



## A Review of Prognostic Models on Diagnosis and Therapeutic Strategies of Typhoid Fever

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ARTICLE INFO	ABSTRACT
<p><b>Article type:</b> Review Article</p> <hr/> <p><b>Article history:</b> Received: 10 Feb 2018 Revised: 16 Mar 2018 Accepted: 21 Mar 2018 Published: 15 May 2018</p> <hr/> <p><b>Keywords:</b> Gastrointestinal disorders, Nanoparticles, Salmonella, Typhoid.</p>	<p><b>Background:</b> Typhoid infection is an insidious onset type of fever and some other gastrointestinal disorders which may have a fatal outcome. The causative agents are <i>Salmonella typhi</i>, <i>Salmonella paratyphi A</i>, and <i>Salmonella paratyphi B</i>. Clinical features include, gradual rising fever, white coated tongue, and severe degree of malaise, drowsiness and pain in abdomen, perforation with bleeding in the intestines, shock and death. It involves mostly male victims of school going age. It is water born disease which spreads due to poor sanitation mostly in congested populated areas. According to World Health Organization sixteen to seventeen million typhoid fever cases were reported annually, out of which 600,000 died. Typhoid fever is 10 to 29 times more in subcontinent than China. Infection only occurs when food is handled by infected person. Isolated strains of <i>Salmonella</i> spp from suspected cases show resistance against routine antibiotics and the modern antibiotics are much more expensive and unaffordable.</p> <p><b>Conclusion:</b> Need of this review is especially for Silver Nanoparticles (AgNPs) manufactured by some types of fungi introduced by recent researchers have an edge to control or treat some sort of infections due to their antibacterial properties. In this study these (AgNPs) in the form of suspension, give positive results against the <i>Salmonella</i> species. It enables us to treat the typhoid infection in a less expensive way.</p>

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## Introduction

*Salmonella* is a food-borne pathogen all over the globe that causes substantial weakness (1, 2). There are two species *Salmonella bongori* and *Salmonella enterica* (*S. enterica*). In the updated classification of the genus *Salmonella*. There are more than 2500 serotypes of *S. enterica*. This genus mainly leads to food-borne salmonellosis, a zoonosis of worldwide economic significance. *Salmonella* lives in the intestinal tracts of vertebrates and follows consequences in environmental contamination (3, 4). In Lahore, the silent carrier is present in different reaction centers, different food spots and grows through workers of food, animals, the infected equipment and bench area (5). Consumption of contaminated water at work place (6, 7). Using water from other than government supply (8). Intake of ice cream and other open eatable items from streets (9). Morbidity of enteric fever is highest in Asia that is ninety-three percent of the world in this continent. As shown in table 1 the incidence of typhoid fever globally Occurrence in Southeast Asia has about 110 cases per 100,000 people, which is 3rd greatest occurrence rate in a continent. In Pakistan children are badly affected (12). In America two to four million typhoid fever cases are reported annually, out of which five hundred died. Only outbreaks are investigated while sporadic cases not. In Asia, Africa and Central America only 1-10% of the actual cases are reported (13, 14). Typhoid fever is 10-29 times more frequent in Pakistan and India than China and Vietnam (15). The historical details of *Salmonella* summarized in table 2.

### Epidemiology in Pakistan

In Lahore, the source of infection was different short inn, food spots and reaction centers. The growth of Typhi were found on equipment and bench area, the people were also found salient carrier for the disease (5). In Pakistan there are seasonal changes of enteric fever. From 06/1999-12/2001 data was taken in 2 quitters in Karachi,

Pakistan, establishing two clinics, each under supervision of one doctor and 5 health workers. Patients having sustained high-grade temperature from 3 or many days were medically sorted out at these clinics. Blood culture and Typhi dot tests were performed. 1/3rd out of 4198 patients have illness of 3 or many days determined in the community were sorted out at these clinics, 341 cases showed the doubtful clinical enteric fever. Also, 49 cases were having positive culture report, and 161 cases were having positive serology. Among these, 10 patients were MDR. Occurrence of positive culture enteric fever was about 170 per one lakh people, on the basis of serology occurrence were 710 per one lakh people.

The Peak occurrence was reported in October, after May and June. High temperature months have increased occurrence of enteric fever than others. Health care attitude based studies will give better study results (10). Typhoid fever mostly affects children below 5 years and young adults and again decrease in middle age. Previous researches showed that all over the world, the enteric fever patients are twenty-one million out of which two lakh death per year (11). In past it was sixteen million with more than six lac deaths (12). The resistant Multidrug- *Salmonella typhi* has become a major public health problem in Pakistan (16). The therapeutic options are severely limited and diseases become a burden on the country. The Typhi (*S. typhi*) and *Salmonella enterica* serovar *Paratyphi A* (*S. paratyphi A*) showed a great resistance to multidrug, between 2009 and 2011 (17).

### Risk factors

Occurrence of typhoid fever in travelers is round about 3 to 30 patients per one lack who travel to rich countries. Now it is clear that travelers who are VFR, like travelers who travel to Indian sub states are commonly infected with typhoid fever and need special focus during travelling. The recently increased occurrence of paratyphoid fever in Asia, not controlled by typhoid vaccines and occurrence of infections due to antimicrobial

(Fluoroquinolone) resistant strains. Typhoid vaccine is required for many travelers who travel to endemic countries, due to nonspecific clinical findings of typhoid fever, it is necessary for travelers who have traveled to endemic countries. Enteric fever is caused by *Salmonella typhi* or *Salmonella paratyphi*, both have only human reservoir and have no environmental reservoir other than human. Typhoid fever caused by intake of fecal infected food or water. Continuously excretions of microbes by symptomless carriers or peoples who have recently recovered from typhoid fever are major source of infection. In endemic countries, typhoid fever occurs due to drinking of infected water, eating food made outside the house, having a close relative infected with typhoid fever, and living in unhygienic homes. A recent research of Indonesia indicate intake of food from street seller and floods are also important cause of paratyphoid fever (18). While enteric fever was caused by risk factors present at home, like presence of people having recently infected with enteric fever, hand washing without soap and eating food from same utensil. Round about twenty-two million new patients of typhoid fever and two lack deaths occur per year (19). Many patients are related to developing countries, where typhoid fever is endemic; most loads are in Indian sub states and in South-East Asia. Regions having greatest occurrence of typhoid fever cases are lesser than one hundred patients out of one lakh peoples annually are from South Central Asia and South East Asia. Ten to one hundred patients of typhoid fever out of one lakh occur annually in rest of the world instead of Australia and New Zealand. In Delhi, India occurrence of typhoid fever is 9.8% patients out of one thousand peoples annually (20). In developed countries, typhoid fever is endemic disease that mostly infects returned travelers. Approximately occurrence of enteric fever in travelers of developing countries is three to thirty patients out of one lakh travelers. Recently it was studied that seventy-four percent cases of enteric fever were studied in US Centers for Disease Control and Prevention from 1994 to 1999 (21). Most of these patients had traveled to Indian sub

states, 17% had traveled to Mexico and Central America, 8% had traveled to Philippines, and 5% had traveled to Haiti. Another research in US between 1985 to 1994, present that occurrence of enteric fever in US peoples who traveled to Indian sub states was about 18 times greater than other areas. In a ten-year study, 41 cases of enteric or paratyphoid fever in Parisian hospital, about 30% patients were from Indian sub states (20). While research cases of enteric fever in US was about 400,000 patients, annually. Typhoid fever patients who travel abroad the US was increased up to 62% from 1975 to 1984 and 72% from 1996 to 1997 (22). Recently, travelers who go to VFR have increased risk as compared to other travelers for many diseases, like typhoid fever (23). In US, these people were born outside the United States and are now the resident of US, and their kids who visit their home countries, these peoples were greater than 40% who travel outside the country while visiting their family or friends. One year study of all observed patients of enteric fever in US revealed that 4% patients were travelers, while tourists VFR was lesser than 40% (23, 24).

#### *Distinguishable epidemics within different hosts*

A study of Epidemics due to considerable strains of MDR *S. typhimurium* DT 104 in different hosts showing examples of collection of strains from animals and humans (25,26,27). Samples were collected from all hosts and processing them with resistant genes. The whole genome sequencing can dissect the phylogenetic arrangement of bacteria and its resistance genes through the duration of epidemic (28). They demonstrate that the microorganism and its genes which represent its resistance were maintained within human and animal kingdom separately with less transmission. As compared to the stable core genome of bacterium shows integrated genomic data which can help to explore the ecology of zoonosis and multiple drug resistance of antibiotics (29, 30, 31). Different serotypes were active in different hosts and they cause infection in one type of host but not in others. This study confirms that the specific

serotypes are active in human being but not active in animals (32, 33). So the transfer of infection from animals to human being was not possible and there spread only focused to the personal cleanliness and utmost possible improved sanitary conditions (34).

#### *Prevalence of waterborne diseases*

Enteritis causing bacteria including *S. typhi* spread through fecal oral route, populated areas, inadequate sanitation, unethical use of antibiotics and contamination of water (35). Greatly increase the prevalence of salmonellosis. The organism was first discovered in 1880, subsequently numerous serotypes were discovered near about 2540 and classified by Kauffman-White scheme. *Salmonella* spp., are a major cause of death, different antigens such as somatic (O), flagellar (H) and capsular (Vi) antigens along with *Salmonella* pathogenicity islands (SPI) (36, 37, 38). On the chromosomes, each SPI determined various cellular activities regarding virulence factors. These virulence factors may also have detected in plasmids. Bacteria may be detected by different methods like Widal test, Typhidot tests and biochemical tests but PCR is the method of choice to confirm the said organism. Primary reservoirs of infection included intestinal tracts of birds and animals, chiefly poultry and swine through fecal oral route (38). Different species of *Salmonella* can survive for a long time in the environment and transmitted by different vectors such as rats, flies, and birds. *Salmonella typhi* and *S. paratyphi* A are not transmitted through animals but they are transmitted by food handlers, poor sanitation, and contamination of water (39).

#### *Causative agent and its detection*

Infection by *Salmonella* is important health issue for the peoples all over the world. Economic impacts are sensitive and important due to cost of laboratory tests and management of typhoid fever. As research on *Salmonella* has achieved more interest for Researcher. The aim of this review is

to classify, and found characteristic, occurrence, epidemic and serological tests for diagnosis of infection in mankind (40). In nineteenth century it was named as *Salmonella* in the respect of Salmon. Additional research leads to identification of other serotypes of *Salmonella* (41). Classification of *Salmonella* on the basis of antigen was first of all done by White and later on by Kauffman which now have greater than twenty-five hundred forty isolates (42). Now use of *Salmonella* group, sub group, isolates etc. create problems for Scientists (43). Nomenclature of *Salmonella* was established in 1973. Other Nomenclature of *Salmonella* was done on the basis of Clinical and Biochemical properties that divide into further subgroup and serotypes (44)

#### *Rapid evaluation of diagnostic test in typhoid*

Laboratory identification of typhoid causing microorganisms requires culture and identification of *S. enterica* serotypes. In areas where this disease is endemic and laboratory capability is not so developing. Recent research in molecular immunology has led to the identification of sensitive and specific markers for enteric fever and technology to manufacture practical and inexpensive kits for their rapid detection. We evaluated three commercial kits for serologic diagnosis of typhoid fever (45). Patients with history of 4 days of fever were selected at two hospitals in Southern Vietnam. Cases included patients infected with serotype *S. typhi*, isolated from blood samples, and controls were patients with other laboratory-confirmed illnesses (46). Serotype *S. typhi* isolates were confirmed and tested for antimicrobial susceptibility at the Pasteur Institute in Ho Chi Minh City. Initially the Widal test was run at the hospitals and in the Pasteur Institute. Sera were shipped frozen to the Centers for Disease Control and Prevention and tested by using Multi-Test Dip-S-Ticks, Typhidot test, and TUBEX to detect IgM & IgG, both IgM and IgG, respectively. Package inserted protocol instructions were followed. They selected 59 patients and 21 controls. The sensitivity and

specificity findings were as follows: 89 and 53% for Multi-Test Dip-S-Ticks, 79 and 89% for Typhidot test, 78 and 89% for TUBEX, and 64 and 76% for Widal tests in hospitals and 61% and 100% for Widal test at the Pasteur Institute. For all assays, the sensitivity was highest in the second week of illness. The Widal test was insensitive and displayed inter operator variability. Two rapid kits, typhidot test and TUBEX, gave clear results. These results greatly help in detection of typhoid fever in the initial stages, which guide the treating physicians for the management of enteric infection to avoid further complications (47).

#### *Salmonella enterotoxin genes (STN)*

*Salmonella* enterotoxin gene (STN) was extracted from *Salmonella* serotypes, *typhimurium*, *Paratyphi* A and B. The pattern from all the four sequences of the serotypes *S. typhimurium*. One of the method for diagnosis of this organism, four pairs of primers peptides was produced to amplify different fragments of this important pathological marker (48-50). The procedures were compared and contrast with serotype *S. typhimurium* in such a way to complete the PCR reaction in one and a half hour. These primers were found to generate specific amplicons with all the serotypes of *Salmonella* tested. The PCR tests were found to be highly specific amplifications. Specific or non-specific, were found when reactions were run using non-*Salmonella* DNA as template. The employment of a nested PCR markedly increased the sensitivity of the assay system in natural water samples. The virulence of the bacteria is due to enterotoxin (STN) which is located in pathogenicity islands and secretion system 111 and 2. The main difference between virulent and mutated strains is the presence of specific proteins (OmpA) in virulent strains.

#### *Pathogenesis*

The intensity of enteric infection depends upon the type of *Salmonella* spp. Involved and the status

of the patient resistance, children and middle aged individual persons are much more exposed to the infection. The organism invades and flourish in the host cells, destroy the epithelium and cause inflammation and ulceration resulting in perforation of gut.

*Salmonella* represents specific characteristic during its invasion of non-phagocytic human host cells (51). Whereby it actually induces its own phagocytosis in order to gain access to the host cell. The remarkable genetics underlying this ingenious strategy is found in *Salmonella* pathogenicity islands (SPIs), gene clusters founded at the chromosomal DNA region and encoding for the structures involved in the invasion process (52). When the bacteria gain enter through mouth via contaminated water or food, they penetrate the epithelial cells of gut lining. SPIs encode for type III secretion systems, specific proteins that allow *Salmonella* to inject its effectors across the gut epithelial cell membrane into the cytoplasm. The bacterial effectors then activate the signal transduction pathway and trigger reconstruction of the actin cytoskeleton of the host cell, resulting in the outward extension or ruffle of the epithelial cell membrane to engulf the bacteria (53).

The capacity of *Salmonella* to survive in the host cell is crucial for pathogenesis, as strains lacking this ability are nonpathogenic, following the engulfment of *Salmonella* into the host cell, the bacterium is enclosed in a membrane called a vacuole, which is composed of the host cell membrane. Normally the presence of the bacterial foreign body would activate the host cell immune response, resulting in the fusion of the lysosomes and the secretion of digesting enzymes to degrade the intracellular bacteria. However, *Salmonella* uses the type III secretion system to inject other effector proteins into the vacuole, causing the alteration of the compartment structure. The changed vacuole blocks the fusion of the lysosomes and this allows the intracellular survival and replication of the bacteria within the host cells. The capability of the bacteria to survive within macrophages allows them to be carried prolonged

infection and disturb the immune system of the host (54).

### *Resistance against antibacterial agents*

#### Emergence of resistance

The *S. enterica* and *S. paratyphi* A, blood isolates, samples were taken from different hospitals of Kolkata, India and sensitivity were tested with various antibiotics. Multi drug resistant strains were tested for variety of antibiotics, the ultimate goal of the study is to facilitate the therapy of MDR cases of enteric infection. It was concluded that *S. typhi* and *S. paratyphi* A, were of the two major strains of causing enteric fever in Kolkata, increasing resistance including (FQ) which was previously the drug of choice, and it was difficult to treat enteric fever. It was decided to formulate the continue studies on different strains of Salmonella there mode of spread and study of MDR and molecular subtypes of strains causing enteric fever in the endemic regions (55).

#### *MinION nanopore technology*

Using MinION Nanopore technology to Study the bacterial antibiotic resistance by pathogenicity islands to observe the sequencing of *Salmonella*. They identify the chromosomal arrangement of repetitive insertion sequences that typically arrange the plasmid genes transfer horizontally. There results show the potential of the MinION device in clinical labs. It is about a USB size memory stick). In this way they explore the process by which the pathogenic bacteria spread as an epidemic by increasing resistance. The scientists show that plasmid R 27 has a strong impact; it replicates at low temperature and act better in stationary stage including regulatory genes pathogenicity islands (56). The results greatly help clinical laboratories to detect bacterial resistance and their clinical role in spread of epidemic. Plasmid mediated antibiotic resistance has a commanding role in helping *S. typhi* increasing prevalence among epidemic areas (57).

The researchers adopted the procedure in both ways and found that the above said mechanism was more beneficial for detection of resistant strains (58).

#### *Resistance against Fluoroquinolones (FQ)*

A group of antimicrobial drugs like Fluoroquinolones (FQ) usually prescribed for enteric fever caused by *Salmonella enterica* serotype *typhi*. It is practiced that certain strains become resistant to above said antibiotic which produced difficulties in treating the patients and also in controlling infection. They had selected 11 different strains of resistant mutated constituents. FQ target genes, *gyr A*. and *par C*. The FQ resistance was naturally maintained, this research greatly helps the treatment of typhoid infection (59). These resistant genes may be located in pathogenicity islands. These resistant strains required more sophisticated antibiotics of wider range or broad spectrum Azithromycin or Ceftrizone; it may give an opportunity to try combination of antibiotic (60).

#### *Susceptibility and management*

##### Role of turmeric in drug resistance

As the enteric fever is a serious life threatening infective disorder which may treated with expertise skill of prescribing antibiotics, Ciprofloxacin may remain a drug of choice, it is a gyrase inhibitor which produce fragmentation of chromosomes to kill the bacteria. This research target the role of spices in treatment of *Salmonella* infection especially the curcumin, an active ingredient of Turmeric which commonly used in Asia. They investigate the role curcumin and reach to the point that it interferes with antibacterial action of Ciprofloxacin in vitro and vivo. They used the RT-PCR, DNA fragmentation and co focal microscopic magnification. The active ingredient of turmeric interferes the gyrase inhibition effects to obstruct the antibacterial action of ciprofloxacin. In this way the growth of

bacteria flourished and drug resistant may observe, they infect the mice with *Salmonella* and fed it by turmeric resulting increased load of bacteria, antioxidant property of curcumin protects bacteria from oxidative action of ciprofloxacin (61).

#### *Nano technology as antibacterial effects*

By increasing the multiple drug resistance creating problems for the treatment of enteric fever and other common bacteria. This gave an opportunity to try other substances in this field like Nano particles (NPs). There are many types of NPs in practice; different compounds of AgNPs are designed to produce antibacterial effects. In this study AgNPs used for diagnostics, biomarkers, cell labeling, contrast agents for biological imaging, drug delivering system, therapeutic use and as antimicrobial agents. AgNPs were prepared by spark discharging, electro chemical reduction, solution irradiation and cryo chemical synthesis (62). These AgNPs after processing, used for multiple drug resistant bacteria and compared against different antibiotics. Gram positive and Gram negative bacteria are differing in their cell wall composition and content of peptidoglycan (63). The exact mechanism of action of AgNPs was not clearly understood. Different factors may influence the bactericidal effect of AgNPs like its size, shape, and dose. It was concluded that AgNPs of 10-100 nm have strong bactericidal effects against the Gram positive and Gram negative bacteria (64).

#### *Multi drug resistance*

Enteric fever is a disease caused by *Salmonella typhi*. Duration of disease depends on age, gender and resistance of causative agent. In this study data of 581 enteric fever cases were included. All were admitted with *Salmonella typhi* culture positive to two hospitals in Vietnam during 1993-1995 and 1997-1999. During these periods a change in resistance pattern of *Salmonella typhi* was observed, i.e. causative bacteria susceptible to antibacterial drugs, resistance to Chloramphenicol,

Ampicillin and Co-trimaxazole (MDR), and on 2nd number susceptible drug was Ciprofloxacin. Duration of disease before admission to hospital and the presence of multi drug resistance or 2nd number ciprofloxacin sensitivity to causative microbes was examined, causative factors of severe enteric fever during hospital admission was also analyzed. It was observed that occurrence of severe typhoid fever was 15.5% (ninety out of five hundred eighty-one patients) and GIT bleeding 7.4% (forty three), hepatitis 5% (twenty nine), encephalopathy 2.8% (sixteen), inflammation of heart 2.1% (twelve), intestinal perforation 1% (six) shock due to dehydration 0.9% (five) and death 0.5% (three). Severity of infection was increased with increase in age, in patients of longer duration of disease and patients suffering from bacteria having 2nd number susceptible to ciprofloxacin. It was noted that multi drug resistant *Salmonella typhi* was not cause of severe illness. Severe disease was caused by infectious organism having 2nd number sensitivity to ciprofloxacin. It was concluded that patients of enteric fever caused by *Salmonella typhi* having 2nd number sensitivity to ciprofloxacin were admitted in hospital and these patients were treated with Fluoroquinolone before admission to hospital. Ciprofloxacin and Ofloxacin should be used carefully in cases of typhoid fever caused by *Salmonella typhi* and having 2nd number sensitivity to Ciprofloxacin (65).

#### *Role of silver NPs. as antibacterial agents*

NPs may be obtained from utilizing various fungi, bacteria and plants. To overcome microbial resistance to antibiotics is use of metals as constituents to control infections. Many enzymes and change in gene sequences may overcome MDR by altering the mechanism of drugs to come out of the cells (66). Due to which scientists are thinking on new lines to control bacterial resistance. Microbiologists have used metal NPs, to control some infectious bacteria causing various diseases (67, 68). NPs of Ag, Cu, and Au have been proved to be effective against some microbes and

fungi (69). As compared to others NPs, silver nanoparticles have been studied on large scale due to their specific properties like conduction, chemically stable, enhance enzyme action, antibiotic like activity against bacteria (69). Due to their antibacterial activity they are used in catheters (70) and different type of clothes used in surgery. The preparation of silver nanoparticles is economical and mixing these particles into plastics utensils, clothes, beauty creams, and bath soaps, make them valuable. *Aspergillus fumigatus* usually used to prepare the silver, gold and platinum NPs biological synthesis. Fungal cells changed silver ions to AgNPs by surface acting enzymes. Eight different strains of resistant bacteria were isolated and selective antibiotics were applied by Kirby-Bauer disk diffusion method to observe the sensitivity of the antibiotics. AgNPs suspension was prepared and also applied on disk diffusion method by dissolving 0.1 mg of synthesized AgNPs in 1 ml solution which was sterilized by autoclave. This study show, *Aspergillus fumigatus* was found to be an effective biological tool for the extracellular biosynthesis of stable AgNPs. The antibacterial activity of various drugs like imipenem, gentamycin, vancomycin, and ciprofloxacin was augmented when impregnated with AgNPs. They conclude from this study, that biologically synthesized AgNPs may function by binding to thiol (SH) groups of membrane proteins, enzymes, and phosphate groups of DNA, and can be efficiently used as antibacterial agents. This study may be a breakthrough in the field of treatment or management of resistant bacterial infection (71).

## Conclusion

Male population suffered greatly. There are no any considerable changes recorded in Hb, TLC, sugar and Liver enzyme during typhoid infection. Low tendency of positive culture growth seen in sero-positive cases due to early medication and quackery. Modern antibiotic play a considerable role in treatment response but they are much expansive and out of reach of a common man.

Silver Nanoparticles (AgNPs) produced by some fungi increasing field of research with tremendous prospects for the improvement of the diagnosis and treatment of human diseases against the *Salmonella* species. It enables us to treat the typhoid infection in a less expensive way.

## Conflict of interest

None declared.

## Financial disclosure

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