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A REVIEW OF CLINICAL PARAMETERS, HEALTH BURDENS AND THE GLOBAL PATTERN OF ANTIBIOTIC SUSCEPTIBILITY AGAINST *SALMONELLA ENTERICA*

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Abstract

Salmonella enterica belongs to the gram-negative, rod-shaped anaerobic bacteria family called Salmonellae. Salmonellosis infections can be foodborne, non-food-borne transmission between animals and between humans and animals. Pathology of salmonella enterica is influenced by the type of host population including the risk group like elderly, children and immunocompromised patients, virulence and colonization factor of the organism. Abdominal discomfort, bloody or non-bloody diarrhoea, nausea, and vomiting are all of the disease's primary symptoms, and they can cause systemic, non-intestinal, and intestinal complications. Routine antimicrobial therapy is not advised for mild or moderate infections in healthy persons. However, antibiotics are given to individuals in health-risk groups or if the colon infection extends to other bodily parts. Both in underdeveloped and industrialized nations, the overall incidence of enteric fever and rates of resistance to antibiotics are a serious burden worldwide. Different pathological mechanisms like changes in the genes and chromosomes, clonal groups, genes responsible for virulence factors and antimicrobial resistance can cause antibiotic resistance and multi-drug resistance. Global efforts must be made to lessen the spread of salmonellae through food and other channels. The discovery and deployment of effective vaccinations, in addition to the construction of water and sanitation infrastructure, should all be done in an attempt to manage these infections on a global scale.

Keywords: Salmonella enterica, health-risk groups, burden, antibiotic susceptibility, resistance, vaccine, global pattern.

Introduction

A family of anaerobic, rod-shaped, gram-negative bacteria called Salmonellae includes 2,579 serovars, two distinct species, and a total of six subspecies. Salmonella is a genus that includes *Salmonella enterica* and *Salmonella bongori*. Based on biochemical and genetic traits, *S. enterica* is divided into the subspecies *enterica, salamae, arizonae, diarizonae, houtenae,* and *indica*.[1,2]

Exposure to human

The major part of non-typhoid salmonellosis infections in people are foodborne, however, there is a substantial risk of professional exposition to *Salmonella enterica* in places like veterinary clinics, labs for research, and fields where the disease is acknowledged to occur. Some sources and sites of contamination include household members with clinical illnesses, pets with subclinical infections, contaminated objects, toilet bowls, carpets, floors, refrigerators, and kitchen sinks and worktops with clinical conditions, pets with subclinical infections, contaminated objects, toilet bowls, carpets, floors, refrigerators, and kitchen sinks and worktops are some of the sources and sites of contamination [3]. A pig, a calf, and a toddler were identified as contaminated with *Salmonella enterica* serovar Typhimurium on an agricultural property in the Netherlands. These isolates couldn't be differentiated by phenotyping or genotyping techniques, suggesting non-food borne transmission between animals and from animal to human. People should be cautious about this threat if they routinely interact with livestock [4].

Pathology

Almost all variants of *Salmonella* are morbific because they can enter, reproduce, and thrive in human host cells, where they can cause a fatal disease. *Salmonella* triggers phagocytosis on its own to invade the host cell. *Salmonella* Pathogenicity Islands (SPIs) as well gene clusters in the enormous chromosomal DNA region that code type III secretion mechanisms and multi-channel proteins that transport effectors through the gastrointestinal epithelial cell membrane which activate signal transduction and the actin cytoskeleton for the colonization are exceptional instances of this sort of genetics. The host cell immune system is triggered by the bacterium's encapsulation in a vacuole made by the host cell membrane, causing the internal bacteria to be naturally degraded. However, *Salmonella* uses the altered vacuole to prevent the lysosomes from fusing together, which would otherwise allow the bacteria to survive and replicate inside cells and form the reticuloendothelial system (RES) [5].

Influencing parameters

Risk factors

The host's defence system, past exposure, the strain's pathogenicity, and local protective factors all serve a part in this illness's pathophysiology [6].

Population

Salmonella infection is more likely to affect immunosuppressed patients, elderly persons, and children under the age of five than it is healthy adults.

Colonization factors

Aspects of bacterial virulence that aid in the infiltration of innate immune cells and intestinal cells are necessary for intestinal colonization and infection. Colonization elements that are peculiar to hosts and alleles of *S. enterica* imply a part in the regulation of particular host characteristics. Additionally, research contends that intestinal colonization factors boost the local Salmonella density, which promotes the horizontal gene transfer of genes for antibiotic resistance [7].

Systematic effects

Clinical symptoms

Salmonella enterica causes substantial morbidity and mortality in humans. *S. enterica* is still one of the main causes of illness in both people and animals and is accountable for 99% of overall infections around the world. The main signs and symptoms of this illness include nausea, vomiting, bloody or non-bloody diarrhoea, and abdominal discomfort [8].

Complications

The three main illnesses caused by *Salmonella* in humans are typhoid fever, non-invasive non-typhoidal salmonellosis (NTS), and invasive non-typhoidal salmonellosis (iNTS). Typhoid fever and paratyphoid fever are both systemic disorders caused by S. enterica serovar Typhi and S. Paratyphi, which are only found in humans. They are significant contributors to febrile sickness in people living in crowded, impoverished areas with poor sanitation who consume contaminated food and water, as well as tourists visiting regions where the virus is widespread [9]. The central neurological system (3-35%), cardiovascular system (1-5%), pulmonary system (1-86%), bone and joint (1%), hepatobiliary system (1-26%), and genitourinary system are just a few of the extra-intestinal problems that can result from S typhi infection. (Table 1)

Table 1: Extra intestinal complication details of Salmonella in human

System	Complication	Clinical manifestation
Central nervous system	Encephalopathy, Meningitis, Parkinsonism, Motor neuron disorders, Cerebral abscesses etc.	Fever, Headache, Vomiting, Seizures, Altered states of consciousness etc.
Cardiovascular system	Endocarditis, myocarditis, pericarditis, congestive heart failure, arteritis	fever, chest pain, palpitations, murmur, cardiac arrhythmias etc.
Pulmonary system	Pneumonia, empyema, bronchopleural fistula	fever, chills, cough, pleuritic pain, coarse crackles and bronchial breathing on auscultation, leucopenia etc.
Musculoskeletal system	Osteomyelitis, septic arthritis	Fever with local tenderness, rigidity, pain etc
Hepatobiliary system	Cholecystitis, hepatitis, splenic abscess, peritonitis, paralytic ileus	fever, jaundice, nausea, vomiting, and abdominal pain
Renal system	Urinary tract infection, renal abscess, pelvic infections, testicular abscess, prostatitis, epididymitis	structural or functional abnormalities of the urinary tract, bladder, pelvic organs, irregular menstrual cycles etc
Haematological system	Lymphadenopathy, hepatosplenomegaly, coagulopathy,	Pancytopenia, hyperbilirubinaemia, hyperferritinaemia etc[6]

Glimpse on therapy

Routine antibiotic therapy is not advised in healthy people for mild or moderate disease because of the chance that antimicrobial drugs could fail to completely eliminate the pathogens and may instead favour resistant forms, that could leave the therapy insignificant. However, persons who are at higher risk for illness, such as those under the age of 5, older adults, and those with weakened immune systems, might need to take antibiotics. Antibiotics are also used if the infection extends beyond the colon to various areas within the body. Treatment recommendations should be regularly reassessed, considering the worldwide increase in antibacterial resistance while also taking into account the pattern of bacterial resistance based on the local monitoring system [10].

The initial medication prescribed for typhoid was chloramphenicol, which decreased mortality from 20% to less than 2% in 1948. Although resistance has been present, it is still a popular medicine owing to its affordability in developing nations. Chloramphenicol-resistant strain-related infections have been successfully treated with ampicillin and trimethoprim-

sulphonamide. Additionally, effective are more recent quinolones (ciprofloxacin, norfloxacin) and cephalosporins (ceftriaxone). When given the appropriate antibiotic medication, patients experience improved symptoms within 24 to 48 hours, a return to normal body temperature within 3 to 5 days, and general recovery between 10 to 14 days [11].

Geographical snapshot on the health burden

Salmonella infection is a significant burden in both industrialized and impoverished countries. *Salmonella* must be prevented from spreading through food and other sources by making global efforts. The overall incidence of enteric fever and rates of antibiotic resistance were found to be high throughout Africa and Asia. High levels of antibacterial resistance were identified with fluoroquinolone in 61% of *Salmonella* isolates and multidrug resistance was reported in 44% of isolates [12].

The cycling and the new subclade of *Salmonella enterica* serotype both contained isolates from the breakouts in the United States of America and Canada that took place between 2017 and 2019. The rise of a new *Salmonella* turkey subclade, which occurred concurrently with an increase in marketable turkey breeding in addition to human incidences in the USA and Canada, suggests that emergent strains with a higher potential for niche success were probably vertically transferred and quickly dispersed from a common source. Its superficial ongoing success in commercial turkeys and its capacity to infect people may have been caused by important genetic alterations. Genomic differences between the subclades indicate that some possible causes of the superficial overthrow of currently disseminating subclades include modifications in the activity of beta-glucuronidase, colicin resistance and plasmid acquisitions join forces susceptibility pattern of antibiotics [13].

The rupture of the chromosomal region around the phase II flagellants, gene of flagellin fljB, leading to monophasic traits, is a gradual adaptive process with less impact on bacterial health. Furthermore, antimicrobial-resistant *Salmonella* lineages successfully invaded and persisted in the epithelial and phagocyte cells in Australia without significantly increasing cell toxicity and damage, indicating that the host immune system may have been suppressed, which may have helped *Salmonella* survive [14]. According to the United Kingdom Health Security Agency (UKHSA) and World Health Organization (WHO), the disease-causing variant discovered between 2021 and 2022 in the European region was resistant to common antibiotics like penicillins, aminoglycosides, phenicols, sulfonamides, trimethoprim, and tetracyclines. Children and the elderly were prone to suffer from serious effects from the outbreak-related dehydration [15,16].

Susceptibility pattern of antibiotics

In the United Kingdom (UK), the non-typhoidal *Salmonella enterica* Whole Genome Sequencing (WGS) method identified genes and chromosomal changes as the cause of phenotypic resistance. Tetracyclines, sulphonamides, and ampicillin were shown to have resistance based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria[18] when determining phenotypic susceptibilities for antibiotics. Sulphonamides and tetracyclines have shown multidrug resistance (MDR). Extended-spectrum beta-lactamase genes were found, along with many alterations in ciprofloxacin-related chromosomal genes [17].

Salmonella enterica serovar Enteritidis bacteria were discovered to be resistant to sulphonamide, trimethoprim-sulfamethoxazole, nalidixic acid, gentamicin, and tetracycline in southern Brazil. In poultry, food, and human isolates, a clonal group that produces resistance was spread, according to a dominant pulsed-field gel electrophoresis genotype [18]. *Salmonella* serovar strains were studied using a genomics-based approach that combined antimicrobial resistance gene typing with virulence gene typing in European countries. The results showed that the serovar had a wider virulence-associated gene complement that allows *Salmonella* to become accustomed to a range of conditions in the setting, which might be reflected in serovar-specific nature and several kinds of genes associated with resistance [19].

Ampicillin, chloramphenicol, gentamicin, kanamycin, spectinomycin, streptomycin, sulfadiazine, tetracycline, and trimethoprim resistance have been recognized in S. Typhimurium isolates. The results emphasize the involvement of class 1 integron and non-class 1 integron-associated multi-resistance in different serotypes as well as the uniqueness of genes that are resistant to *S. Typhimurium* or non- *S. Typhimurium* serotypes [20]. Clustered regularly interspaced short palindromic repeat polymorphism (CRISPOL) typing was used to subtype the subset of *S. Typhimurium* isolates. Overall, there was a significant rate of resistance to first-line conventional medications, but a low degree of resistance to several additional antimicrobials, like fluoroquinolones. Whole genome sequencing was used to analyze the majority of the antibiotic resistance genes found in the West African strain that produces extended spectrum beta lactamases (ESBLs) [21].

The significant number of integron-positive varieties in the multidrug-resistant (MDR) strains of Salmonella indicated that infectious genetic components were widespread across the *Salmonella enterica* serovars and were linked to decreased susceptibility to traditional antibiotics like ciprofloxacin and ceftriaxone [22]. Several human group C S*almonella enterica*

isolates gathered from Turkey showed high antimicrobial resistance rates to tetracycline, chloramphenicol, ampicillin, and amoxicillin/clavulanic acid. Serogroup C1 is more susceptible to ciprofloxacin than serogroups C1 and C2. Isolates from group C1 did not demonstrate multi-resistance; in contrast, 13% of isolates from group C2 did. These results revealed that dual antibiotic resistance was a common trait of S. enterica [23].

Salmonella with gained genes that provide resistance to specific antibiotics are referred to be multidrug-resistant (MDR) strains. The swimming and swarming mobility of MDR S. Typhimurium is influenced by Several parameters, such as drug type, concentration of antibiotics, resistance gene, and isolate-specific traits. Kanamycin and streptomycin restricted swimming, however, both drugs had a far smaller impact on reducing swarming. Interestingly, one of the isolates showed a substantial increase in swarming in response to kanamycin [24].

Salmonella Typhimurium bacteria in Italy were not significant to ampicillin, sulfonamides, tetracycline, streptomycin and chloramphenicol. The majority of human strains exhibited decreased susceptibility and were resistant to nalidixic acid [25]. In the USA, the disease multidrug-resistant Typhimurium has expanded widely. To interrupt the spread of MDR Typhimurium and to reduce the chances of antimicrobial resistance in different species of S*almonella*, it is important to use the agents more carefully in farm animals and to avoid sickness on farms [26].

Increased levels of *S.* Typhimurium resistance have been observed in Italy. Animal and food isolates often exhibited greater rates of resistance and multi-resistance than human strains. Isolates with human origins exhibited trimethoprim-sulphamethoxazole resistance. This confirms that animals serve as a reservoir for *Salmonella* species that are drug-resistant [27]. In low-income countries, the common *Salmonella enterica* species, *Salmonella typhi*, and *paratyphi* isolates exhibited sensitivity to cephalosporins and macrolides in the disk-diffusion test. Nevertheless, isolates from the nalidixic-acid-resistant Salmonella (NARS) strain were resistant to quinolones (fluoroquinolones) [28].

Although *Salmonella typhi* was resistant to ceftriaxone and meropenem, it was most sensitive to imipenem and azithromycin and least sensitive to ciprofloxacin. *Salmonella typhi* is causing an increase in antimicrobial drug resistance in typhoid fever patients; particularly, the strains of *Salmonella typhi* that are highly drug-resistant are spreading significantly in Pakistan. To stop the establishment of new resistant strains, individuals with *Salmonella typhi*-caused typhoid fever must be prescribed antibiotics for a long enough period of time, based on culture and sensitivity [29]. Tetracycline, gentamycin, and ceftriaxone were effective against Salmonella enterica serovar Typhi isolates, while ciprofloxacin, gentamycin, and tetracycline were

effective against the Paratyphi isolates. Ampicillin and chloramphenicol resistance persisted across all isolates and many of the types exhibited resistance to several medications in eastern Ethiopia [30].

Southern Delhi had significant levels of third-generation cephalosporin resistance to S. Typhi and *S. Paratyphi*, fair sensitivity to macrolides, and average sensitivity to ofloxacin. Ampicillin and chloramphenicol showed lesser resistance whereas imipinem and tigecycline were sensitive to both *S.* Typhi and *S.* Paratyphi. Not a single of the identified strains was discovered to be drug-sensitive. Typhoid bacilli's pattern of antibiotic sensitivity is constantly evolving. The effectiveness of newer medications like tigecycline, imipenem, and macrolide is excellent. Due to relatively restricted usage, medications have low resistance, while cephalosporins exhibit great resistance to typhoid bacilli [31].

New insights

A thorough analysis of phylogenetic and genomic features of a worldwide compilation of *S. enteritidis* genomes of human isolates from China, the U.S., Africa, and Europe for genetic variety, their virulence strength, and antibiotic resistance supported the continued existence and present development of *S. enteritidis* within a specific geographic area when the mutant was released and founded. Antimicrobial resistance genes (ARGs) with the maximum frequency in Chinese isolates were aph (3′)-IIa, blaCTX-M-55, and blaTEM-1B, while ARGs with the uppermost prevalence in African isolates were aph(6)-Id/strB, sul1, sul2, drfA7, and aph(3")-Ib/strA. Prophages, other accessory genes, and *salmonella* Pathogenicity Islands (SPIs) were all shown to have phylogenetic variations in their loci[32]

A promising real-time PCR test for the Salmonella enterica subspecies enterica serovar Abortusequi was assessed. This technique allows particular subspecies to be quickly and accurately detected from clinical samples like plasma, vaginal swabs, and tissue[33]. By reducing and replacing the amino acid sequence in acidocin J1132, a bacteriocin made by the *Lactobacillus acidophilus* probiotic, a new antimicrobial peptide known as A11 was developed. This bacteriocin exhibits strong inhibitory activity against *S. typhimurium*, including drug-resistant strains and its monophasic variants, with little to no toxicity in humans. Through membrane adhesion, penetration, and subsequent depolarization and temporary permeabilization, as well as intracellular processes, it killed *S. typhimurium*. At temperatures as high as 100 °C, A11 demonstrated thermal stability. Significantly, it proved effective against *S. typhimurium* in vitro when combined with nisin. Future research should take into account the effectiveness of such a combination in food or in living organism modelling to promote product development for the food business [34].

Promising approach

Two vaccines against typhoid fever have been developed and were authorized for practice over the past few years. In accordance with *S. enterica*, a parental capsular polysaccharide vaccine variant was first developed [35]. Second, an oral vaccine comprising attenuated and live *S. enterica typhi* strain Ty21a. Two of these vaccinations were found to be effective in providing typhoid fever immunization [36].

Candidates for the non-typhoidal Salmonella (NTS) vaccine are live-attenuated, subunit-based, and recombinant antigen-based. Based on immuno-epidemiological investigations and animal research, it is acknowledged that immunological reactions on the cellular and humoral levels are necessary to ward against iNTS illness. To guard against the predominant serovars *S.* Typhimurium and *S.* Enteritidis, a bivalent or a multivalent vaccine that interacts with another intestinal vaccine, like a typhoid conjugate vaccination, to enable delivery, would be desirable. Several iNTS vaccines are currently in the primary stages of either preclinical or clinical development. Before 2019, the only candidate being tested in humans was a live attenuated vaccine candidate WT05. Although WT05 has produced significant anti-lipopolysaccharide (LPS) antibody responses in some healthy human volunteers and demonstrated great tolerability, the candidate has not progressed further due to the continued fecal shedding of bacteria. Glycoconjugate vaccines against iNTS are also being developed, to generate a protective antibody response against the surface polysaccharide, the Core O-PolySaccharides (COPS) in NTS serovars. Coupling with a protein carrier flagellin FliC engages CD4+ T-cell help and enhances polysaccharide immunogenicity. A trivalent iNTS-typhoid conjugate (iNTS COPS:FliC coupled with a Vi-tetanus toxoid typhoid conjugate vaccine) is in Phase 1 currently.

The usage of outer membrane vesicles (OMVs) as a vehicle to transport iNTS O-Ag i.e. the primary polysaccharide component of the Gram-negative LPS is another potential strategy. General Components for Membrane Antigens (GMMA), a low-cost, scalable, and standardized manufacturing method for creating GMP-quality OMVs, has been created. Soon, a GMMA-based bivalent vaccine will begin clinical Phase 1 trials against to the invasive S. Typhimurium and S. Enteritidis in Africa. Additionally, a Vi-CRM197 typhoid conjugate vaccine will be used in conjunction with this GMMA-based iNTS candidate. Other vaccines are in the pre-clinical stages of development, including live attenuated vaccines and vaccinations based on outer membrane proteins [37].

Conclusion

Antibiotic therapy is administered to patients who have risk indicators as a preventive approach to stop widespread transmission. To establish effective treatment protocols and to observe It's important to monitor antimicrobial resistance (AMR) in non-typhoidal *Salmonella enterica* (NTS) to prevent the spread of resistance from livestock and food to humans. The significant prevalence of enteric fever in the world demands several measures to expand sanitation and water systems and create effective vaccinations to achieve worldwide eradication of these diseases. When considered collectively, these findings offer fresh perspectives on the molecular processes underlying the evolution of MDR *S.* Enteritidis. More clinical *S.* Enteritidis genomes from different nations should be included in future phylogenetic analyses, which will assist in shed light on *S.* Enteritidis development as well as its worldwide AMR supply and distribution.

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