of clinical response to fluoroquinolones. One of the largest prospective studies of EF reported a worrisome result: *S paratyphi A* was significantly more likely to be resistant to nalidixic acid (75.25% vs. 50.5%) and ofloxacin (3.6% vs. 0.5%) than *S. typhi* (53). The currently largest and longest retrospective study in Nepal showed that the trend of fluoroquinolone resistance in *S. paratyphi A* is more rapidly increasing compared with that of *S. typhi* (54). Moreover, MICs of other antibacterial were also higher in *S. paratyphi* A. a high-level ciprofloxacin resistant strain has been reported in India (MIC 8 mg/mL) and Japan (MIC 128 mg/ mL) (55, 56). The development of ciprofloxacin resistance can be explained by exposure to this drug at concentrations near the MIC. It is due to a chromosomally mediated trait and different from other drugs where resistance is mainly plasmid mediated. Furthermore, rising antibiotic-resistant strains of *S. paratyphi A* have also been reported in travelers. A study from 10 European countries showed an increasing incidence of multidrug-resistant *S. paratyphi A*. It rose from 9% in 1999 to 25% in 2001, and the incidence of decreased susceptibility to ciprofloxacin also increased from 6% to 18%. Most of these resistant strains have been associated with travelers returning from the Indian subcontinent where resistant strains are endemic (57, 58). The increasing isolation rates of antibiotic-resistant *S paratyphi A* herald serious clinical and public health consequences such as delayed response to treatment and prolonged bacterial shedding time (59).

CONCLUSION

Salmonella infection has become a worrying public health threat globally. The genetic make-up of the *Salmonella* strains allows their adaptation in various environments, including human, animal and non-animal hosts. This enhances the difficulty in eliminating the bacteria. Moreover, the emergence of MDR *Salmonella* strains poses a great challenge in terms of successful treatment of the infections caused by these strains. Several preventive measures have been suggested to prevent the spread of *Salmonella* infection, and the restriction of irrational use of antimicrobials in food animals is by far one of the most effective measures. Further research on the development of vaccines for all *Salmonella* spp. may potentially result in great benefits for affected countries.

Conflict of Interest:

Authors declared no conflict of interest.

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References:

1. Kim AY, Goldberg MB, Rubin RH. Salmonella infections. Gorbach SL, Bartlett JG, Blacklow NR, eds. Lippincott Williams and Wilkins. Infectious Diseases. 3rd ed. 2004;2004:68.
2. Sirui Han, Yingxi Li, Haichun Gao. Generation and Physiology of Hydrogen Sulfide and Reactive Sulfur Species in Bacteria. (2022).
3. Waddington CS, Darton TC, Pollard AJ. The challenge of enteric fever. J Infect. 2014;68:S38–S50.
4. Cunha BA, Gran A, Munoz-Gomez S. Typhoid fever vs. malaria in a febrile returning traveler: typhomalaria revisited: an Oslerian perspective. Travel Med Infect Dis. 2013;11(1):66-9.
5. Stuart BM and Pullen RL. Typhoid: clinical analysis of 360 cases. Arch. Intern. Med. (Chic.). 1946;78:629–661.
6. Old DC, Threlfall EJ. Salmonella. In: Collier L, Balows A, Sussman M (ed.) Topley and Wilson‟s Microbiology and Microbial Infections Vol. 2,9thedn. London: Arnold. 1998; 969-997.
7. Tanveer K, Panezai NK, Qadir MA, Lashari Y, Mariam S, Saboor A, Shah SZ, Yousaf M, Umer M. Detection of Pathogenic Salmonella Spp. from Raw Meat (Beef, Mutton, Chicken) and Seafood Items by Standard Microbiological Methods. Pak-Euro Journal of Medical and Life Sciences. 2021;4(3):171-8.
8. Lynch MF, Blanton EM, Bulens S, Polyak C, Vojdani J, Stevenson J, Medalla F, Barzilay E, Joyce K, Barrett T, Mintz ED. Typhoid fever in the United States,1999- 2006. JAMA. 2009; 302(8):859-65.
9. Olsen SJ, Bleasdale SC, Magnano AR, Landrigan C, Holland BH, Tauxe RV. Outbreaks of typhoid fever in the United States, 1960–99. Epidemiol. Infect. 2003;130(1):13–21.
10. Bhan MK, BahlR, BhatnagarS.2005.Typhoid and paratyphoid fever. Lancet. 366(2):749– 762.
11. Gonzalez-Escobedo G, Marshall JM, Gunn JS. Chronic and acute infection of the gall bladder by Salmonella Typhi: understanding the carrier state. Nat Rev Microbiol. 2011;9:9–14.
12. Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. The New England Journal of Medicine. 2002;347:1770–1782.
13. Marr JS. Typhoid Mary. Lancet. 1999;353:1714.
14. Mortimer PP. MrNthemilker and DrKoch‟s concept of the healthy carrier. Lancet. 1999;353:1354–1356.
15. Levine MM, Black RE, Lanata C. Precise estimation of the numbers of chronic carriers of Salmonella typhi in Santiago, Chile, an endemic area. The Journal of infectious diseases. 1982; 146(6):724-6.
16. Buchwald DS and Blaser MJ. A review of human salmonellosis: II. Duration of excretion following infection with nontyphi Salmonella. Rev. Infect. Dis. 1984;6:345–356.
17. Hohmann EL. Non typhoidal salmonellosis. Clinical Infectious Disease. 2001;15(32):263–269.
18. Aserkoff, B & Bennett, JV. Effect of antibiotictherapy in acute salmonellosis on the fecal excretion of Salmonellae. N. Engl. J. Med. 1969; 281:636–640.
19. Dryden MS, Gabb RJ, and Wright SK. Empirical treatment of severe acute community-acquired gastroenteritis with ciprofloxacin. Clin. Infect. Dis. 1996; 22:1019–1025.
20. Jong HK, Parry CM, van der Poll T, Wiersinga WJ. Host–pathogen interaction in invasive Salmonellosis. PLoS Pathog. 2012; 8(10):e1002933.
21. Gorvel JP, Méresse S. Maturation steps of the Salmonella-containing vacuole. Microbes and infection. 2001; 3(14-15):1299-303.
22. Coombes BK, Coburn BA, Potter AA, Gomis S, Mirakhur K, Li Y. Analysis of the contribution of Salmonella pathogenicity islands 1 and 2 to enteric disease progression using a novel bovine ileal loop model and a murine model of infectious enterocolitis. Infect Immune. 2005;73(11):7161–9.
23. Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on toll-like receptors. Nat Immunol .2010;11(5):373–84.
24. Schroder K, Tschopp J. The inflammasomes. Cell. 2010;140(6):821–32.
25. Wilson RP, Raffatellu M, Chessa D, Winter SE, Tükel C, Bäumler AJ. The Vi-capsule prevents toll-like receptor 4 recognition of *Salmonella*. Cell Microbiol. 2008;10(4):876–90.
26. Brien GC, Wang JH, Redmond HP. Bacterial lipoprotein induces resistance to Gram- negative sepsis in TLR4-deficient mice via enhanced bacterial clearance. J Immunol. 2005;174(2):1020–6.
27. Janeway CA, Travers P, Walport M, Shlomchik MJ. Immunobiology. New York: Garland Science (2001).
28. Delves PJ, Martin SJ, Burton DR, and Roitt IM. Essential Immunology. New Jersey: Wiley- Blackwell. 2011.
29. Rescigno M, Urbano M, Valzasina B, Francolini M, Rotta G, Bonasio R. Dendritic cells express tight junction proteins and penetrate gut epithelial monolayers to sample bacteria. Nat Immunol. 2001;2(4):361–7.
30. Jones BD, Ghori N, Falkow S. *Salmonella* Typhimurium initiates murine infection by penetrating and

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destroying the specialized epithelial M cells of the Payer's patches. J Exp Med. 1994;180(1):15–23.
31. Crawford RW, Rosales-Reyes R, Ramírez-Aguilar Mde L, Chapa-Azuela O, Alpuche- Aranda C, Gunn JS. Gallstones play a significant role in *Salmonella* spp. gall bladder colonization and carriage. Proc Natl Acad Sci USA. 2010;107(9):4353–8.
32. Hurley D, McCusker MP, Fanning S, & Martins M. Salmonella–host interactions–modulation of the host innate immune system. *Frontiers in immunology*.2014;5:481.
33. Kröger C, Dillon SC, Cameron AD, Papenfort K, Sivasankaran SK, Hokamp K, Chao Y, Sittka A, Hébrard M, Händler K, Colgan A. The transcriptional landscape and small RNAs of Salmonella enterica serovar Typhimurium. Proceedings of the National Academy of Sciences. 2012;109(20):E1277-86.
34. Shah J, Desai PT, Chen D, Stevens JR, Weimer BC. Preadaptation to cold stress in Salmonella enterica serovar Typhimurium increases survival during subsequent acid stress exposure. Appl Environ Microbiol. 2013;79(23):7281–9.
35. Connor BA, Schwartz E. Typhoid and paratyphoid fever in travellers. The Lancet Infectious Diseases. 2005;5:623–628.
36. Thielman NM, Guerrant RL. Acute infectious diarrhea. The New England Journal of Medicine. 2004;350:38–47.
37. Kuvandik C, Karaoglan I, Namiduru M, Baydar I. Predictive value of clinical and laboratory findings in the diagnosis of the enteric fever. The New Microbiologica. 2009;32:25– 30.
38. Woods DF, Reen FJ, Gilroy D, Buckley J, Frye JG, Boyd EF. Rapid multiplex PCR and real-time TaqMan PCR assays for detection of Salmonella enterica and the highly virulent serovars Choleraesuis and Paratyphi CJ. Clin Microbiol. 2008;46:4018–4022.
39. Shimoni Z, Pitlik S, Leibovici L, Samra Z, Konigsberger H, Drucker M, Agmon V, Ashkenazi S, Weinberger M. Nontyphoid Salmonella bacteremia: age-related differences in clinical presentation, bacteriology, and outcome. Clinical Infectious Diseases. 1999;28:822–827.
40. Arii J, Tanabe Y, Miyake M, Mukai T, Matsuzaki M, Niinomi N, Watanabe H, Yokota Y, Kohno Y, Noda M. Clinical and pathologic characteristics of nontyphoidal salmonella encephalopathy. Neurology. 2002;58(11):1641–1645
41. Coughlin LB, McGuigan J, Haddad NG, & Mannion P. Salmonella sepsis and miscarriage. Clinical microbiology and infection. 2003;9(8):866-868.
42. Lazcano-Ponce EC, Miquel JF, Munoz N, Herrero R, Ferrecio C, Wistuba II, Alonso de Ruiz P, Aristi UG, Nervi F. Epidemiology and molecular pathology of gallbladder cancer. CA Cancer J Clin. 2001;51: 349-364.
43. Levin B. Gallbladder carcinoma. Ann Oncol. 1999; 10 (Suppl 4): 129-130.10.1023/a: 1008325911628.
44. Wistuba II, Gazdar AF. Gallbladder cancer: lessons from a rare tumour. Nat Rev Cancer.2004;4:695-706.
45. Randi G, Franceschi S, La Vecchia C: Gallbladder Cancer worldwide: Geographical distribution and risk factors. Int J Cancer. 2006;118:159-602.
46. Caygill CP, Hill MJ, Braddick M, Sharp JC. Cancer mortality in chronic typhoid and paratyphoid carriers. Lancet. 1994;343: 83-4.
47. Welton JC, Marr JS, Friedman SM. Association between hepatobiliary cancer and typhoid carrier state. Lancet. 1979;1:791-794.
48. Woodward TE, Smadel JE, Ley HL, Green R, Mankikar DS. Preliminary report on the beneficial effect of chloromycetinin the treatment of typhoid fever. Ann Intern Med. 1948;29:131–134.
49. Kapil A, Sod S, Reddaiah VP. Paratyphoid fever due to Salmonella enterica serotype Paratyphi A. Emerg Infect Dis. 1997; 3:407.
50. Sood S, Kapil A, Dash N. Paratyphoid fever in India: an emerging problem. Emerg Infect Dis.1999;5: 483 – 484.
51. Chandel DS, Chaudhry R, Dhawan B. Drugresistant Salmonella enterica serotype paratyphi A in India. Emerg Infect Dis. 2000;6: 420–421.
52. Mohanty S, Renuka K, Sood S. Antibiogram pattern and seasonality of Salmonella serotypes in a North Indian tertiary care hospital. Epidemiol Infect. 2006;134:961 – 966.
53. Maskey AP, Day JN, Phung QT. Salmonella enterica serovar Paratyphi A and S. enterica serovar Typhi cause indistinguishable clinical syndromes in Kathmandu, Nepal. Clin Infect Dis. 2006;42:1247 – 1253.
54. Maskey AP, Basnyat B, Thwaites GE. Emerging trends in enteric fever in Nepal: 9124 cases confirmed by blood culture 1993-2oo3. Trans R Soc Trop Med Hyg. 2008;102:9 –95.
55. Harish BN, Madhulika U, Parija SC. Isolated highlevel ciprofl oxacin resistance in Salmonella enterica subsp. enterica serotype Paratyphi A . J Med Microbiol. 2004; 53:819.47.
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56. Adachi T, Sagara H, Hirose K, Watanabe H. Fluoroquinolone- resistant Salmonella Paratyphi A . Emerg Infect Dis. 2005;11:172–174.
57. Threlfall EJ, Fisher IS, Berghold C. Trends in antimicrobial drug resistance in Salmonella enterica serotypes Typhi and Paratyphi A isolated in Europe, 1999-2001. Int J Antimicrob Agents. 2003;22:487–491.
58. Fangtham M & Wilde H. Emergence of Salmonella paratyphi A as a major cause of enteric fever: need for early detection, preventive measures, and effective vaccines. Journal of Travel Medicine. 2008;15(5):344-350.
59. FangthamM, & WildeH. Emergence of Salmonella paratyphiA as a major cause of enteric fever: need for early detection, preventive measures, and effective vaccines. Journal of Travel Medicine. 2008;15(5):344-350.
60. Society for Microbiology and Infection care [Internet]. Slideshare. 2014. Available from: https://www.slideshare.net/doctortvrao/enteric-fever-31809820

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