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SALMONELLA TYPHI AS A PATHOGENIC ORGANISM

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Abstract

Salmonella typhi is flagellated, rod shaped, gram negative, motile, aerobic to facultative anaerobic bacteria which have the size of 0.7-1.5 by 2.0-5.0 µm. The term was derived from the Greek word "typhus" which meant "smoky". Salmonella typhi is responsible for typhoid fever and has been a burden on developing nations for generations. Typhoid fever is more common in children and young adults and is associated with low-income areas in which poor sanitation is prevalent. In 2000, typhoid fever was estimated to cause 21.7 million illnesses and 216,000 deaths globally, and the International Vaccine Institute estimated that there were 11.9 million cases of typhoid fever and 129,000 deaths in low to middle-income countries in 2010. Salmonella typhi is usually contracted by ingestion of contaminated food and water. An infectious dose of Salmonella typhi in healthy individuals ranges between 1000 and 1 million organisms but can be related to the host's defense mechanisms. Salmonella typhi serotype typhi enter the sub mucosal region of the small bowel by either direct penetration into the epithelial tissue mediated by the cystic fibrosis transmembrane conductance regulator (CFTR) or via the M-cell, a specialized lymphoid epithelial cell. Once within the submucosa, the bacterium causes hypertrophy of the Peyer's patches. Classically, Salmonella typhi can be cultured from the bone marrow even after anti-microbial therapy has been initiated. Patients will typically present after a 7 to 14-day asymptomatic period after initial inoculation with Salmonella typhi.

Keywords: *Facultative anaerobe, Salmonella–macrophage, S. paratyphi, S. typhi, Typhoid*

INTRODUCTION

Salmonella typhi is flagellated, rod shaped, gram negative, motile, facultative anaerobic bacteria with the size of 0.7-1.5 by 2.0-5.0 µm (1). *Salmonella typhi* is the causative agent of Typhoid fever and gastro-intestinal problems in human which can be spreaded by poor sanitations, half-cooked food vegetables and infected water. Salmonellosis has same effect on animals and humans (2).

The chromosome sequence is 4,809,037 bp in length with a G+C content of 52.09%. The chromosome was sequenced through the method of shotgun sequencing with 97,000 shotguns reads. Since then, *Salmonella typhi* has undergone evolutionary change and has become resistant to antibiotics. *Salmonella typhi* has a complex regulatory system, which mediates its response to the changes in its external environment. Sigma factors, which are global regulators that alter the specificity of RNA polymerase, are examples of such regulation. Some sigma factors direct transcription to produce stress proteins, which increases the chances of the bacteria surviving environmental changes. RNA polymerase is produced in response to starvation and changes in pH and temperature. It regulates the expression of up to 50 other proteins and is also involved in the regulation of virulence plasmids.

In order to survive in the intestinal organs of its hosts where there are low levels of oxygen, *Salmonella typhi* has to be able to learn to use other sources other than oxygen as an electron acceptor. Therefore, Salmonella has adapted to grow under both an aerobic and anaerobic conditions. Salmonella's most common source of electron acceptors is nitrogen. Examples of other electron acceptors are: nitrate, nitrite, fumigate, and dimethly sulphoxide. Global and specific regulatory systems of anaerobic gene expression, like the ones mentioned above, are implemented to make sure that the most energetically favorable metabolic process is used. Evidence shows that the availability of oxygen is an environmental signal that controls Salmonella's virulence.

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Low incidence of typhoid fever is found in Africa, North America, Latin America and Caribbean Europe as well as the remainder of the world. The Preschoolers and young people are more infected and elevated cases of the illness are reported in the South region of Central Asia & South East region**(3)**. Investigation has evaluated the occurrence of typhoid in different countries like India, Indonesia, China, Vietnam& Pakistan (4). Typhoid has been reported in China: 15.3 cases per 100,000 people/yr. while in 2-15 year old have been reported 451.7 cases per 100,000 people/yr in Pakistan(5). The recurrence of typhoid among kids of Pakistan is reported 573.2, in India 430.1 and in Indonesia 148.7/100,000 individuals/year (6). The degree extensively more prominent in the regions of South-Asia (Pakistan and India) than in countries (Indonesia, China and Viet Nam), North East region of Asia and region of South East Asia. In Pakistan, in Karachi it has been reported about of 170/100,000 individuals while a study based on serology suggested 710/lac cases of typhoid (7). In Pakistan, because of certain aspects like unsafe drinking water, conditions of unhygienic packing, absence of education, the fever of typhoid is prevalent. This endemic malady sometime leads to huge mortality because of lack of treatment and further advancing of the disease (8). In high hazard territories, to control fever of typhoid the enhancement of cleanliness, plan of water supply and mass vaccination are suggested. To control this problem fast and demonstrative research center strategies are essential. Blood culture, PCR, ELISA including serological analysis is important for the diagnosis of this disease (9).

The biochemical properties of *Salmonella typhi* show that almost all *Salmonella typhi* do not produce indole hydrolyze urea and de-aminate pheylalanine or tryptophan. Most of the *Salmonella* serovars consume variety of carbohydrates with the production of acid and reported to be negative for Voges-Proskauer (VP) reaction (10).

This disease is more distinctive in youngsters with respect to overall public and about 33% and even more event occur in youngsters less than 10 years. South regions of Central Asia & South East regions are extra prone to typhoid fever.

With the current spread of Salmonella, researchers are looking for easier ways to detect typhoid fever in order to better treat patients. Another project has to do with dipstick assay which detects antibodies and analyzes the effect of typhoid fever in patients. It found specific IgM antibodies on patients in 43.5%, 92.9%, and 100% for samples collected 4-6 days, 6-9 days, and greater than 9 days after the onset of fever, respectively, the number of antibodies increasing during the length of the duration. Testing of serum samples from culture negative patients with a clinical diagnosis of typhoid fever resulted in staining of the dipstick in 4.3% of the samples collected on the day of admission and in 76.6% one week later. This shows the late development of antibodies in the blood for a large number of patients. The advantages of the dipstick assay are that the result can be obtained on the same day allowing a prompt treatment. No special laboratory equipment is really needed to perform the assay and one would only need a small amount of serum. What makes it even better is that the simplicity of the assay would allow it to be used in places that lack laboratory facilities, such as third world countries that lack modern facilities and where disease is running high.

Salmonella typhi is an important intracellular pathogen. Among more than 2,300 closely-related *Salmonella* serovars bacteria recognized, *S. typhi* is the only one that is pathogenic exclusively for humans,which causes typhoid or enteric fever. *S. typhi* evades the immune system and is transported, via the liver and spleen, to the gall bladder and bone marrow, in which the bacteria can persist. Thus, significant numbers of people infected with typhoid including those asymptomatically infected with *S. typhi* become chronic carriers of the pathogen and reservoirs of a disease that poses a considerable threat to public health. From the perspective of *S. typhi*, however, this "stealth" strategy is essential to its survival. The pathogen has been around for many years and many studies have been done in an effort to combat it. Molecular and biologic features of *S. typhi* and host factors and immune responses involved in *Salmonella* invasion have been extensively studies.

Various analytical (genotype and phenotype) tools commonly are used for characterization of *Salmonella typhi* strains. The presence of Vi antigen, the secretion, invasion and the formation of Lipopolysaccharide are the third most important factors associated with the organism's virulence.

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Implementation of proper food-handling practices and provision of safe water supplies are keys for the development of an effective prevention program.

The genome of *S. typhi* is approximately 5 million base pairs long and codes for some 4,000 genes of which more than 200 are functionally inactive. This is in line with other genomes of enteric bacteria sequenced so far which feature a single chromosome with 4.3-5.0 Mb in length (7-10).

SYMPTOMS OF TYPHOID FEVER

Loss of appetite, joint pain, headache, fever (103°F or fever 104°F) constipation, sore throat is basic symptoms of typhoid fever. When fever increases, patient become hyperthermia and restless due to high temperature. If fever sustains its intensity than heart beat become slow and exhaustion is observed. After 2-5 days and in second week, often it is observed that 10% patient become victim of pink spots on abdomen and chest. Almost 3-5% patient are observed with perforation problem, intestinal bleeding and pneumonia. Liver and gallbladder may become infected. When typhoid fever prolongs it can lead to bones infection, occluded heart valves, the genitourinary tract, meninges and kidneys problem (11).

DIAGNOSIS AND BIOCHEMICAL CHARACTERISTICS

Salmonella typhi cannot produce de-aminate phenylalanine or tryptophan, indol and hydrolyze urea. Most of the *salmonella typhi* ferment carbohydrates with acid production and nitrate is reduced to nitrite by them and accounted to be negative for Voges-Proskauer (VP) reaction.

Genotypic methods and molecular biological tools are used for subtyping of *Salmonella*. They can be studied by extra chromosomal and chromosomal typing methods. Extra chromosomal typing includes plasmid profiling and plasmid RFLP (Restriction Fragment Length Polymorphism. Very famous method of food borne *S. typhi* detection is nucleic acid (DNA or RNA) based method. In addition, ELISA and Widal are also very common tests in practice for the diagnosis (12).

TREATMENT OF TYPHOID FEVER

Almost from 50 years, typhoid fever has been treated with antibiotics. The antibiotic chloramphenicol was used in 1948 for the treatment of typhoid. The best choice of treatment is fluoroquinolones (Ofloxacin & Ciprofloxacin) with broad spectrum cephalosporins (Cefixime & Ceftriaxone) and now a day's azithromycin is also used as an alternative treatment for typhoid fever. Clinicians have limited therapeutic options for enteric as a result of increasing antimicrobial resistance, and therefore typhoid vaccination is recommended as a preventive measure. As a part of the surveillance for enteric fever in Asia Project (SEAP), we investigated the extent measured the burden of antimicrobial resistance (AMR) among confirmed enteric fever cases in Bangladesh, Nepal, and Pakistan.

Salmonella typhi causes one of the most common blood stream infections, the typhoid fever. However, it can cause pyogenic infections involving different sites as well. Extensively drug resistant (XDR) strains of Salmonella typhi are resistant to all first line anti-typhoidal drugs (chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole) as well as ciprofloxacin and ceftriaxone. XDR-strains were first reported from Pakistan in 2016, and since then the strains have been spreading. These XDR Salmonella cases not only pose a therapeutic challenge but also predispose to complications as a result of prolonged illness and delayed treatment. Here, we report a case of superficial thrombophlebitis at intravenous cannula site in a 49-year male, who was being treated for XDR-typhoid fever.

PREVENTION

To prevent salmonella infection:

- Avoid eating raw or barely cooked eggs beef, pork, or poultry products.
- Refrigerate food properly
- Wash hands well with soap and warm water before and after handling food
- Clean kitchen surfaces before preparing food on them
- Don't mix cooked food with raw food or use the same utensils to prepare them

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- Cook meat to its correct minimum temperature
- Wash hands with soap and water after touching animals, their toys, and their bedding
- Wash raw fruits and veggies well and peel them if possible.

RISK FACTORS

Children, especially those under 5, are more likely than adults to get sick from salmonella. Older adults and people with weak immune systems are also more likely to be infected. Other risk factors include: Salmonella is more common in places with poor sanitation. Inflammatory bowel disease can damage the lining of your intestines, making it easier for salmonella to take hold.

ONTAKING CERTAIN DRUGS

Cancer drugs or steroids can weaken the immune system. Antacids lower much acid is in the stomach, which makes it easier for salmonella to survive there. Antibiotics can kill "good" bacteria in the body and make an infection harder to fight.

CONCLUSION

Salmonella typhi and *Paratyphi A* are host-restricted pathogens whose reservoir is humans. Unlike other *Salmonella* serovars that primarily cause local intestinal inflammation and diarrhea, *Salmonella typhi* and *Paratyphi* A, B, and C characteristically invade from the gastrointestinal tract into the bloodstream, survive and reproduce within macrophages, and in 1–4% of cases result in chronic carriage. The typhoidal *Salmonellas* are estimated to cause over 200 000 deaths per year. Typhoid fever is most common in densely populated urban communities where drinking water is contaminated with human feces. Increasing antimicrobial resistance risks increasing case fatality ratios and disease burden in the coming years. Low-cost vaccines and improved drinking water quality and food safety can reduce the burden of *typhoid* fever.

Salmonella typhi is a host specific pathogen affecting humans. Its virulence is aided by SPIs. SPI-1 is required for invasion of the bacteria to epithelial cells while SPI-2 is essential for survival and replication in the host cells. Salmonella has been around for many years and a lot of studies have been done in an effort to combat its infections. However, formidable challenges have been met in the process. Some of these challenges are multi-drug resistance of the bacteria and failure of vaccines to induce a lasting protective effect. Other challenges are just sheer lack of affordability of the means of treatment and preventive measures in the developing world.

Studies have shown that Vi antigen may be important in the survival of the bacterium within macrophages though this may not be in cellular invasion of the macrophage or the intestinal wall Unlike most other serovars, Salmonella typhi expresses the Vi polysaccharide capsule, an important virulent factor. However, its presence only increases the infectivity of Salmonella typhi and the severity of the disease but is not essential for infection since it has been shown that Vi negative mutants are able to cause a typhoid-like illness in human volunteers. Supporting this view is the fact that there have been reports of outbreaks of typhoid fever caused by Vi-negative *Salmonella typhi.*

Investigation has evaluated the occurrence of typhoid in different countries like India, Indonesia, China, Veitnam & Pakistan (4). Typhoid has been reported in China: 15.3 cases per 100,000 people/yr while in 2-15 year old have been reported 451.7 cases per 100,000 people/yr in Pakistan. The recurrence of typhoid among kids of Pakistan is reported 573.2, in India 430.1 and in Indonesia 148.7/100,000 individuals/year**(13)**. The degree extensively more prominent in the regions of South-Asia (Pakistan and India) than in countries (Indonesia, China and Viet Nam), North East region of Asia and region of South East Asia. In Pakistan, in Karachi it has been reported about of 170/100,000 individuals while a study based on serology suggested 710/lac cases of typhoid.

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Cholera is due to *Salmonella typhi and is* discovered by Daniel Elmer Salmon along with Theobald Smith who is American veterinary pathologist. After their investigation the organism was named *Salmonella*. Typhoid fever was characterized based on clinical signs and symptoms.

The general typhoid disease has been reported in young people due to absence of adequate clean and drinking water in peri-urban territories of Karachi (9).

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