

Review Article

Salmonella: From Food Poisoning to Carcinogenesis

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ABSTRACT

Salmonella has long been an organism of concern especially in the food and health industries. This gram negative, facultative anaerobic and motile bacterium can be classified as Typhoidal Salmonella (TS) and Non Typhoidal Salmonella (NTS) based on their ability or inability to cause typhoid fever respectively. Studies have associated Non Typhoidal Serovars with major foodborne gastroenteritis which has become an increasing menace more so because of the property of antibiotic resistance exhibited by them. The TS have been reported to cause enteric fever in humans. Recent findings have also implicated Salmonella especially the Salmonella typhi with carcinoma of the gall bladder. The present article highlights the involvement of Salmonella in a wide spectrum of diseases worldwide as well as the mechanisms involved in the same. A better understanding of the above would help in generating novel avenues to circumvent the existing problem of transmission and pathogenesis apart from augmenting the present precaution and treatment strategies.

Key Words: Salmonellosis; Typhoidal Salmonella; Non Typhoidal Salmonella; Food poisoning; Cancer

INTRODUCTION

Salmonella, a ubiquitous pathogen is a Gram-negative, flagellated, non-spore forming and facultative anaerobic bacillus. It generally consists of two main species viz.; *S. bongori* and *S. enterica*. The latter is further divided into six subspecies. Most Salmonellae ferment lactose, produce hydrogen sulfide, are oxidase negative as well as catalase positive. Based on the differences in flagellar, somatic and capsular antigens, *S. enterica* subsp. *enterica* can be distinguished to over 2600 serotype.

[1] All the serovars display different host specificity and clinical syndromes. Salmonellosis generally ranges from gastroenteritis including diarrhea and abdominal cramps to septicemia which is usually considered as an intermediate stage of infection, to enteric fever. They have also been associated with focal infections. In some instances, Salmonella exhibit an

asymptomatic carrier stage which has majorly been attributed to contribute towards tumorigenesis. [2] Similar to any gram negative organism, this bacterium possesses lipopolysaccharide in their cell wall which may function as an endotoxin, and is important in determining the virulence of the pathogen. Most of these species cause diseases in humans and other warm blooded animals. Salmonella possesses the ability to cope up with harsh external as well as internal conditions including low pH or high temperature, allowing it to easily survive both outside and inside the host organism. [3] They enter the host body through contaminated food and water taking the fecal-oral route. With the aid of virulence factors, these pathogenic organisms endure gastric acidity and enter the intestinal mucosa where they multiply and induce inflammation. [4] Thereafter, they colonize the mesenteric

lymph nodes and spread throughout the body via systemic circulation. *Salmonella* infects both immunocompetent and immunocompromised hosts with the latter being more predominant. Several disease predisposing factors include extreme age, alteration of intestinal microbiota, diabetes, cancer and many more. Furthermore, kidney stones, gallstones and prosthetic devices serve as a reservoir of *Salmonella*.^[5] The present article discusses the involvement of *Salmonella* in a wide array of diseases including food poisoning and cancer.

TYPHOIDAL AND NON-TYPHOIDAL SALMONELLA (TS AND NTS)

S. enterica subsp I consist of both TS and NTS. Although genetically similar, both display differences in their epidemiology, immune responses and clinical outcomes.^[6] Typhoidal serovars which include Typhi, Paratyphi and Sendai are restricted to humans where they cause life threatening enteric fever. The disease outbreaks generally are observed in areas with poor sanitation and hygiene and account for 27 million cases yearly.^[7] Previous studies have indeed documented the development of typhoid epidemic in developing nations due to consumption of unclean municipality water or through food handlers.^[8] The symptoms of the invasive enteric fever that persist up to twenty one days include fever, chills, abdominal pain, diarrhea or constipation, nausea, anorexia, rose spots, hepatosplenomegaly, headache, and dry cough. Rarely, septic shock and acute respiratory distress are also observed. TS induce minimal inflammation and neutrophil migration post penetrance in the intestinal mucosa.^[9] Nonetheless, they multiply in the lymphoid tissues and result in systemic infection affecting other organs including the bone marrow and gall bladder. A small percentage (1-4%) of infected and especially untreated patients functions as carriers. These carriers excrete the pathogen in stool and occasionally in urine for many years thereby leading to the development of a microbial reserve that aids in re-infection.

^[10] Entry of TS into the human system elicits a cascade of immune response activating both CD4⁺ and CD8⁺ lymphocytes that induce the production of interferons such as IFN- γ in conjunction with cytokines like IL-6, IL-8, IL-10 and TNF- α .^[11] However the immune response is much restrained in TS since it does not lead to any prolonged inflammation or septic shock.

In contrast to Typhoidal serovars, NTS serovars such as Typhimurium and Enteritidis infect a wide range of hosts including warm blooded animals apart from humans. Moreover, the infection is not restricted to developing nations having poor sanitation. Cases of NTS infection have been reported worldwide leading to 93.5 million cases annually.^[12] Infection occurs through intake of contaminated animal food such as poultry, eggs, dairy products as well as vegetables and fruits.^[13-15] The infection can also spread by contact with infected animals and humans.^[5,16,17] The disease usually manifests itself as a self-limiting gastroenteritis with watery diarrhea, vomiting and cramps that stays for a period of not more than ten days with a short incubation period of up to 24 hours. However in several immunocompromised individuals, the pathogen causes an extra-intestinal invasive disease accounting to 5% of the total NTS.^[18] Such *Salmonella* are referred to as invasive Non Typhoidal *Salmonella* (iNTS) which manifest as a secondary infection in individuals who are suffering from Human Immunodeficiency Virus (HIV) infection, malaria or are under-nourished.^[19,20] The gastroenteritis though self-limiting induces acute inflammation accompanied by neutrophil invasion and generation of cytokines including IFN- γ , IL-18, IL-12, IL-15 and TNF- α . Although the disease is generally self-limiting eliciting a major immune response, the symptoms can also persist chronically especially when left untreated. Furthermore, usage of antibiotics has been shown to prolong the carrier state of the disease.^[21] The differences in clinical manifestations of the two types of

Salmonella may be attributed to the ability of the pathogen to induce inflammation and the presence of capsular Vi antigen which is restricted only to *S.typhi*.^[6] Amongst others, the NTS have been shown to be a major cause of foodborne infections.

In order to establish infection, Salmonella is required to fulfill the following conditions: adhesion to host surfaces, production of virulence factors, rapid multiplication and the ability to overcome the host defense mechanisms.^[22] The initial attachment is followed by an irreversible attachment that depends on the adhesive factors of Salmonella and the available host receptors.^[23] Amongst other attachment proteins, fimbriae, which differs between the serotypes, helps the bacteria during adhesion. Some fimbriae may also participate in the formation of biofilms on host surfaces.^[24] The pathogen then utilizes its flagella and other facilitatory proteins such as the T3SS-1 and PagN for attachment and movement.^[25] Adhesion is followed by colonization and multiplication whereby Salmonella resists the host immunological and physical barriers in order to induce inflammation and establish infection.^[26] These bacteria override the hostile conditions imposed by the inherent microflora and also attempt to suppress the innate immune responses.^[27] Apart from animals, this pathogen also infects, colonizes and survives on plants.^[28] Plants therefore serve as an alternative host for Salmonella.

SALMONELLA AND FOOD POISONING

Bacteria have majorly been associated with a variety of foodborne illnesses accounting to around 5 million cases in the United States alone.^[29] Amongst others, Non-Typhoid serovar of *S.enterica* have been shown to be responsible for Salmonella food poisoning with *S. Typhimurium* and *S. Enteritidis* playing a major role according to the reports of the Food and Drug Administration (FDA).^[30] Studies have associated the

above pathogen with acute gastroenteritis resulting from consumption of Salmonella infected unpasteurized eggs, milk, meat and bakery products in different areas of United Kingdom and other countries.^[31,32] In industrialized countries, the increased cases of Salmonella food poisoning may be due to the emergence and advancement of *S. Enteritidis* and *S. Typhimurium* DT104.^[33,34] Recently, Salmonella Alachua has also been implicated in foodborne Salmonellosis.^[35] Only the strains that penetrate the intestinal mucosa induce diarrhea and inflammation. Majority of the Salmonella serovars reside in the intestinal tracts of humans and animals. Contamination of food occurs primarily through horizontal transfer utilizing the fecal-oral route. Lack of hygiene, low educational level, fecal contamination of drinking water, improper food processing in addition to unclean food handling practices enhance cross contamination and disease dissemination. *S. enterica* colonizes the gut for a long duration leading to the development of diarrhea and other flu like symptoms in the affected individuals.^[36] A significant correlation has been observed between fecal shedding and egg shell contamination of Salmonella.^[37] Global trading of animal food products has been on a rise over the past years thereby endangering human health by increasing the chances of spread of infected food between nations. Food producing animals that play an important role in the “farm to fork model” function as big reservoirs of the above pathogen.^[38] The relationship between consumption of contaminated animal food such as poultry or meat and human Salmonellosis has been well documented.^[39,40] *Salmonella*-contaminated food animal carcasses are also a matter of concern because not only do they serve as a source of human food poisoning for but also function as pools of antibiotic-resistant strains.^[41] Furthermore, even vegetables contribute to Salmonellosis. A study from Mexico has associated consumption of raw and under-processed vegetables such as cabbage, broccoli and

potato with acute Salmonellosis. [42] Alarming, NTS has been attributed to infant Salmonellosis that constitutes about 9% of the total cases. [43, 44] The 2004 reports by the Food and Agriculture Organization of the United Nations and the World Health Organization (WHO) implicate *Salmonella enterica* as a risk factor in powdered infant milk. The cases of *Salmonella* infection among infant is approximately 8 times as compared to other age groups in the United States alone. Major outbreaks of Salmonellosis in infants have also been observed in the United Nations and other countries. [45] Consumption of contaminated, unpasteurized and improperly packaged formula milk has been labeled as major culprits for the above. The infection tends to be invasive in the first few months of age decreasing gradually and stabilizing by a year. The *Salmonella* serotypes isolated from infants were mostly Typhimurium, Newport, Javiana, Enteritidis, and Muenchen. The severity and the invasiveness of the disease vary depending upon the kind of serotype and the racial group. Differences in infection sources, host risk factor and rates of breastfeeding may account for this difference. According to the reports of the United States Department of Agriculture's Food Safety and Inspection Service (FSIS) and the FDA, a number of hygienic interventions are required to reduce the risk of *Salmonella* food poisoning. [46] Maintenance of proper food handling and hygienic practices along with adoption of appropriate cooking, pasteurization and packaging procedures is essential for limiting the disease incidence, advancement as well as cross-contamination.

SALMONELLA AND CARCINOGENESIS

Cancer is a disease of abnormal cell proliferation and differentiation that leads to the development of a tumor mass. Microorganisms including a wide variety of bacteria and viruses play a predominant role in tumor formation. [47-49] These oncogenic

pathogens usurp the host cell machineries; interfere with the key signaling pathways and down regulate host immune responses in order to induce carcinogenesis. [50] The association between bacteria and tumors has been well established. [51,52] Bacteria have been shown to cause cancer either by inducing chronic inflammation or by the production of secondary metabolites which in turn activate the tumorigenic pathways. On the other hand they may also cause local infections in tumor tissues under favorable conditions. [53] Reports have associated bacteria with deconjugation of bile acids in the host gut to produce substances that promote cell proliferation. [54] The ability of sustained angiogenesis, immune-suppression, apoptotic resistance, anchorage-independent growth and availability of growth factors along with the capability to survive in hypoxic areas aids in the establishment of tumorigenesis. [55,56] Moreover, bacterial translocation via systemic circulation allows the development of invasive and metastatic tumors. The ability to translocate, multiply and exist in host tissues is dependent on the capacity of these pathogens to invade the tissues in addition to overcoming host defense mechanisms. [57] A strong relationship has been observed between *Salmonella* especially *S. enterica* serovar Typhi and carcinoma of the gall bladder. [58] Gallbladder cancer is a hepato-biliary malignancy associated with poor prognosis in both endemic and non-endemic areas and is more prevalent in women as compared to men. [59,60] The incidence of gall bladder tumors has been on a rise especially in the developing countries of South-East Asia. [38] Factors that lead to gall bladder cancer include obesity, chemical exposure, biliary junction abnormalities and importantly chronic infections of the gallbladder. [61] *S. Typhi* possesses the ability to cause systemic infections in humans which can disseminate to various organs in the body including the gallbladder. In approximately 3-5% of typhoid fever instances, the pathogen persists asymptotically in these

organs constituting a chronic carrier state which has been documented to be the leading cause of S.Typhi induced tumorigenesis. [62] Upon reaching the gallbladder, Salmonella mediates epithelial destruction which promotes infiltration of neutrophils. [63] During the gallbladder stay, the S. Typhi enzymes metabolize primary and secondary bile acids to produce toxic metabolites in increased amounts that induce inflammation mediated pre-malignant transformation. [52] The pre-malignant state is associated with histological changes including hyperplasia, metaplasia as well as dysplasia which in turn induce tumor formation. [64] The survival of Salmonella is facilitated by the development of biofilms on cholesterol gallstones by capsular antigens, the gall bladder environment as well as the selective pressure exerted by mutagenic effects of bile salts. [65, 66] This carrier state therefore requires the presence of both cholesterol gallstones and S. Typhi infection. A careful balance between oncogene activation and the function of tumor suppressor genes is required to maintain the non-tumorigenic state in normal cells. In Salmonella induced neoplasms, an upregulation of proto-oncogene c-myc along with downregulation of tumor suppressor gene p53 has been observed thereby helping in rapid tumor development. [67] Till date, most of the therapeutic strategies available to treat neoplasms are non-specific in nature and hence cause additional havoc by destroying even the normal and healthy cells. Targeted gene therapy, imaging, anti-angiogenic therapies, novel pharmaceuticals and antibody mediated therapy along with the existing drug and radiation therapies may help in resolving the above issues.

EXISTING CHALLENGES OF TREATMENT

Salmonella infection is normally diagnosed by culturing stool samples on selective media such as MacConkey agar, Hektoen agar and selenite with brilliant green. Other techniques such as Polymerase

Chain Reaction (PCR), sequence typing, serotyping and blood tests for detection of lipopolysaccharide O antigen (Widal test) are also employed although the latter is not recommended now-a days due to its non-specific nature. [68] Once detected, a variety of antibiotics are generally employed to curb this menace. However, this pathogen especially S. Typhimurium DT104 has acquired the ability of antibiotic resistance which has been observed with drugs like ampicillin, trimethoprim-sulfamethoxazole, chloramphenicol, tetracycline, streptomycin, cefotaxime and fluoroquinolone. [69] Other resistant strains include Enteritidis, Newport, Heidelberg, Dublin, Weltevreden, Agona, Anatum, Rissen, Typhi, Paratyphi B, and I4. [70] The emergence of the above is largely attributed to prolonged and improper antibiotic usage. Drug resistant strains are mostly found in food animals from where they gain entry into the human body. [71,72] Hence, awareness among food handlers and the population at large is a prerequisite to disease prevention. These Multi Drug Resistance (MDR) strains have been associated with increased virulence and mortality thereby limiting the therapeutic approaches. [73] Majority of the treatment approaches are dependent on the site of infection as well as the severity of the disease. The self-limiting gastroenteritis in healthy individuals can usually be managed with electrolytes and does not require antibiotics. However, systemic and severe infections in immunocompromised patients definitely demand a proper drug regime. Therefore, a careful usage of the available antibiotics, combination therapy and development of new drugs in addition to appropriate hygienic practices is essential for effective treatment.

CONCLUSION

Food poisoning is a major public health concern. Salmonellosis in humans usually takes the form of a self-limiting food poisoning (gastroenteritis), but occasionally manifests as a serious systemic infection (enteric fever) which requires

prompt antibiotic treatment. The incidence of the above is most commonly observed in infants, the aged and immunocompromised individuals. The severity of the pathogen is exemplified by its further association with carcinoma of the gallbladder. In addition, Salmonellosis causes substantial losses of livestock. The intensity of the infection and whether it remains localized in the intestine or disseminates to the bloodstream may depend both on the immunological strength of the patient as well as the virulence of the Salmonella isolate. Since this bacterium has developed mechanisms to combat the influences of many anti-Salmonella drugs, a thorough study is required to overcome the existing issues. A deeper understanding of the involvement of Salmonella in the above diseases will help in generating awareness as well as a better understanding which may henceforth be useful in limiting the spread of these diseases in addition to improvising the current diagnostic and treatment approaches.

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