



CLINICAL SIGNS AND STAGES OF PATHOGENESIS OF TYPHOID FEVER

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Annotatsiya: Ushbu maqolada qorin tifi kasalligining patogenezi, ya'ni organizmda rivojlanish mexanizmlari, shuningdek uning asosiy klinik belgilari va kasallikning bosqichma-bosqich kechishi yoritilgan. Kasallik qo'zg'atuvchisi hisoblangan Salmonella typhi ning organizmga kirishi, ichak limfa tizimi orqali tarqalishi va bakteriemiya rivojlanishi jarayonlari tahlil qilingan. Shuningdek, kasallikning inkubatsion davri, boshlang'ich, avj olish va sog'ayish bosqichlaridagi klinik belgilar batafsil bayon etilgan. Mazkur maqola qorin tifining erta aniqlanishi va samarali davolash choralari uchun muhim ahamiyatga ega.

Kalit so'zlar: qorin tifi, patogenez, Salmonella typhi, bakteriemiya, klinik belgilar, inkubatsion davr, isitma, ichak zararlanishi, diagnostika, bosqichlar.

Аннотация: В данной статье рассматриваются патогенез брюшного тифа, механизмы его развития в организме, а также основные клинические проявления и стадии заболевания. Проанализированы пути проникновения возбудителя Salmonella typhi, его распространение через лимфатическую систему кишечника и развитие бактериемии. Подробно описаны клинические признаки на различных стадиях болезни: инкубационный период, начальная стадия, разгар заболевания и период выздоровления. Статья имеет важное значение для ранней диагностики и эффективного лечения брюшного тифа.

Ключевые слова: брюшной тиф, патогенез, Salmonella typhi, бактериемия, клинические симптомы, инкубационный период, лихорадка, поражение кишечника, диагностика, стадии.

Abstract: This article discusses the pathogenesis of typhoid fever, including the mechanisms of its development in the human body, as well as its main clinical manifestations and stages. The processes of entry of Salmonella typhi into the body, its spread through the intestinal lymphatic system, and the development of bacteremia are analyzed. The clinical features during different stages of the disease—incubation period, initial stage, peak stage, and recovery period—are described in detail. This article is important for early diagnosis and effective treatment of typhoid fever.

Keywords: typhoid fever, pathogenesis, Salmonella typhi, bacteremia, clinical features, incubation period, fever, intestinal involvement, diagnosis, stages.

Introduction

Typhoid fever is an acute infectious disease, characterized mainly by damage to the digestive system, in particular the intestinal lymphatic apparatus, prolonged fever, general intoxication and



various systemic changes. The causative agent of this disease is the bacterium *Salmonella typhi*, which enters the human body mainly through the fecal-oral route, that is, through contaminated water, food products or in cases of non-compliance with hygiene rules. Typhoid fever is one of the diseases known since ancient times, and is especially widespread in areas with insufficiently developed sanitary and hygienic conditions. Even today, typhoid fever remains an urgent problem in many developing countries of the world. In densely populated areas, contamination of drinking water, insufficient sewage systems and low sanitary culture contribute to the widespread spread of this disease. According to the World Health Organization, millions of people become ill with typhoid fever every year, and this disease is still of serious epidemiological importance. The pathogenesis of typhoid fever is complex, and the development of the disease involves the entry of bacteria into the body, their multiplication in the lymphatic tissues of the intestinal wall, and subsequent spread throughout the body through the bloodstream. In this process, various clinical symptoms occur as a result of the struggle between the body's immune system and the pathogen. In particular, damage and necrosis of Peyer's patches in the intestine can lead to a severe course of the disease and the development of complications. Clinical symptoms of the disease develop gradually. Initially, the patient experiences general weakness, headache, loss of appetite, and a gradual increase in body temperature. Later, high fever, bradycardia, abdominal pain, diarrhea or constipation, as well as a characteristic skin rash (roseola) may occur. In severe forms of the disease, dangerous complications such as intestinal bleeding or perforation of the intestinal wall occur.

Etiology

Typhoid fever is an acute infectious disease of bacterial etiology, the main causative agent of which is *Salmonella typhi*. These microorganisms are gram-negative, rod-shaped, and belong to the Enterobacteriaceae family. *Salmonella typhi* is a motile, flagellated, non-spore-forming, and capsule-free bacterium. It is a facultative anaerobe and can survive in the presence or absence of oxygen. The pathogenicity of this bacterium depends on a number of antigens in its composition. In particular, the O-antigen (somatic antigen), H-antigen (flagellar antigen), and Vi-antigen (virulence antigen) are important. In particular, the Vi-antigen helps the bacterium to avoid phagocytosis and ensures its long-term survival in the body. Therefore, *Salmonella typhi* can remain latent in the human body and cause a chronic carrier state. The source of infection is only humans, that is, the disease is anthroponotic. Patients with the disease and carriers of bacteria (especially chronic carriers) serve as the main source of infection. Bacteria are mainly excreted into the external environment through feces and urine. In some cases, they persist in the biliary tract for a long time, creating a carrier state.

Typhoid fever is transmitted by the fecal-oral mechanism. The infection spreads in the following ways:

- through contaminated drinking water (water route),
- through food products that do not meet hygiene requirements (food route),
- through dirty hands and household items (contact-household route).

The spread of the disease is especially observed in the summer and autumn seasons, which is associated with the rapid contamination of water and food. Non-compliance with sanitary and hygienic rules, poor quality of drinking water, and underdeveloped sewage systems lead to the widespread spread of the disease. *Salmonella typhi* is considered to be somewhat resistant to the



external environment. It can survive in water for several weeks, and in soil for a longer time. It multiplies rapidly in food products, especially milk and dairy products. However, it is quickly destroyed by high temperatures, boiling, and disinfectants. The general condition of the body, the strength of the immune system, and the acidity of gastric juice play an important role in the development of infection. Although gastric acid partially destroys bacteria, microorganisms that have entered in large quantities can pass into the intestines and cause the disease. Also, the disease is more severe in people with reduced immunity.

Pathogenesis

The pathogenesis of typhoid fever is a complex and multi-stage process, which is characterized by the spread of the causative agent *Salmonella typhi* throughout the body and the development of pathological changes in various organs and systems. This process develops in several successive stages, and each stage is accompanied by its own morphological and clinical changes. At the beginning of the disease, bacteria enter the body via the fecal-oral route. Usually, they enter the oral cavity through contaminated water or food, and then pass through the stomach into the intestine. Although the hydrochloric acid contained in the gastric juice kills some of the bacteria, a certain part of them survives and reaches the small intestine. Especially in people with reduced gastric acidity or weakened immunity, the probability of survival of the bacteria is high. *Salmonella typhi*, having reached the small intestine, adheres to the intestinal mucosa and penetrates the intestinal wall mainly through Peyer's patches (intestinal lymph nodes). In this process, bacteria penetrate the intestinal epithelium through enterocytes and M-cells using special invasion mechanisms. As a result, they enter the lymphoid tissues and begin to multiply there. At this stage, a local inflammatory reaction occurs, but clinical signs may not yet be clearly manifested. In the next stage, the bacteria travel through the lymphatic vessels to the mesenteric lymph nodes. Here they actively multiply, causing lymphadenitis. Then the bacteria enter the bloodstream from the lymphatic system and primary bacteremia develops. At this stage, the pathogen spreads throughout the body and settles in the organs of the reticuloendothelial system, such as the liver, spleen, and bone marrow. In the reticuloendothelial system, bacteria are engulfed by phagocytes, but they also live and multiply inside the cells. As a result, the bacteria multiply in these organs and then again enter the bloodstream, causing secondary bacteremia. It is this stage that causes the main clinical signs of the disease (prolonged fever, intoxication). As a result of the breakdown of bacteria, endotoxins are released. These toxins affect the central nervous system, cardiovascular system and other organs, causing a general intoxication syndrome. As a result of the action of endotoxins, body temperature rises, headache, weakness, bradycardia and a decrease in arterial pressure are observed. Also, the permeability of the vascular walls increases, hemodynamic disorders develop. One of the important stages of pathogenesis is the re-entry of bacteria into the intestine through bile. Bacteria that have multiplied in the liver and gallbladder are excreted into the intestine with bile and re-damage the intestinal mucosa. This process leads to even deeper damage to the lymphatic apparatus in the intestinal wall. As a result, severe complications such as necrosis of Peyer's patches, ulceration and even perforation of the intestinal wall can occur. Pathological changes in the intestine develop gradually: first, edema and hyperplasia, then necrosis, then ulceration, and finally scarring are observed. These changes are closely related to the clinical stages of the disease, and the risk of complications is especially high in the 2-3rd week of the disease. In addition, the immune system response plays an important role in typhoid fever. The body's defense mechanisms fight bacteria, but in some cases this response is not effective enough. Therefore, the disease can last a long time or recur. Chronic carrier state is associated with the persistence of bacteria mainly in the gallbladder. The pathogenesis of typhoid fever is not only a simple infectious process, but also a complex set of



interactions between microorganisms and the host organism. This process occurs at the molecular, cellular and systemic levels, and the severity, duration and complications of the disease depend on the specific characteristics of these stages. The ability of *Salmonella typhi* to survive after entering the gastrointestinal tract plays an important role in the onset of infection. The bacterium has mechanisms of acid resistance and is partially preserved in the gastric environment. Upon reaching the small intestine, it adheres to the surface of the intestinal epithelium there. This adhesion (adhesion) is carried out with the help of special surface structures of the bacterium - fimbriae and adhesins.

In the next stage, the bacteria show invasive properties and penetrate the intestinal epithelial cells. In particular, passage through the M-cells in Peyer's patches is important. After *Salmonella typhi* enters the cell, it undergoes phagocytosis, but unlike many other bacteria, it does not die inside the macrophages. On the contrary, it stops binding to the phagolysosome and is able to live and multiply inside the cell. This causes the bacteria to establish a latent and long-lasting infection in the body. Bacteria that have multiplied inside the macrophages reach the mesenteric lymph nodes through the lymphatic system. Here a strong immune response begins: lymphocytes are activated, cytokines are released (interleukins, interferons), but due to the ability of the bacteria to survive inside the cell, the immune system cannot completely destroy it. As a result, the bacteria enter the bloodstream and bacteremia develops. During bacteremia, microorganisms spread throughout the body, especially accumulating in the organs of the reticuloendothelial system - the liver, spleen and bone marrow. Hyperplasia (tissue growth), inflammation and functional changes occur in these organs. For example:

- In the liver - hepatocytes are damaged, signs of mild hepatitis appear
- In the spleen - splenomegaly (enlargement) develops
- In the bone marrow - blood cell production is impaired

The role of endotoxins in pathogenesis is of particular importance. When *Salmonella typhi* breaks down, lipopolysaccharide (LPS) is released, a natural endotoxin. This toxin acts in the body as a strong pyrogen (fever-causing agent). It affects the thermoregulation center in the hypothalamus, increasing body temperature. In addition:

- blood vessels dilate
- arterial pressure decreases
- heart rate slows down (relative bradycardia)
- the central nervous system is damaged (apathy, adynamia, sometimes delirium)

Endotoxins also increase capillary permeability, which leads to edema and impaired microcirculation in the tissues. As a result, hypoxia (oxygen deficiency in the tissues) develops.

Allergic and immunopathological reactions also play an important role in the pathogenesis of typhoid fever. In the later stages of the disease, the body enters a state of hypersensitivity to bacterial antigens. This causes severe inflammation, necrosis and ulceration of the intestinal wall. In particular, the following stages are observed in Peyer's patches:



- Hyperplasia stage - lymphoid tissue increases
- Necrosis stage - tissue death begins
- Wounding stage - ulcers appear on the intestinal mucosa
- Purification and scarring - the ulcer heals, a scar forms

It is during the ulceration stage that severe complications such as intestinal bleeding or perforation occur. Another important aspect is the ability of the bacteria to survive in the gallbladder. *Salmonella typhi* is adapted to the bile environment and can live in the gallbladder for a long time. This creates chronic carriage. Even if such people themselves are asymptomatic, they become a source of infection for others.

Clinic and stages of typhoid fever

Typhoid fever is an infectious disease that begins clinically gradually, is accompanied by prolonged fever, general intoxication, and damage to the intestinal system. Its clinical picture is formed depending on the biological properties of *Salmonella typhi* that has entered the body, the dose of infection and the immune status of the patient. The disease usually develops in stages, and each stage is characterized by its own symptoms. Therefore, in order to fully understand the clinical course of typhoid fever, it is important to study it in separate periods.

The first stage of the disease is the incubation period, which lasts from the moment the infection enters the body until the first clinical symptoms appear. Usually this period is about 7–14 days, but in some cases it can last from 3 to 21 days. During this period, the patient does not express any specific complaints, since the bacteria are still in the process of multiplying in the intestinal lymphatic system and adapting to the body. However, some patients may experience mild weakness, loss of appetite, or general malaise. These symptoms are often ignored because they are very mild. The next stage is the initial or prodromal period. During this period, the disease begins to manifest itself gradually. The patient feels weakness, fatigue, headache, sleep disturbance, and a sharp decrease in appetite. The body temperature rises not suddenly, but gradually, reaching a high level within a few days. It is precisely the gradual increase in fever that is one of the characteristic signs of typhoid fever. During this period, intestinal activity also changes: constipation is often observed, and sometimes diarrhea may also occur. Abdominal distension, flatulence, and discomfort in the abdominal area appear. The patient's appearance also changes - the skin turns pale, the face is pale. The tongue is covered with a thick coating, and its edges are red. The heartbeat slows down compared to body temperature, which is called relative bradycardia and is an important characteristic of typhoid fever. The most severe and pronounced period of the disease is the exacerbation or fully developed stage. During this period, all clinical signs are maximally expressed. The body temperature is constantly high (39–40 ° C), which does not decrease for a long time. The patient's general condition deteriorates sharply: he becomes pale, apathetic, and his interest in the environment decreases. In some cases, confusion, delirium, and even hallucinations are observed. This condition is called “typhoid fever” and is associated with damage to the central nervous system by toxins. At this stage, characteristic signs appear on the skin - roseola. They are small pink spots located mainly in the abdomen and chest, which temporarily disappear when pressed. Roseola usually persists for a short time, but can reappear. Serious changes also occur in the intestinal system: abdominal distension increases, pain appears, diarrhea or constipation persists. Pain, especially in the right iliac region, is associated with damage to Peyer's patches. The liver and spleen enlarge,



which indicates increased activity of the reticuloendothelial system. The tongue during this period takes on a very characteristic appearance: it is dry, covered with a brown or gray coating in the center, and the edges are clean and red. In the cardiovascular system, arterial pressure decreases, the pulse slows down. Due to general intoxication, metabolic processes in the body are disrupted. It is during this period that the most dangerous complications of the disease can develop. The ulcers in the intestinal wall deepen, causing intestinal bleeding or perforation of the intestinal wall. This is a life-threatening condition. The final stage of the disease is the period of recovery or convalescence. If the patient is treated in a timely and correct manner, a gradual recovery process begins during this period. The body temperature gradually decreases, the general condition improves, and the appetite is restored. The patient's sleep returns to normal, and intestinal activity normalizes. However, during this period, the body has not yet fully recovered, so the patient quickly gets tired and remains weak. In some cases, a relapse of the disease or a state of bacterial carriage may develop.

Treatment of typhoid fever

Treatment of typhoid fever is carried out in a complex manner and includes etiological (elimination of the pathogen), pathogenetic (correction of disorders in the body) and symptomatic (reduction of symptoms) directions. Treatment is usually carried out in a stationary setting, that is, in a hospital, since the disease can be accompanied by severe complications. The most important part of treatment is etiological therapy, that is, the use of antibiotics against *Salmonella typhi*. The following antibiotics are widely used in modern medicine:

- — fluoroquinolones (for example, Ciprofloxacin),
- — 3rd generation cephalosporins (for example, Ceftriaxone),
- — macrolides (for example, Azithromycin).

The choice of antibiotic is determined depending on the patient's condition, the severity of the disease and the sensitivity of the bacteria to drugs. Treatment usually lasts 7–14 days. It is very important to take the full course of antibiotics, otherwise the disease may relapse or bacterial carriage may develop. Pathogenetic treatment is aimed at reducing intoxication in the body and restoring impaired functions. For this purpose, detoxification therapy is carried out, that is, intravenous fluids are administered (saline solution, glucose solutions). This helps to remove toxins from the body. In severe cases, hemodialysis or other plasma-substituting solutions may be used. Symptomatic treatment is aimed at relieving the symptoms observed in the patient. When the fever is high, antipyretic drugs, such as Paracetamol, are used. When intestinal function is impaired, appropriate medications are prescribed. When the cardiovascular system is weakened, heart-supporting drugs can be used. Diet is also important in typhoid fever. The patient should eat foods that are easily digestible and do not irritate the intestines. Mostly liquid and semi-liquid foods are recommended: soups, porridges, boiled vegetables. Spicy, fatty, fried foods are prohibited. It is recommended to drink plenty of fluids. It is necessary to strictly observe bed rest, especially during the exacerbation of the disease. This plays an important role in preventing complications such as intestinal perforation or bleeding. The patient should avoid physical exertion. In cases of developing complications, special measures are taken. For example, hemostatic agents are used in case of intestinal bleeding, and surgical intervention is required in case of intestinal perforation. In case of infectious-toxic shock, resuscitation measures are carried out. After treatment, the patient should be under medical supervision for a certain period of time, even after complete recovery. The main goal of treatment is to eliminate the causative agent *Salmonella typhi* from the body, reduce intoxication,



eliminate pathological changes in the intestines and other organs, and prevent complications. Therefore, treatment is carried out comprehensively and includes several directions. First of all, the patient must be treated in a hospital setting, since typhoid fever is a contagious and potentially severe disease. During the exacerbation of the disease, strict bed rest is prescribed, since physical activity can increase pressure on the intestinal wall and increase the risk of intestinal bleeding or perforation. The patient should rest completely and avoid excessive exercise. The most important part of treatment is etiological therapy, that is, the use of antibiotics against bacteria. Currently, the most commonly used drugs against typhoid fever include Ceftriaxone, Ciprofloxacin, and Azithromycin. These antibiotics stop the growth of bacteria and help eliminate them from the body.

The course of treatment is usually 7–14 days, and sometimes longer in severe cases. It is very important to take the full course of antibiotics, because if treatment is stopped early, the likelihood of relapse or bacterial carriage increases. Pathogenetic treatment is aimed at correcting the disorders that have occurred in the body. Due to the development of severe intoxication in typhoid fever, detoxification solutions are administered to the body. For this, saline solution, glucose solutions, and, if necessary, plasma substitutes are administered intravenously. These measures improve blood circulation, help to remove toxins more quickly, and alleviate the general condition. Symptomatic treatment is aimed at reducing the symptoms observed in the patient. In case of high fever, antipyretics, such as Paracetamol, are used. In case of abdominal pain, pain, or intestinal disorders, the doctor will prescribe appropriate medications. In cases of heart failure, heart support drugs may be given. Diet (diet therapy) plays a very important role in typhoid fever. The patient should eat easily digestible foods that do not irritate the intestines. Liquid and semi-liquid foods are mainly recommended: soups, liquid porridges, boiled vegetables and lean dishes. Fatty, fried, spicy and hard-to-digest foods are strictly prohibited. The patient should also drink plenty of fluids, as this helps reduce intoxication. In some cases, especially in severe cases of the disease, vitamins, immunostimulants and liver-protecting drugs can be used as additional therapy. This speeds up the recovery process of the body. If complications develop, treatment becomes more complicated. For example, if intestinal bleeding is observed, hemostatic drugs and blood substitutes are used. In case of intestinal perforation, urgent surgical intervention is required. In patients with infectious-toxic shock, resuscitation care, intensive therapy and potent intravenous drugs are used. The post-disease period is also important, as the patient remains under surveillance for some time after recovery. This is because the bacteria can persist in the body and become chronic carriers. In such cases, the patient, even if he or she appears healthy, can become a source of infection.

Conclusion

Typhoid fever is an infectious disease caused by *Salmonella typhi*, characterized by a severe course and a long duration, which is accompanied by complex pathogenetic processes that develop gradually in the body. Clinical symptoms of the disease begin gradually, and then manifest as increasing fever, general intoxication, intestinal damage, and changes in the central nervous system. These symptoms are directly related to the incubation, initial, exacerbation, and recovery stages of the disease. The main danger of the disease is the possibility of severe complications. Conditions such as intestinal bleeding, intestinal perforation, and infectious-toxic shock pose a serious threat to the patient's life. Therefore, early detection and prompt treatment of typhoid fever are important. Although modern medicine has the ability to effectively treat the disease with antibiotics, the emergence of drug-resistant strains further complicates the problem. Therefore, treatment is not limited to medications alone, but also includes a comprehensive approach - bed rest, proper diet, detoxification, and symptomatic therapy.



REFERENCES

1. Jawetz, Melnick & Adelberg. Medical Microbiology. 28th Edition. McGraw-Hill Education. (Salmonella typhi, qorin tifi etiologiyasi, patogenezini va klinikasi bo'limlari)
2. Murray, Rosenthal & Pfaller. Medical Microbiology. 9th Edition. Elsevier. (Enterobacteriaceae oilasi va typhoid fever bo'limi)
3. Sherris. Medical Microbiology. 7th Edition. McGraw-Hill. (Qorin tifi patogenezini va immun javob mexanizmlari)
4. Mandell, Douglas, and Bennett. Principles and Practice of Infectious Diseases. 9th Edition. Elsevier. (Typhoid fever, klinik kechishi va davolash tamoyillari)
5. World Health Organization (WHO). Typhoid Fever Fact Sheet. (Kasallik tarqalishi, epidemiologiya va profilaktika ma'lumotlari)
6. O'zbekiston Respublikasi tibbiyot oliy ta'lim muassasalari uchun "Mikrobiologiya" darsligi. (Enterobakteriyalar, Salmonella typhi va yuqumli kasalliklar bo'limi)
7. Yuqumli kasalliklar (Infeksion kasalliklar) klinik qo'llanma. (Qorin tifining klinikasi, davolash va asoratlari bo'yicha ma'lumotlar)