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Review of Current Concepts of Diagnosis and Treatment of Typhoid Fever

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ABSTRACT

Typhoid fever is a pathological condition caused by *Salmonella enterica typhi*, which has simple prevention, through sanitary measures, but affects populations in situations of social vulnerability, especially in developing countries. Therefore, the objective of the present study is to point out the clinical and laboratory findings, as well as to survey the main causes and therapeutic methods inherent to typhoid fever. It is an integrative review of the literature developed through a bibliographic survey in the Medline, PubMed and Science Direct databases. The search strategy used was "Typhoid Fever", "Infection", "*Salmonella typhi*" and "Diagnosis". *Salmonella typhi* causes infection exclusively in humans. The main form of transmission is the ingestion of water or food contaminated with human feces or, less frequently, with urine containing the bacteria, however, it can rarely be transmitted through direct contact (hand-mouth) with feces, urine, respiratory secretion, vomiting or pus from an infected individual. Considering that the clinical findings of this disease, it is similar to others such as malaria, bacterial endocarditis, tuberculosis and systemic lupus erythematosus, it is important that health professionals are able to diagnose and treat this condition, also based on biochemical tests and blood. It should also be noted that as important as paying attention to clinical aspects is also to consider laboratory tests. In this way, the correct diagnosis can be established, as well as the therapeutic conduct, mostly based on the prescription of oral and/or intravenous antibiotics.

INTRODUCTION

New cases of typhoid fever have been estimated at 21.6 million people a year, resulting in 220,000 global deaths in the early 21st century affecting all ages. Its transmission is mainly oral-fecal, both indirectly and directly, with improved access to health services to the disease fortunately has been declining significantly. However, it is important to emphasize that the improvement in hygiene and quality of water, food and basic sanitation are more concentrated in central countries such as Europe, Japan and Anglo-Saxon America thanks to governmental efforts that began in the early 20th century and reflect on present. However, hygiene conditions in developing countries create a serious public health problem, aggravating the chances of transmission of various infectious diseases such as typhoid fever[1]. Recent numbers from March 2019 demonstrate that typhoid fever has caused, in the world, 17 million new cases, 178 thousands of which are fatal. Although the data has significantly reduced, the number of people who are affected by the infection is still large[2].

In Brazil, typhoid fever is endemic and seasonal (periods of rain), especially in the north and northeast regions, with the states of Bahia and Amazonas being the most frequent. When this information is crossed with the socioeconomic profile of these regions, it is concluded that social vulnerability is directly linked to the risk of contamination by the bacteria. The etiologic agent of typhoid fever is the bacterium *Salmonela Enterica thypi*, a gram-negative, mobile (flagellated) and facultative anaerobic bacillus (an enteric subspecies of the typhi serotype), belonging to the Enterobacteriacea family. This microorganism has a high virulence, that is, it is easy to infect and cause the disease in humans, but with slow progression, so that the initial stages of the disease can manifest in a tenuous and nonspecific way, late in the diagnosis. This contributes to the transmission of bacteria and maintenance of the disease in the population associated with the fact that Salmonella is resistant to degermation and freezing, being effectively eliminated from surfaces by heat heating treatments[3].

The disease if left untreated can be fatal. In about 10% of infected people, death occurs. An acute manifestation of fever, malaise, headache, nausea, vomiting, abdominal pain, diarrhea, lack of appetite, weight loss, relative bradycardia, splenomegaly, pink spots on the body trunk, dry cough, myalgia may occur be accompanied by skin rashes[4,5].

The route of transmission is fecal-oral, with contaminated food being the main vehicle. In this sense, it is necessary to pay attention to the food preparation process, preventing them from being improperly undercooked/fried and thus preventing infection[4,6]. Water and food can be contaminated through contact with urine or feces human actions beyond direct action by the hand brought to the mouth without proper hygiene. It is also evident that the ingestion of raw foods washed in water contaminated with sewage containing *Salmonella typhi* are equally important as means of contamination[4,7].

In the digestive system, despite the chemical acidity barrier of the gastric groove, this does not prevent the colonization of *Salmonella typhi* since it is aciduric, and can progress in the digestive transit to its attack niche, which is the small intestine where it invades the intestinal wall and, piercing the jejuno-ileal mucosa, it reaches the blood circulation. As soon as *Salmonella typhi* reaches the bloodstream, symptoms begin to appear. It can enter any organ and multiply inside the defense cells. It normally invades the liver, spleen, bone marrow, gallbladder and intestine. As it is a bacterial infection, the treatment of choice is based on the administration of antibiotics, which may vary according to the individual's physiological profile, duration of the disease, degree of infection and the type of strain, for example [2,3,7,8].

For the effective diagnosis of typhoid fever as important as considering the clinical aspects is to pay attention to biochemical and blood tests. Therefore, this article aims, through an integrative literature review, to point out clinical and laboratory findings, as well as to survey the main causes and therapeutic methods inherent to this disease, which represents a public health problem in many countries, including Brazil.

MATERIALS AND METHODS

It is an integrative review of the literature developed through a bibliographic survey in the Medline, PubMed and Science Direct databases. The search strategy used was "Typhoid Fever", "Infection", *"Salmonella typhi"* and "Diagnosis". Twenty nine studies published between 2014 and 2019 were selected, included based on the following inclusion criteria: availability of the full text, publication in Portuguese, English and Spanish and clarity in the methodological details used. As for the language inherent in the selected articles, English, Portuguese and Spanish were used. The abstracts were read and evaluated by the authors and categorized as relevant or not to the topic according to the inclusion criteria previously elucidated.

LITERATURE REVIEW

The bacterium that gives rise to typhoid fever also known as "dirty hand disease" was first described in 1880 by Karl Joseph. *Salmonella typhi* is also known as the bacillus of Elberth, named after its discoverer in 1907. Mary Mallon (the original “Mary typhoid”) was the first carrier to be identified after an epidemic in the United States where such fever killed several famous characters[9,10,11].

The Japanese, on the other hand, used the bacterium as a biological weapon in World War II, in a direct attack against Russian forces. Similarly, in 1984 a religious sect from the State of Oregan (USA) used *Salmonella typhi* to contaminate salad buffets, a fact that caused gastroenteritis in 751 people, without leaving any dead[12]. In the 1970s, relations of this bacterium were observed with reptiles. Since then and until today, researchers have verified several cases of the disease that were born from contact with green turtles, a fact that led in 1975, an American government agency, to veto the sale of aquatic turtles smaller than 10 centimeters, thus preventing children from placing them in mouth and contracting illnesses[13].

Only a small percentage of the disease is related to reptiles, most of the transmission is through food. In Brazil, cases of food infection caused by *Salmonella typhi* in restaurants and prisons are not uncommon, due to food contamination, which can originate from a product or from unhygienic food processing. Typhoid fever can be more severe in people with poor health. Treatment is based on antibiotics and rehydration processes in the body. Depending on the patient's clinical condition, treatment can be done at home with oral measurement[3].

The distribution of the disease is universal, but it is more prevalent in countries and regions where basic sanitation is inadequate. It is estimated that 12 to 33 million cases occur each year worldwide, with approximately 600 thousand deaths. About 60% of reported cases occur in Asia and 35% in Africa[14]. In developed countries, only occasional outbreaks of typhoid occur. In developing countries, mainly in the Indian subcontinent, Southeast Asia, Africa, Central and South America, the disease is endemic. This is due to rapid population growth, increased urbanization, limited access to clean water and health services[15].

In Brazil, cases are recorded in all regions of the country, mainly in the North and Northeast. In the last ten years, Bahia (1,765) and Amazonas (1,447) are the States with the highest number of cases[14]. More recent data from the Ministry of Health indicate that in the period from 2010 to 2017, 969 cases of typhoid fever. As for the years with the highest incidence,

2014 (187 cases), 2011 (161 cases) and 2010 (154 cases) stand out. In the period evaluated, the North (71.4%) and Northeast (18.6%) regions concentrated the largest number of cases. However, the reliability of these data must consider the guidelines inherent to laboratory diagnosis, as well as the reality of underreporting, common to health systems[16].

The risk of infection by the bacteria during travel depends on the itinerary, the road conditions and the traveler's medical history. Individuals with decreased gastric acidity, gastrectomized patients, and patients with chronic intestinal diseases or immunodeficient people have a higher risk of acquiring typhoid fever. The use of antibiotics also increases susceptibility to the disease, as it changes the intestinal microbiota that normally competes with pathogenic bacteria. The consumption of foods such as milk, butter, cheese and fish are considered to be of high risk, as they have the ideal pH (4.4 to 7.8) for the growth of *Salmonella typhi*. In developed countries, with adequate sanitation, the risk of acquiring typhoid fever is significantly lower. In most diagnosed cases, the infection occurred while staying in other places (imported cases) with poor sanitary structure. However, it is possible that cases associated with the food source may occur, since a significant portion of the food consumed in developed countries originates from other regions and can be contaminated at the source or during preparation, if there is no adequate hygiene. In developing countries, in addition to the risk related to food being higher (origin and preparation), the lack or inadequate treatment of sewage favors the contamination of drinking water reservoirs. The identification of *Salmonella typhi* resistant to various antibiotics, mainly in the Indian subcontinent, is occurring with increasing frequency. The emergence of resistant bacteria makes treatment difficult, increasing the lethality and spread of the disease[17].

Salmonella typhi causes infection only in humans. The main form of transmission is the ingestion of water or food contaminated with human feces or, less frequently, with urine containing *Salmonella typhi*. But rarely, it can be transmitted by direct contact (hand-mouth) with feces, urine, respiratory secretions, vomiting or pus from an infected individual. Gastric acidity is the body's first defense mechanism against *Salmonella typhi*. When it can resist stomach acidity, *Salmonella typhi* reaches the small intestine, where it competes with bacteria in the normal intestine microbiota. If it survives, *Salmonella typhi* invades the intestinal wall and reaches the bloodstream.

The presence of the bacteria in the blood determines the onset of symptoms. S. typhi can invade any organ and multiply inside defense cells (mononuclear phagocytic cells), with

liver, spleen, bone marrow, vesicle and intestine (terminal ileum) being more frequent[18]. O time between exposure and the onset of symptoms (incubation period) can vary from 3 to 42 days, ranging from 7 to 14 days in most cases. However, the infection may not result in illness[1].

An infected person eliminates *Salmonella typhi* in the feces and urine, regardless of whether or not the clinical manifestations are present. Adequate treatment decreases the time of elimination of the bacteria in human excreta, which can be up to three months in untreated individuals. About 1 to 3% of people, even when treated, become chronic carriers, which is particularly more common in children under[5], the elderly and women with biliary pathologies. Chronic carriers can eliminate *Salmonella typhi* in the faeces for more than a year, having importance in maintaining the transmission of the disease[3,4,19]. In general, contaminated water has a low concentration of bacteria, resulting in a lower infection rate among those exposed and, in those where the infection develops, the incubation time is usually longer. *Salmonella typhi* can survive in polluted waters for up to 4 weeks and is resistant to freezing. However, it cannot withstand temperatures above 60 ° C, nor the proper treatment of water with chlorine or iodine[3].

Food can be contaminated directly by the water used to wash or prepare it, through the contaminated hands of chronic carriers and, more rarely, by exposure to insects (such as flies). Although the initial concentration of bacteria in the newly contaminated food may be insufficient to cause human disease, under favorable environmental conditions, significant bacterial multiplication occurs, resulting in large inocula upon ingestion[18]. Most people infected with *Salmonella typhi* remain asymptomatic during the incubation period, although transient diarrhea is possible (in 10 to 20% of cases). At the end of this period, coinciding with the phase of continuous bacteremia, the fever appears, which initially is low, but becomes progressively higher. In this initial phase, the simultaneous occurrence of headache (severe frontal or diffuse headache), body pain, pain in the abdomen, fatigue, loss of appetite, nausea and alteration of intestinal transit, manifested by diarrhea or constipation (arrest of intestinal). There is also a frequent complaint of transient sore throat and sometimes the appearance of a dry cough[7].

At the end of the first week, it is possible, in a significant number of patients, to detect an enlarged spleen and liver and the already high fever tends to become continuous and remain so throughout the second week, which is marked by intensification of fatigue and prostration.

The appearance of pink spots on the chest (rosacea) can be seen more easily in fair-skinned individuals. In 10 to 25% of cases, neuropsychiatric manifestations become progressively exuberant, including disorientation, delirium, neck stiffness, seizures and more rarely stupor and coma. If left untreated, the disease can progress for weeks or even months, resulting in death. It should be noted that, in the absence of specific treatment, relapses are common[15]. Complications such as intestinal perforation and hemorrhage resulting from lesions caused by *Salmonella typhi* in the intestinal mucosa can occur at any stage of the disease, being more common after the third week and in untreated people. Intestinal bleeding is the most common complication and results from erosion of the intestinal wall due to bacterial proliferation. Most of the time, the bleeding is small and stops spontaneously. Intestinal perforation, which occurs in up to 3% of hospitalized people, is a more serious complication. It usually manifests with worsening abdominal pain, increased heart rate and drop in blood pressure. Treatment is surgical and must be performed immediately. Typhoid fever tends to be more severe in people who have remained ill for a longer time, in malnourished people, in immunodeficient people, in people with gallbladder diseases and in individuals with certain genetic characteristics. Additionally, peculiarities of the infecting strain and the amount (inoculum) of bacteria ingested can influence the presentation and clinical evolution[15].

Therefore, it is important to pay attention to the fact that the manifestations of typhoid fever, especially in the first week of illness, maybe similar to that of other febrile diseases such as malaria. Even if they have a history of risk for typhoid fever, people who have been in a malaria transmission area, and who have a fever, during or after their trip, should have this disease investigated[19]. As typhoid progresses, it is more easily confused with infections that may have a slow evolution, such as bacterial endocarditis, tuberculosis, or autoimmune diseases, such as systemic lupus erythematosus[2]. The diagnosis of typhoid fever is confirmed by isolating the bacterium in culture, usually made from blood, feces, urine or biopsy of skin lesions. The cultivation of bone marrow aspirate is less used, despite the high yield, as obtaining the material brings discomfort to the patient, but its use may be justified in the most severe cases and with more difficult diagnosis. Isolation of bacterial samples is essential, as it makes it possible to determine their susceptibility to antimicrobials[7,8].

The bacteria are ingested, invade, and enter a specialized type of cell in the organ's epithelium, the M cell, by endocytosis and then pass to the submerger. Then they are phagocytized by macrophages, but resist intracellular destruction. Like these mobile

lymphatic cells, they are transported to lymph tissues throughout the body, such as lymph nodes, liver, skin, bone marrow and spleen. Its initial spread is through lymph, and then blood. In the early stage of the disease, there are usually no symptoms. From the first week, they start to appear. The first symptoms are fever of about 40 ° C, fatigue, headaches, bradycardia, restlessness, and sometimes pink spots may appear on the skin. After about three weeks, they may have a lack of appetite, nosebleeds, vomiting and diarrhea, splenomegaly (enlarged spleen), coughing, delirium, and then septicemia (severe general infection of the organism by pathogenic germs), with possible deadly septic shock (acute infectious cause circulatory failure). The main target organs affected in typhoid fever are liver, spleen and gastrointestinal tract[12].

The most used method for diagnosis remains the culture of isolated colonies. The culture media and clinical material depend on the location of the infection and the stage of the disease. The techniques used for culture and identification of the agent can be blood culture, more used in the first two weeks of the disease, and blood should be collected before the administration of antibiotics. In addition, it is recommended to collect 2 to 3 samples. For co-culture, more than one stool sample must be collected between the 2nd and 4th weeks of the disease. Myeloculture is considered the most sensitive test (90% sensitivity), but it has a more efficient result. However, patient discomfort and the need for medical personnel with specific training for spinal puncture are disadvantages in relation to other methods. Uroculture, in turn, has limited diagnostic value, with maximum positivity occurring in the 3rd week of the disease, while the Widal Reaction is simple and quick to perform, and is therefore widely used. Its correct interpretation requires knowledge of the behavior of antibodies against O (somatic) and H (flagellar) antigens, in addition to the collection of successive samples to assess their levels. The blood count, in turn, usually helps in the detection of anemic conditions, or leukopenia, with lymphocytosis, neutropenia, absence of eosinophils and thrombocytopenia. In the phase of bleeding and intestinal perforation, the blood count shows leukocytosis[4].

Salmonella typhi infections are generally limited to the administration of antibiotics in the treatment of gastroenteritis, which does not always accelerate the patient's recovery, even, and may prolong the period of excretion of the agent. On the other hand, antibiotics are recommended for salmonellosis with systemic complications and in cases of typhoid fever, both in the acute phase and in the disease carrier phase. However, the treatment of

Salmonella typhi infections has been hampered by the growing number of antibiotic-resistant samples, so drugs like chloramphenicol, sulfamethoxazole-trimethoprim, ampicillin or amoxicillin, are being replaced by third generation cephalosporins and fluoroquinolones[7]. There are also vaccines, but they are not recommended in young people, as they are not very effective. Among them, there is the Ty21a vaccine administered orally, which requires several doses to achieve a reasonable rate of protection. Other vaccines use Salmonella typhi auxotrophic mutants, with deficiency in the biosynthesis of aromatic amino acids, purines, among others[2].

DISCUSSION

Salmonellosis is a disease that affects humans and can have two different presentations, but both forms are transmitted from person to person, with no transmission by animals being described[1]. Typhoid-type salmonellosis is caused by *Salmonella typhi*. In contrast, salmonellosis of the paratyphoid type has *Salmonella* Paratyphi A, B or C as its etiological agent. The symptoms inherent to this first type are more prolonged and severe, as well as the incubation period is longer when compared to the first[4].

Regarding the pathogenesis of typhoid fever, studies show that approximately 90% of the *Salmonella typhi* genome is related to sequences present in other Salmonella serotypes, a fact that facilitates its colonization, infection and transmission. Allied to this, the fecal transmission of this bacterium occurs in the clinical and subclinical stages of the disease. It is noteworthy that untreated patients and chronic carriers of typhoid fever continue to eliminate the etiological agent for years, with the possibility of these organisms mutating, becoming more resistant[20].

Still in this context, it is worth remembering that typhoid toxin plays a central role in the development of symptoms. The proof of this is that its administration in experimental animals is capable of reproducing the pathognomonic signs of the disease, such as lethargy and malaise. On the other hand, the development of fever is not observed in these experiments, thus suggesting that some symptoms of typhoid fever may not only be a consequence of the inflammatory response to the infection, but also a result of the involvement of the central nervous system[9].

A study of 421 patients with suspected typhoid fever treated at an Ethiopian hospital found that in relation to the clinical presentation, all participants were febrile for at least 3 days, in

addition to having a headache. Most 85% had fever for a maximum of 5 days, while 82.7% showed fatigue and 64.8% loss of appetite. Constipation (18.1%), diarrhea (28.5%), abdominal pain (15.4%), coughing (44.4%) and rash (1.9%) could also be diagnosed. It is worth mentioning that fever, abdominal pain and rash revealed a more significant association with typhoid fever, as well as those who had fever for a period greater than or equal to 5 days. With regard to the source of contamination, contaminated food prevailed, since it was responsible for 85% of the cases[21].

As for the diagnosis of this fever, the importance of the clinical assessment of the patient, the history of where he has been and what he has consumed, the hygiene habits and the conditions of housing and basic sanitation, where he lives, is evident. This is because such a condition can make a differential clinical diagnosis with diseases such as pneumonia, tuberculosis, meningitis, chagas disease, malaria, toxoplasmosis and schistosomiasis, for example[21]. As a way of promoting a correct diagnosis, the World Health Organization list containing a series of characteristics necessary for the tests used to identify the said disease to be effective, in that sense they must be economically accessible, sensitive, specific, easy to use, fast and delivered to those who requested[19].

In face of this, the laboratory diagnosis is based on the isolation and identification of *Salmonella typhi*, through blood culture, co-culture and urine culture. This first being the most performed exam, especially in the first two weeks after the onset of symptoms. The finding of *Salmonella typhi* in the blood should raise the hypothesis of typhoid fever and the strain, in Brazil, should be sent to the Public Health laboratory for effective serotyping. Coproculture can be done after the second week and uroculture in the transition period. In addition to these, the Widal reaction is also used and is based on the identification of antigens of the etiologic agent through specific antisera[20].

With regard to blood isolation, factors that may affect it are the culture medium, previous exposure to antibiotics, as well as the severity and duration of the disease before the samples are collected[22]. Therefore, the blood culture sensitivity rate may vary from 40 to 60%. Regarding treatment, the antibiotic chloramphenicol is indicated as the first indication, as well as ampicillin and trimethoprim sulfamethoxazole for up to 14 days, at least[20]. In addition to these, the use of cotrimoxazole is common[4]. However, the appearance of strains presenting resistance to multidrug resistance is one of the main problems that further complicate the treatment and management of enteric fever. In view of these microorganisms, the prescription

of third generation cephalosporins or fluoroquinolones is indicated. However, in cases where the infection persists, intravenous azithromycin or carbapenemics is indicated[19].

CONCLUSION

Despite the improvements associated with living conditions and basic sanitation in many countries, a significant portion of society still suffers from diseases related to the lack of assistance from public services and socioeconomic inequalities, such as typhoid fever, for example, which predominates in countries and countries poorly developed regions, since the most prevalent form of transmission is fecal-oral, with an emphasis on contaminated food and water, via sewage.

The etiological agent of this disease is *Salmonella typhi*, which when it infects the human body is capable of manifesting different symptoms, including headache, body aches, pain in the abdomen, fatigue, loss of appetite, nausea and alteration of intestinal transit. Parallel to this, organs such as the liver, spleen and gastrointestinal tract can be colonized, which leads to more severe conditions such as perforation and intestinal hemorrhage. It should also be noted that as important as paying attention to clinical aspects is also to consider laboratory tests, especially blood culture, co-culture, urine culture and Widal reaction. Only then, the correct diagnosis can be established, as well as the therapeutic conduct, mostly based on the prescription of oral and / or intravenous antibiotics.

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