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SUMMARIES OF LECTURES ON INTESTINAL INFECTIONS

Manual

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The manual covers frequently occurring acute intestinal infections in adults and children, provides information on etiology and pathogenesis. It also covers the epidemiological aspects and prevention of these diseases. The manual is intended for independent classroom and extracurricular study of students at medical universities in the specialty “General Medicine” in English.

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CONTENT

INTRODUCTION

Acute intestinal infections are diseases of various etiologies, but with common epidemiological patterns, similar pathogenetic mechanisms of clinical manifestation and development of diarrheal and toxic syndromes. The problem of intestinal infections is one of the most pressing in the countries of the Asian subcontinent. 70% of cases of intestinal infections are diseases with an unspecified pathogen, which explains the "syndromic" approach to establishing a diagnosis of this group of infections.

The proposed training manual presents the most common and frequently encountered intestinal infections. In epidemic intestinal infections, earlier isolation and identification of the pathogen become the most important task, which, unfortunately, requires significant time and a well-equipped laboratory. Therefore, conducting a differential diagnosis to begin adequate therapy is the most necessary skill in the daily practice of physician of any specialization.

CHOLERA

Definition

Cholera is an acute anthroponous infectious disease characterized by watery diarrhea, with rapid development of dehydration and moderate symptoms of intoxication.

Etiology

The causative agent of cholera, Vibrio cholerae, belongs to the genus Vibrio of the family Vibrionaceae. Cholera vibrio is a slightly curved gram-negative pleomorphic bacterium. It is highly mobile, does not form spores or capsules, is a facultative anaerobe, and resembles a school of fish in a smear.

V. cholerae has a somatic O-antigen and a flagellar H-antigen (serogroup O139 has a capsular K-antigen). According to the structure of the O-antigen, more than 200 serogroups (206) are distinguished, and only serogroup O1 and serogroup O139 (V. cholerae bengal) are the causative agents of cholera in humans. V. cholerae serogroup O1 is divided into biovars Cholerae and Eltor. Within serogroup O1 (both biovars), three O-antigens are distinguished – A, B, C, by the combination of which such serovars as Ogawa (AB), Inaba (AC) and Hikoshima (ABC) were identified. The H-antigen is a heat-labile protein flagellin. This antigen is common to the entire genus Vibrio. The cholera pathogen also has pili (fimbriae) – thin flexible thread-like formations on the surface of the bacterial cell. The cholera pathogen has pathogenicity factors:

- ✓ The flagellum, which determines the mobility of the bacterium, which is one of the diagnostic signs of the pathogen;
- ✓ Pili necessary for colonization of the microvilli of the small intestine and participating in the formation of biofilm on the body surface of aquatic inhabitants;

- ✓ Enzymes (mucinase, protease, lecithinase) that promote adhesion and colonization by destroying substances that are part of the intestinal epithelial mucus;
- ✓ Exotoxin is a choleragen, which is the main factor that determines the pathogenesis of the disease.

In the external environment, the V. Cholerae is sensitive to drying, UV radiation, at 50°C they die in 30 minutes, at 80°C – in 5 minutes, at 100°C – in a few seconds. Cholera vibrios are very sensitive to disinfectants. It is well preserved and reproduced at temperatures above 10–12°C. In open water bodies and wastewater rich in organic matter, the pathogen persists for 2–3 weeks; in sea water – up to 47 days, in river water – from 3–5 days to several weeks, in soil – from 8 days to 3 months, in fresh feces of the patient it persists for up to 3 days, on linen contaminated with feces of patients – up to 2 days, on damp material – a week, on boiled products (rice, noodles, meat, cereals, etc.) V. Cholerae survive for 2–5 days, on raw vegetables – 2–4 days, on fruits – 1–2 days, in milk and dairy products – 5 days. In the refrigerator, the survival period of the pathogen increases by 1–3 days.

Epidemiology

Cholera is a typical anthroponosis infection. The reservoir of infection is contaminated water; the source of infection is a sick person from the first days of the disease and a bacteria carrier. A person sick with cholera releases from 10 million to 1 billion vibrios into the external environment in 1 ml of feces, and a bacteria carrier – up to 100 thousand microbial cells. Persons who have recovered from the disease excrete the cholera vibrio for 7–10 days after symptomatic recovery. The infectious dose is about 1 million microbial cells. The main transmission mechanisms are faecal-oral and household. Transmission factors are water, food products, and environmental objects. The routes of cholera infection are water (through water used for drinking, bathing, and household needs), alimentary (food), and contact. Susceptibility to cholera is universal. People with low gastric

acidity (chronic gastritis, pernicious anemia, helminthic invasions, alcoholism) are most susceptible to the disease. Cholera typically occurs in the summer and autumn.

Pathogenesis

The entry point for cholera infection is the digestive tract. Once in the human body, a significant portion of the vibrios dies in the stomach under the action of hydrochloric acid. The disease develops only when the pathogens overcome the gastric barrier. The remaining part of the pathogen reaches the small intestine, the alkaline environment of which is favorable for the reproduction of the cholera vibrio. Cholera is a non-invasive infection, since the vibrios are localized on the surface of the mucous membrane and in the lumen of the small intestine, without penetrating into the enterocytes. Having overcome the mucus layer on the surface of the small intestine, the cholera vibrios attach to the mucous membrane of the small intestine. After adhesion, the cholera vibrio produces an exotoxin.

Exotoxin, or choleragen, or CT (cholera toxin) is the main factor determining the development of the disease, i.e. cholera is a toxin-mediated infection. CT consists of components A and B. Component B performs the function of binding the vibrio to enterocytes, and component A performs a catalytic (toxic) function. Component B recognizes a specific receptor (ganglioside Gm1) on the surface of the enterocyte, binds to it and forms an intramembrane channel for the passage of component A into the cell. Then, component A penetrates the cell cytoplasm by endocytosis and, under the action of intracellular enzymes, releases the active fragment A1. This fragment interacts with protein G, localized on the inner surface of the cell membrane, and blocks its inhibitory effect on adenylate cyclase, resulting in an increase in the concentration of cyclic adenosine monophosphate (cAMP) inside the cell. Hyperproduction and accumulation of large amounts of cAMP disrupts the function of the transmembrane electrolyte pump in enterocytes: channels open for the release of chlorine, sodium, potassium, hydrocarbonate

ions and water (Na^+, HCO_3^-, K^+, Cl^-, H_2O) into the intestinal lumen. Violation of the water-salt balance leads to vomiting and diarrhea, in which the body loses up to 2 liters of water per hour. The volume of feces can reach 20-30 liters per day, resulting in dehydration. The stool acquires a characteristic "rice water" consistency due to the presence of intestinal epithelial cells in the saline solution. Loss of water and electrolytes leads to severe dehydration, shock due to hypovolemia, hypokalemia and metabolic acidosis, seizures, cholera algid and intestinal paresis.

Clinical classification

I. According to the type:
   1) Typical type.
   2) Atypical type:
      - ✓ Hypertoxic;
      - ✓ Dry cholera
      - ✓ Latent
      - ✓ Subclinical

II. According to the severity:
   1) Mild;
   2) Moderate;
   3) Severe.

III. According to the course:
   1) Acute (up to 1.5 months).
   2) Carriage of vibrios.

Clinical manifestations

The incubation period lasts from several hours to 6 days, on average 1–2 days. The onset of the disease is acute. The main symptoms of the initial period of cholera are: diarrhea, vomiting, convulsions.

Diarrhea. The disease begins suddenly with diarrhea. The release of feces occurs without pain, involuntarily. The patient constantly leaks a massive amount of fluid, which can reach 6 liters in 24 hours.

The evolution of the stool is a differential sign. After turning into a turbid liquid, without any traces of bile, whitish grains appear in the feces. The stool takes on the character of "rice water". These grains contain leukocytes, drops of fat and epithelial cells and, of course, V. Cholerae. A characteristic feature is the sweetish "fishy" (not fecal) smell of the feces (the smell of raw grated potatoes).

Vomiting occurs a few hours after diarrhea. If these two symptoms are not managed, they will inevitably lead to death.

Cramps. They initially occur in the calf muscles, but can occur anywhere. When palpated, the muscles are rigid.

A patient with cholera is apathetic, constantly thirsty, but an attempt to swallow provokes vomiting. As dehydration increases, the patient develops a characteristic appearance – the skin is dry, wrinkled, does not smooth out. The face is characteristic: sunken eyes, sharpened features, dry and purple lips. The abdomen is sunken.

According to Pokrovsky's classification (1978), there are 4 degrees of exsicosis: at degree I, fluid loss is up to 3% of body weight, degree II – 4–6%, degree III – 7–9%, degree IV – 10% or more.

Dehydration I degree:

At this degree of dehydration, many symptoms of cholera are not expressed, the disease is abortive. The first symptom of the disease is loose stool, in 2/3 of patients it is watery and 1/3 mushy, in 5% it can be formed.

Diarrhea from 3-4 to 10 times a day. Duration of diarrhea is no more than 3 days. Stools are not abundant. Vomiting is observed in half of the patients. The skin is moist, turgor is unchanged, there is no cyanosis. In 2/3 of patients, dryness of the oral mucosa. Hemodynamics are not impaired.

Dehydration II degree.

This degree of dehydration develops in approximately 20% of cases. In most cases, the prodrome is not expressed or is short-term.

The onset of the disease is characterized by the appearance of loose stools, which quickly become watery and in 1/2 of patients resemble "rice water". Vomiting is observed 5–10 times a day. The total loss of fluid with diarrhea and vomiting averages 5–6 liters. Patients quickly experience weakness, dizziness and fainting. Blood pressure decreases, the pulse quickens (100 beats per minute). Temperature decreases. Urine excretion decreases. Dry mouth, pale and dry skin, decreased skin turgor, acrocyanosis, and cramps in the calf muscles are characteristic. Signs of hemoconcentration are minimal, due to compensatory dilution (Ht = 0.46–0.50%). Electrolyte disturbances are compensated. Compensated acidosis (pH 7.36–7.40; buffer capacity-2-5 mmol/l). Hypokalemia, hypochloremia.

Dehydration III degree.

Dehydration degree III occurs in approximately 10% of patients during the outbreak. The onset is acute and stage III dehydration develops after 10–12 hours. Stool and vomiting in the form of "rice water". Vomiting more than 20 times a day. Adynamia, thirst, agitation, muscle cramps in the extremities (usually in the calves) are observed, subfebrile temperature, facial features are sharpened, eyeballs are sunken, the "dark glasses" symptom, skin turgor is sharply reduced, the voice is hoarse, speech is in a whisper. Pulse is 120 beats per minute, threadlike. BP is less than 50 mm Hg. Oliguria to anuria. Hemoconcentration (Ht – 0.55%). Decompensated acidosis. Hypokalemia. Hypochloremia.

Dehydration IV degree

Algide (Latin algidus – cold) is decompensated dehydration, since the body is unable to maintain water-salt homeostasis. Patients experience profuse watery stool and vomiting, severe muscle cramps, a drop in blood pressure, shortness of breath, and cyanosis of the skin. As a result of dehydration, facial features become sharper, eyes become sunken, the voice becomes hoarse, and sometimes aphonia is observed. A characteristic sign of dehydration is the "Hippocratic face" (facies hippocratica): sunken eyes, sharpened facial features with sharply

protruding cheekbones. The skin is wrinkled, “washerwoman’s hands”, hypothermia (body temperature drops to 30°C), no peripheral pulse and blood pressure, tachypnea, anuria. The skin is cold, covered with sticky sweat, the “dark glasses” symptom, the eyeballs roll back. The patient’s face and appearance express suffering. Cramps are constant. When cramping the arms, an "Obstetrician's hand" spasm is observed. In some patients, a “horse foot” is detected or the foot freezes in a sharply extended position. Convulsive contractions of the diaphragm cause excruciating hiccups. Cholera algid is always accompanied by acute renal failure.

Convalescence stage:

- ✓ A pulse appears;
- ✓ Breathing becomes easier, the patient calms down;
- ✓ Cyanosis and cooling of the skin, as well as sticky secretion of the skin disappear, body temperature normalizes;
- ✓ The stomach restores its tone and retains food.
- ✓ The stool acquires a fecal character.
- ✓ Diuresis is restored.
- ✓ Physical activity is gradually restored.

Diagnosis

The diagnosis of cholera is based on clinical and epidemiological data confirmed by laboratory tests.

Clinical and epidemiological criteria:

- ✓ Staying in an endemic region;
- ✓ Sudden onset of diarrhea;
- ✓ Normal or subfebrile temperature;
- ✓ Stool and vomiting like rice water;
- ✓ Involuntary defecation, gaping anus, projectile vomiting;
- ✓ Absence of pain syndrome;
- ✓ The leading syndrome is dehydration (exicosis);
- ✓ There is no intoxication.

Laboratory diagnostics:

- ✓ There are no signs of inflammation in the complete blood count, but there are signs of hemoconcentration (increased hematocrit, thrombocytosis);
- ✓ Bacteriological test:

The material for research is feces, vomit, bile, autopsy material (fragments of the small intestine and gall bladder), bed linen and underwear contaminated with feces, water, silt, waste water, hydrobionts, swabs from environmental objects, food products. To detect the carriage of bacteria, feces are examined.

- ✓ Fluorescent antibody test (FAT), polymerase chain reaction (PCR), and indirect hemagglutination assay (IHA) are also used.

Treatment

If cholera is suspected, patients are hospitalized in specialized units.

The main goals of multipurpose therapy for cholera are:

- ✓ relief or prevention of dehydration, which should be considered as an urgent measure;
- ✓ restoration of acid-base balance and hemodynamics (micro-circulation);
- ✓ restoration of hemostasis disorders;
- ✓ impact on the pathogen;
- ✓ prevention and elimination of disorders of various organs and systems of the body.

Infusion therapy should be performed as soon as possible. Rehydration is performed in 2 stages (both oral and intravenous):

Stage I of rehydration is aimed at compensating for fluid loss that developed before the start of therapy (initial or primary rehydration).

Primary oral rehydration. Its volume and regime depend on the degree of dehydration and the age of the patient and is carried out during the first 4 hours with an oral rehydration solution (ORS).

In patients with dehydration I degree, oral solutions are used in a volume of 30–40 ml/kg per hour. The volume of liquid taken orally should be 1.5 times greater than the volume of urine and feces.

In cases of severe **(III–IV**) degree dehydration or when ORS cannot be taken due to frequent vomiting, *primary rehydration* begins with intravenous fluid administration. Standard saline solutions such as Trisol, Disol, Acesol, Khlosol, Ringer's solution, Quartasol, and Laktasol are used.

Primary intravenous rehydration for children over 1 year of age and adults is carried out in a volume of 100 ml/kg for 3 hours (30 ml/kg in the first 30 minutes and 70 ml/kg over the next 2.5 hours).

Infusion is carried out with constant half-hour monitoring of the pulse (frequency, filling) and blood pressure for timely correction of the rate of administration of solutions. When the ability to swallow appears, infusion therapy is supplemented with oral rehydration in a volume of 5 ml/kg/h.

Stage II of rehydration therapy is compensatory rehydration, carried out taking into account the ongoing loss of fluid with vomiting and diarrhea. At the end of primary rehydration, the patient's condition is monitored to determine the evolution of dehydration and hemodynamics (heart rate, blood pressure, electrolyte content hematocrit, restoration of diuresis etc.)

After vomiting has stopped and hemodynamic disturbances have been eliminated, the required volume of fluid, with preserved renal function, can be administered orally. The volume of fluid should be equal to the amount of fluid lost with feces.

Etiotropic therapy

Etiotropic therapy is indicated for any degree of cholera severity (including latent course) both in the acute period and in the period of early convalescence. The following are recommended as etiotropic agents:

- ✓ furazolidone,
- ✓ trimethoprim/sulfamethoxazole,
- ✓ erythromycin,
- ✓ chloramphenicol,
- ✓ ciprofloxacin,

Tetracycline and doxycycline are used in people over 8 years of age.

The duration of antibacterial therapy, regardless of the drug chosen and the degree of dehydration, is 5 days. Antimicrobial therapy accelerates recovery, reduces the need for rehydration, and shortens the time of excretion of the pathogen.

Recovery criteria:

- ✓ persistent normalization of temperature (for more than 24 hours);
- ✓ absence of intoxication;
- ✓ disappearance of dehydration;
- ✓ normalization of stool;
- ✓ normalization of laboratory parameters.

Prevention

Non-specific:

- ✓ sanitary supervision of food and water supply;
- ✓ anti-epidemic measures in cholera outbreaks include: early detection, isolation and hospitalization of patients, detection and treatment of carriers of the bacteria.

Specific:

Specific prevention of cholera has not found wide application and has an auxiliary value; most authors consider vaccination against cholera to be unjustified. Oral cholera vaccines (OCVs) are safe and provide effective immunity against cholera caused by V. cholerae. They are administered in a 2-dose course, with booster doses recommended 2 years after completion of vaccination for people at risk of cholera infection.

ESCHERICHIOSIS

Definition

Escherichiosis is a group of bacterial anthroponotic infectious diseases caused by pathogenic (diarrheagenic) strains of Escherichia coli and characterized by toxic and gastrointestinal syndromes.

Etiology

Escherichia coli (E. coli) are facultative anaerobic, gram-negative bacteria that are members of the Enterobacteriaceae family. Most intestinal E. coli do not cause diarrhea. E. coli is a commensal intestinal flora, but pathogenic strains are virulent and associated with disease.

E. coli contain somatic (O-antigens – 173 serotypes), capsular (K-antigens – 73 serotypes) and flagellate (H-antigens – 56 serotypes). Based on clinical, biochemical and genetic criteria, 6 main categories of E. coli (diarrheagenic E. coli) were characterized:

1) Enterotoxigenic E. coli (ETEC);
2) Enteroinvasive E. coli (EIEC);
3) Enteropathogenic E. coli (EPEC);
4) Shiga toxin-producing E. coli (STEC), also known as entero-hemorrhagic;
5) Enteroaggregative E. coli (EAEC or EggER);
6) Diffusely adhesive E. coli (DAEC).

E. coli are stable in the environment and can survive for months in soil and feces. They tolerate drying well. They have the ability to reproduce in food products, especially in milk. They quickly die when exposed to disinfectants, instantly when boiled, and after 10 minutes at 60°C. Many strains of E. coli are polyresistant to antibiotics.

Epidemiology

In developing countries, the various escherichiosis (diarrheagenic E. coli) are common infections during the first few years of life; E. coli are responsible for 30–40% of all cases of childhood diarrhea worldwide. Increased incidence (seasonality) of escherichiosis occurs during the warm months in temperate climates and during the rainy months in tropical climates.

The main source of infection are patients with escherichiosis (usually inapparent infection); carriers of bacteria are less significant as a source of infection, since a large dose of inoculum is required for the disease to occur.

The transmission mechanism is fecal-oral. This mechanism is realized by food, and the main factors of transmission are milk and dairy products. The second most important is the water route of infection transmission. In some cases, especially in diseases caused by EPEC, household spread of the disease occurs.

Susceptibility to escherichiosis is significantly higher in childhood. Moreover, EPEC causes diseases only in children under 2 years of age.

Immunity. The incidence of the disease decreases rapidly by the age of 4 and remains low in all subsequent age groups, indicating the development of immunity.

Pathogenesis and clinical manifestations

The mechanisms of the pathological process in E. coli infections depend on the category of the pathogen.

ENTEROTOXIGENIC ESCHERICHIOSIS (ETEC)

ETEC account for a significant proportion of dehydrating childhood diarrhea in developing countries (10–30%) and travellers' diarrhea (20–60% of cases).

ETEC cause little or no structural damage to the intestinal mucosa. Diarrhea is caused by colonization of the small intestine and subsequent production of enterotoxins. ETEC strains secrete heat-labile and/or heat-stable enterotoxins. Heat-labile enterotoxin is a large molecule consisting of 5 receptor-binding subunits and 1 enzymatically active subunit, structurally, functionally, and immunologically similar to cholera toxin produced by Vibrio cholerae. Heat-labile enterotoxin stimulates adenylate cyclase, resulting in increased levels of cyclic adenosine monophosphate. Heat-stable enterotoxin is a small molecule that also, like cholera toxin, stimulates guanylate cyclase, resulting in increased levels of cyclic guanosine monophosphate.

Colonization of the intestine requires fimbriae, which facilitate adhesion to the intestinal epithelium. ETEC strains also share pili produced by commensal and pathogenic E. coli strains. Among the non-fimbrial adhesion factors is the TibA protein, a potent bacterial adhesin that mediates bacterial attachment and invasion of cells.

Of the more than 180 serogroups of E. coli, only a relatively small number are typically ETEC. The most common representatives of this category of escherichiosis are O6, O8, O128, and O153.

Typical signs and symptoms include explosive, watery, non-mucous, non-bloody diarrhea, abdominal pain, nausea, vomiting, and low or no fever. The illness is usually self-limited and resolves in 3-5 days, but sometimes lasts longer than 1 week.

ENTEROINVASIVE ESCHERICHIOSIS (EIEC)

EIEC strains behave like Shigella in their ability to invade intestinal epithelium and cause dysentery-like disease. The invasive process involves initial cell entry, intracellular replication, intra- and intercellular spread, and host cell death.

EIEC comprises a small number of serogroups (O28ac, O29, O112ac, O124, O136, O143, O144, O152, O159, O164, O167). These serogroups,

like Shigella, are non-motile (they lack H or flagellar antigens) and do not usually ferment lactose. EIEC cause colonic lesions with ulceration, hemorrhage, mucosal and submucosal edema, and polymorphonuclear leukocyte infiltration.

EIEC manifests itself as dysentery syndrome with blood, mucus and leukocytes in the stool, as well as fever, intoxication, spastic abdominal pain, tenesmus and imperative urges. The disease resembles bacterial dysentery.

ENTEROPATHOGENIC ESCHERICHIOSIS (EPEC)

EPEC is a major cause of acute and persistent diarrhea in children under 2 years of age in developing countries (20% of diarrhea in infants).

EPEC colonization causes villous flattening, inflamation, and sloughing of superficial mucosal cells; these changes are found from the duodenum to the colon. These morphologic changes are associated with tight attachment of bacteria to the epithelial surface and abrasion of host cell microvilli, leading to malabsorption.

Profuse watery, non-bloody diarrhea with mucus, vomiting, and low-grade fever are common symptoms. Prolonged (>7 days) and persistent (>14 days) diarrhea may lead to malnutrition, a potentially serious outcome of EPEC infection in infants in developing countries.

Typical EPEC serogroups include strains from 12 serogroups O: O26, O55, O86, O111, O114, O119, O125, O126, O127, O128, O142, and O158.

ENTEROGEMORRAGIC ESCHERICHIOSIS (EHEC) (Shiga toxin-producing E. coli (STEC), Verotoxin-producing E. coli strains)

STEC most commonly infect the colon. These organisms attach to intestinal cells, and most strains that infect humans cause flattening and effacement of the microvilli of the intestinal epithelium, similar to that seen in EPEC. In addition to attaching to enterocytes, these

bacteria produce toxins that destroy the cells. These toxins (Shiga toxins [Stx]) are key virulence factors in STEC. In the past, these toxins were also called verotoxins or Shiga-like toxins. There are two main families of Shiga toxins, Stx1 and Stx2. Some STEC produce only Stx1, and others produce only one variant of Stx2, but many STEC have genes for multiple toxins. It is believed that toxins enter the bloodstream after translocation through the intestinal epithelium and damage vascular endothelial cells, leading to activation of the coagulation cascade, formation of microthrombi, intravascular hemolysis and ischemia.

The outcome of STEC infection depends on both epithelial adherence and the toxin(s) produced by the infecting strain. The Stx2 family of toxins is associated with a higher risk of hemolytic uremic syndrome (HUS). Strains that produce only Stx1 often cause only watery diarrhea and are rarely associated with HUS.

STEC cause a wide range of diseases. STEC infections may be asymptomatic. Patients who develop intestinal symptoms may have mild diarrhea or severe hemorrhagic colitis. Gastrointestinal disease is characterized by abdominal pain with diarrhea that is initially watery but may become bloody or severely bloody within a few days. Although the presentation resembles shigellosis or EIEC disease, it differs in that fever is a rare manifestation. Most people infected with STEC recover from the infection without complications. However, 5–10% of children with STEC hemorrhagic colitis develop complications such as hemolytic uremic syndrome (HUS) (Gasser syndrome) within a few days, characterized by acute renal failure, thrombocytopenia, and microangiopathic hemolytic anemia. Severe disease most often occurs in children aged 6 months to 10 years. Younger children who test positive for STEC, have bloody diarrhea, and neutrophilic leukocytosis in the early stages of diarrhea are at risk of progression to HUS. Older adults may also develop HUS or thrombotic thrombocytopenic purpura.

The most common STEC serotypes are O157:H7, O111:NM, and O26:H11, although several hundred other STEC serotypes have also been described. E. coli O157:H7 is the most virulent serotype and is most commonly associated with HUS; however, serotypes other than O157 also cause the disease.

ENTEROAGGREGATIVE ESCHERICHIOSIS (EAEC)

EAEC is associated with acute persistent diarrhea in children in developing countries, predominantly children under 2 years of age and malnourished children; acute and persistent diarrhea in HIV-infected adults and children; and acute travellers' diarrhea, in which EAEC is the second most common diarrhoea after ETEC.

EAEC form a biofilm on the intestinal mucosa and induce villus shortening, hemorrhagic necrosis and inflammation. The described model of EAEC pathogenesis includes 3 phases:

1) adhesion to the intestinal mucosa by aggregation of adherent fimbriae or fimbrial-related adhesins;
2) increased mucus production;
3) production of toxins and inflammation, which lead to damage to the intestinal mucosa and increased intestinal secretion;

Diarrhea caused by EAEC is predominantly of a secretory mechanism. Virulence factors of EAEC include AA fimbriae, some strains produce toxins including enterotoxin, and virulence factors include the bacterial outer membrane and secreted proteins such as dispersin and dispersin-transporting complex.

Typical enteroaggregative E. coli infection presents with watery, mucous, diarrhea, mild fever, and mild vomiting. Diarrhea may last 14 days or more. In some studies, most patients had copious bloody stools.

E. coli strains classified as EAEC include O3, O7, O15, O44, O77, O86.

DIFFUSE-ADHESIVE ESCHERICHIOSIS (DAEC)

Although the consideration of diffusely adherent Escherichia coli strains as pathogens is questionable, multiple studies in both developing and developed countries have shown an association of Escherichia coli of this category with diarrhea, particularly in children over 1–2 years of age.

DAEC strains have been identified based on their diffuse adhesion pattern on cultured epithelial cells. Two adhesion factors have been described for DAEC strains. One adhesion factor is the surface fimbriae (designated F1845), and the second adhesin associated with diffuse adhesion is an outer membrane protein designated AIDA-I. The only documented secreted factor associated with DAEC infection is SPATE Sat. Bacteria producing adhesins interact with membrane-bound receptors including breakdown-accelerating factor. Structural and functional lesions caused by DAEC include loss of microvilli and decreased production and enzymatic activity of functional brush border-associated proteins. DAEC produce a secreted autotransporter toxin that causes marked fluid accumulation in the intestine. Serogroups of DAEC strains are less well defined than those of other diarrheagenic E. coli.

Clinical classification

I. According to the type:
   1) Typical type.
   2) Atypical type
   - ✓ inapparent
   - ✓ colisepsis
   - ✓ asymptomatic (carrier)

II. According to the severity:
   1) Mild;
   2) Moderate;
   3) Severe.

III. According to the course:

1) Acute;
2) Progressive (more than 1,5 months)

- ✓ Uncomplicated.
- ✓ Complicated

Diagnosis

1) The clinical manifestations of escherichiosis are similar to those of other diarrheal infections. The diagnosis is confirmed by bacteriological testing. The diagnosis of Escherichia coli is valid only with bacteriological confirmation.

2) To isolate bacteria, feces, vomit, gastric lavage, blood, urine, cerebrospinal fluid, and bile are examined. They should be collected in the first days of the disease before the etiotropic therapy is prescribed. The culture is performed on Endo, Levin, Ploskirev, and Muller enrichment media.

3) Polymerase chain reaction (PCR);

4) Immunological tests are not conclusive, as false positive results are possible due to antigenic similarity with other enterobacteria. These methods are used for retrospective diagnosis, especially during an outbreak.

Treatment

Hospitalization of patients with escherichiosis is carried out according to clinical and epidemiological indications. Children with moderate and severe types of the disease are hospitalized. In mild cases, patients can be treated in outpatient settings. During the acute period of the disease, frequent breastfeeding is recommended.

In mild cases of escherichiosis, oral rehydration therapy (regidron and other solutions) is sufficient. Enzymes and enterosorbents are indicated for 1–3 days. Such cases of escherichiosis do not require antibiotics.

When treating patients in a hospital setting, bed rest is indicated for the first 2–3 days. In severe and moderate cases, antibacterial therapy is prescribed:

First line antibiotics:

Cefixime 8 mg/kg/day orally or Ceftibuten 9 mg/kg/day orally.

Second line antibiotics:

Ceftriaxone 50–100 mg/kg/day parenterally or

Ciprofloxacin 25–50 mg/kg/day – orally or Ciprofloxacin 25–50 mg/kg/day – IV. After a course of antibacterial therapy, probiotics are indicated for ongoing diarrhea.

In case of nosocomial infection, the antibiotic of choice is Amikacin 15 mg/kg/day IV; alternative antibiotics are enhanced penicillins and carbapenems.

Dehydration management is carried out according to the usual rules.

STEC presents a complex therapeutic dilemma; many antibiotics can induce toxin production and phage-mediated bacterial lysis with release of toxins. Antibiotics SHOULD NOT be given for STEC INFECTION as they may increase the risk of HUS.

Prevention

In developing countries, prevention of illness due to diarrheagenic E. coli is probably best achieved through prolonged breastfeeding, careful personal hygiene, and proper food and water handling procedures.

There are multiple candidate vaccines based on bacterial toxins and colonization factors that have shown promise for the prevention of ETEC in adult travelers, however, long-term protection with these vaccines is suboptimal, particularly in children.

FOODBORNE TOXICOINFECTION (POISONING)

Definition

Foodborne toxicoinfection (poisoning) (FBT) is a short-term acute infectious disease caused by opportunistic bacteria and their exotoxins, which is characterized by damage primarily to the upper gastrointestinal tract (gastritis, gastroenteritis) and electrolyte imbalance with toxic syndrome.

Etiology

The causative agents of FBT are numerous representatives of various genera of bacteria belonging to the families Enterobacteriaceae (E. coli, Kl. aerogenes, Kl. pneumoniae, P. vulgaris, P. rettgeri, P. mirabilis, P. morganii, E. cloaceae, E. aerogenes C. freundii, P. alcalifaciens, S. marcesens, H. alvei, A. hinahavii, Pl. shigelloides), Vibrionaceae (V. parahaemoliticus, V. alginoliticus), Pseudomonaceae (Ps. aeruginosa), Micrococcaceae (St. aureus, St. epideridis), Streptococcaceae (Str. faecalis (enterococcus)). Most of these microorganisms live in the intestines of healthy people and many animals, and are capable of multiplying outside the body and producing exotoxins (enterotoxins and cytotoxins).

Enterotoxins are protein substances of bacteria that increase the secretion of water and salts into the lumen of the gastrointestinal tract. Cytotoxins are also protein molecules that damage the membranes of epithelial cells and cause inflammatory processes in them.

Both bacteria and their toxins are stable in the external environment over a wide range of temperatures. The destruction of bacteria both in food products and in the gastrointestinal tract is accompanied by the release of lipopolysaccharide components of microbes, which are endotoxins that are involved in the appearance of symptoms of FBT.

Epidemiology

The source of infection are various animals and people. Most often, these are people suffering from purulent diseases (panaritium, tonsillitis, furunculosis, etc.); among animals – cows and sheep suffering from mastitis. All of them secrete bacteria (usually staphylococci), which get into food products during their processing, where the bacteria multiply and accumulate. The mechanism of transmission of the infection is faecal-oral, the route of transmission is food only.

For the occurrence of FBT caused by opportunistic bacteria, a massive dose of pathogens or a certain time for its reproduction in food products is required. Most often, FBT are associated with contamination of milk, dairy products, canned fish in oil, meat, fish and vegetable dishes, as well as confectionery products containing cream. People are highly susceptible to FBT. Often 90–100% of people who have consumed an infected product become ill. FBT is characterized by group and explosive outbreaks (all participants in the outbreak become ill within a few hours). The incidence of FBT is recorded throughout the year, but more often in warm weather.

Pathogenesis

For the development of the infectious process, two conditions are necessary:

1) the infectious dose should be at least 10^5–10^6 microbes in 1 g of substrate;
2) virulence and toxicity of strains.

The produced exotoxins and their producers enter the stomach through the mouth and then into the proximal parts of the small intestine, where they bind to epithelial cells and change the enzymatic processes in epithelial cells without morphological disturbances.

Enterotoxin interacts with the adenylate and guanylate cyclase systems of the cell, increases the activity of cAMP and cGMP,

prostaglandins, histamine, interleukins, which leads to active secretion of water and salts into the intestinal lumen and the appearance of vomiting and diarrhea. Excitation of the chemoreceptors of the vomiting center located in the rhomboid fossa of the IV ventricle is important. Vomiting is a protective reaction aimed at removing toxic substances from the stomach. With prolonged vomiting, hypochloremic alkalosis may develop.

Cytotoxin damages the membranes of epithelial cells and disrupts protein-synthetic processes in them. This leads to increased permeability of the intestinal wall for various toxic substances (lipopolysaccharides, enzymes) of bacterial origin, and in some cases, the bacteria themselves. All this leads to the development of intoxication, disruption of microcirculation and inflammation in the mucous membrane of the stomach and intestines.

Thus, FBT caused only by the effect of enterotoxin is less severe and occurs, in most cases, without hyperthermia and any inflammation in the mucous membrane of the stomach and intestines. In cases where both enterotoxins and cytotoxins accumulate in food products, the disease is more severe, with a short-term but high temperature, inflammation of the mucous membrane of the gastrointestinal tract.

The self-limiting course of FBT is associated with a short-term presence of pathogens and the cessation of the action of toxins on epithelial cells after their desquamation. Unbound toxin molecules are inactivated by proteases.

Clinical classification

I. According to localization:
   1) Gastritis;
   2) Gastroenteritis;
   3) Gastroenterocolitis;

II. According to the severity:
   1) Mild;

2) Moderate;
3) Severe.

III. According to the course:
1) Uncomplicated.
2) Complicated.

Clinical manifestations

The incubation period varies from 30 minutes to 1 day (usually 2–6 hours).

The onset of the disease is acute with nausea followed by vomiting. Vomiting is repeated, with food eaten, then with bile. Vomiting is sometimes uncontrollable, debilitating. Diarrhea develops simultaneously with vomiting. The stool is loose, watery from 1 to 15 times a day, enteric without mucus and blood, foul-smelling, light yellow or brown. Pain of varying intensity and localization often occurs. Abdominal pain can be diffuse, cramping, less often constant. Fever is observed in 60–70% of patients. It can be subfebrile; in some patients it reaches 38–39°C, sometimes 40°C. The duration of fever is from several hours to 2–4 days. Sometimes (with staphylococcal intoxication) hypothermia is observed.

Physical findings include pale skin, shortness of breath, muscle weakness, chills, headache, joint and bone pain, tachycardia, hypotension, and muffled heart sounds. The abdomen is soft on palpation, painful not only in the epigastric region but also in the umbilical region. The tongue is coated with a white-gray coating and is dry. In some cases, fainting and short-term collapse states develop. Signs of dehydration may include dry skin and mucous membranes, decreased skin turgor, thirst, sharpened facial features, sunken eyes, pallor, cyanosis (acrocyanosis), tachycardia, hypotension, decreased diuresis, and muscle cramps in the extremities. The liver and spleen are not enlarged. The disease lasts 1–3 days.

Clinical manifestations of FBT do not depend on the type of pathogen, but sometimes it is possible to trace clinical and epidemiological "peculiarities" depending on the suspected pathogen.

Staphylococcal FBT. Poisoning is caused by enterotoxigenic strains of Staphylococci. They are resistant to environmental factors, tolerate high concentrations of salt and sugar, but die when heated to 80^0C. Staphylococcal enterotoxins can withstand heating to 100°C for 1–2 hours. Staphylococcal contaminated products are indistinguishable from benign products in appearance, taste, and smell. Enterotoxin is resistant to digestive enzymes, which makes it possible to absorb it in the stomach. It affects the parasympathetic nervous system, promotes a significant decrease in blood pressure, and activates the motility of the stomach and intestines.

The onset of the disease is acute and rapid. The incubation period is from 30 minutes to 4–6 hours. Intoxication is pronounced, fever up to 38–39°C, but can be normal or low. Intense epigastric pain is characteristic. Weakness, dizziness, and nausea are also noted. 50% of patients' experience repeated vomiting for 1–2 days, diarrhea lasts 1–3 days. In severe cases, tachycardia, muffled heart sounds, hypotension, and oliguria are characteristic. Short-term loss of consciousness is possible. In the vast majority of patients, the disease ends in recovery, but in weakened patients and the elderly, pseudomembranous colitis and staphylococcal sepsis may develop. The most severe complication is infectious toxic shock (ITS).

Clostridial FBT. Poisoning is caused by the consumption of contaminated home-cooked meat products, canned meat and fish. The disease is characterized by a severe course, high mortality. Toxins damage the intestinal mucosa, disrupt absorption. When entering the blood, toxins bind to the mitochondria of liver, kidney, spleen, lung cells, damage the vascular wall and develop hemorrhages.

Clostridiosis occurs as acute gastroenterocolitis with signs of toxicosis and dehydration. The incubation period lasts 2–24 hours. The disease begins with intense, stabbing pain in the abdomen. In mild and

moderate cases, fever, repeated vomiting, loose stools (up to 10–15 times) with mucus and blood, and abdominal pain upon palpation are noted. The duration of the disease is 2–5 days. The following severe types are possible:

- ✓ Acute gastroenterocolitis is characterized by severe intoxication; yellowness of the skin; vomiting, diarrhea (more than 20 times a day), mucus and blood in the stool; severe abdominal pain upon palpation, enlarged liver and spleen; decreased RBC and Hb, increased indirect bilirubin. As the disease progresses, tachycardia, hypotension, anaerobic sepsis, and ITS develop;
- ✓ The cholera-like type manifests itself as acute gastroenterocolitis in combination with dehydration of I–III degree, development of necrosis of the small intestine, peritonitis with characteristic stool in the form of meat slops.

Cereosis (Bacillus cereus) is mild in most patients. Gastroenteritis symptoms predominate in clinical manifestations. Severe course is possible in elderly people and in immunodeficiency states. Rare cases of ITS with fatal outcome are known.

Klebsiella is characterized by fever for 3 days and toxic symptoms. Acute gastroenterocolitis dominates in clinical manifestations, less often – colitis. Diarrhea lasts up to 3 days. Moderate course of the disease prevails. It is most severe in people with concomitant diseases (sepsis, meningitis, pneumonia, pyelonephritis).

Proteosis in most cases is mild. The incubation period is from 3 hours to 2 days. The main symptoms are weakness, intense, sharp pain and loud rumbling in the abdomen, foul-smelling stools. Cholera-like and shigellosis-like variants of the disease are possible, leading to the development of ITS.

FBT of Streptococcal etiology is characterized by a mild course. The main symptoms are diarrhea and abdominal pain.

Complications

1) Infectious toxic shock;
2) Regional circulatory disorders:
   - ✓ coronary (myocardial infarction);
   - ✓ mesenteric (thrombosis of mesenteric vessels);
   - ✓ cerebral (acute and transient cerebrovascular accidents).
3) Pneumonia.
4) Acute renal failure.

Diagnosis

The diagnosis of FBT is based on the following criteria:

- ✓ connection of disease with food consumption;
- ✓ short incubation period;
- ✓ acute onset;
- ✓ symptoms of acute gastritis, enteritis, gastroenteritis;
- ✓ symptoms of intoxication (chills, fever, headache);
- ✓ outbreak where all victims consumed the same product.

Lab tests:

- ✓ In CBC, there is moderate leukocytosis with a shift to the left for band cells. In case of dehydration, there is an increase of Hb and RBC, and an increase in Ht (hematocrit).
- ✓ Urine analysis shows proteinuria.
- ✓ Blood electrolyte composition – hypokalemia and hyponatremia.
- ✓ Bacteriological testing of blood (if sepsis is suspected), vomit, feces and gastric lavage. Isolation of opportunistic bacteria. Research is carried out in the first hours of the disease and before the start of treatment.
- ✓ Serological tests: agglutination test (AT) and direct hemagglutination test (DHT) from the 7^{th}–8^{th} day of illness, the diagnostic titer is 1:200 and higher.

Treatment

1) Hospitalization for FBT is carried out according to clinical and epidemiological indications. Severe and moderately severe patients, severely weakened and burdened with concomitant pathology of the person are strictly hospitalized.

2) Initial gastric lavage with boiled water to collect a sample for bacteriological testing, and then with a 2% sodium bicarbonate solution. Gastric lavage is contraindicated in high blood pressure; in people suffering from coronary heart disease, gastric ulcer, in the presence of shock symptoms, suspected myocardial infarction, poisoning with chemicals.

3) After gastric lavage, enterosorbents are prescribed to bind and remove toxins (and partially microbes) from the gastrointestinal tract.

4) Rehydration therapy for normalization of water-electrolyte balance and acid-base status, restoration of microcirculation and hemodynamics, elimination of hypoxia. Rehydration therapy for elimination of existing and continuing fluid losses is carried out in two stages. For oral rehydration (at the first degree of dehydration and absence of vomiting) official salt compositions for oral rehydration are used:
   - ✓ glucosolan (oralit);
   - ✓ citroglucosolan;
   - ✓ rehydron and its analogues.

These solutions are given to drink in small portions until thirst is quenched, and then in quantities 1.5 times greater than the loss of fluid through feces, urine, and vomit. The volume of fluid administered orally depends on the degree of dehydration and the patient's body weight. The rate of administration of oral rehydration solutions is 1–1.5 l/h; the temperature of the solutions is 37°C.

The first stage of oral rehydration therapy continues for 1.5–3 h (enough to achieve a clinical effect in 80% of patients).

At the second stage, the amount of fluid administered is determined by the amount of ongoing losses. In case of uncontrollable vomiting, dehydration of II–IV degree, rehydration is carried out only by intravenous administration of such water-electrolyte solutions as Quartasol, Trisol, Chlosol, Lactasol, and in their absence - Ringer's solution or 0.9% sodium chloride solution.

5) Enzyme medicines

Antibiotics are not used to treat patients with food poisoning. They can only be used in cases of prolonged fever (more than 2 days), in the presence of hepatosplenic syndrome, colitis. In severe clostridiosis, metronidazole is indicated, and in cases of pseudomembranous colitis, vancomycin is indicated.

Prevention

Nonspecific prevention of FBT:

Sanitary and hygienic monitoring of water supply sources, water supply and sewerage networks, treatment facilities; enterprises associated with the procurement, storage, transportation and sale of food products (introduction of modern methods of processing and storing products; strengthening sanitary control over compliance with cooking technology), medical monitoring of the health of public catering workers. Sanitary and veterinary control at meat and dairy industry enterprises. In the outbreak of FBT, in order to identify the source of infection, it is mandatory to conduct bacteriological and serological tests on the decreed professionals.

There is no specific prevention.

SALMONELLOSIS

Definition

Salmonellosis is an acute zoonotic-anthroponotic infection caused by numerous bacteria of the genus Salmonella, characterized by toxic and gastrointestinal syndrome, sometimes with generalization.

Etiology

Salmonella are gram-negative, small, mobile (due to peritrichous flagella) rod-shaped bacteria of the genus Salmonella from the Enterobacteriaceae family. They do not form spores or capsules. They are cultivated on ordinary media. They produce exotoxins, enterotoxins and cytotoxins, the functions of which are similar to those in FBT. When a bacterial cell is destroyed, endotoxin is released.

Salmonella have a complex antigen structure. They contain O-antigens (somatic) and H-antigens (flagellate). Some salmonella have K-antigen. According to the pathogenicity for humans, salmonella are divided into anthroponoses (cause typhoid fever and paratyphoid A and B) and zoonoses (pathogenic for humans and animals non-typhoid salmonellosis). Based on the genome analysis, according to the current classification, Salmonella are divided into two species such as S. bongori (not pathogenic for humans) and S. enterica, which have a large number of serovariants. In general, salmonellae are divided by antigens into 46 serogroups and more than 2500 serotypes. To differentiate salmonella, the Kaufman-White scheme (serological classification) is used, which includes 2579 serological variants that differ in antigenic structure.

At the same time, new serotypes of these bacteria are isolated annually in national salmonella centers (40–60 per year) and their epidemiology is studied. The division into subspecies has a certain epidemiological significance, since the main, natural reservoir of salmonella subspecies I and II are warm-blooded animals, and

for such subspecies as IIIa, IIIb, IV, VI and the species S. bongori – V, the reservoir is cold-blooded animals and the environment.

Each salmonella serovar causes disease predominantly in one animal species – S. choleraesuis in pigs, S. dublin in calves, and S. enteritidis in birds. At the same time, there are serovars that can cause disease in many animal species and humans, for example, S. typhimurium.

Salmonella pathogens survive in the environment for a long time: in water – up to 5 months, in soil – up to 18 months, in meat – up to 6 months, in bird carcasses – more than a year, on eggshells – up to 24 days. They tolerate low temperatures well, and die instantly at 100^0C.

Epidemiology

Salmonellosis is mainly zoonotic, therefore, the source of infection is sick animals: cattle, pigs, horses, poultry. They have an acute disease or as a carrier. Meat can be infected during life, and also during slaughter, cutting of carcasses, storage, transportation and cooking. In addition to meat, confectionery products made with infected eggs can be a source of infection. Salmonellosis in animals can be clinically manifested or as a carrier. Animals that are carriers of bacteria can excrete the microorganism in urine, feces, milk, nasal mucus, saliva. The duration of their carrier state can last for months or years. The mechanism of transmission of infection is faecal-oral, this mechanism is realized through water, food and household contacts.

A person (either a patient or a carrier) can be a source of S. typhimurium.

Unlike many other bacteria, salmonella can multiply at temperatures of 4–6°C and remain in frozen meat products for a long time without changing their external and organoleptic properties.

Both adults and children are equally susceptible to salmonellosis. However, the disease is more severe in children. Cases of the disease are registered throughout the year, but more often in the summer season due to worse storage conditions for food products. Sporadic

and group morbidity is observed. Post-infection immunity lasts less than a year.

Pathogenesis

Salmonella enters the human body through contaminated food or water. The infectious dose is 10^3–10^6 CFU (colony forming units). Conditions that reduce either gastric acidity (age <1 year, antacid use, or any hypoacid conditions) or intestinal integrity (inflammatory bowel disease, previous gastrointestinal surgery, or changes in intestinal flora due to antibiotic use) increase susceptibility to Salmonella infection.

Having overcome the acid barrier of the upper gastrointestinal tract, salmonella reach the small intestine, where they penetrate the intestinal mucosa. Salmonella penetrate the epithelial cells by bacterial endocytosis. After invasion of the intestinal epithelium, salmonella encounter macrophages in the lymphoid tissue associated with the intestine. The interaction of salmonella with macrophages leads to the activation of proinflammatory mediators, receptors or adhesion molecules and anti-inflammatory mediators. This leads to inflammation and cell death (entero- or colonocytes) or their apoptosis, the pathogen dies along with the cells with the release of endotoxin, causing toxic syndrome. Salmonella that have penetrated enterocytes produce an exotoxin (enterotoxin), the mechanism of action of which is the activation of enzymes (adenylate cyclase, guanylate cyclase) leading to diarrhea and dehydration.

In most diarrhea-associated salmonellosis, infection does not extend beyond the lamina propria and local lymphatics. However, bacteremia is possible with any Salmonella serotype, especially in immunocompromised individuals.

Clinical classification

I. According to the type:
   1) Typical (gastrointestinal) types:

- ✓ Gastritis;
- ✓ Gastroenteritis;
- ✓ Gastroenterocolitis;
- ✓ Enteritis;
- ✓ Enterocolitis;
- ✓ Colitis.

2) Atypical types:
- ✓ Typhoid-like;
- ✓ Septic;
- ✓ Latent (carrier);
- ✓ Mixed.

II. According to the severity:
1) Mild;
2) Moderate;
3) Severe.

III. According to the course:
1) Uncomplicated.
2) Complicated;
3) Progressive (more than 6 weeks)

Clinical manifestations

The incubation period for salmonellosis can range from 6 to 48 hours (2 days), on average 12–24 hours. With nosocomial infection (S. typhimurium) the incubation period lasts 3–5 days. The most common gastrointestinal types of salmonellosis are the following:

The gastritis variant of salmonellosis is rare and is characterized by an acute onset, mild toxic syndrome, repeated vomiting and pain in the epigastrium. Diarrhea does not occur with this variant of salmonellosis.

The gastroenteritis variant of salmonellosis is the most common. The disease begins acutely, with symptoms of toxicosis: fever, headache, chills, muscle aches, abdominal pain. Nausea, vomiting, and diarrhea

are added. The stool is initially fecal, but quickly becomes watery, foamy, foul-smelling, sometimes with a greenish tint and looks like "swamp mud". Physical findings include pale skin, and in more severe cases, cyanosis. The tongue is dry and coated. The abdomen is bloated, painful on palpation in all areas, especially in the epigastrium and right iliac region, and rumbles. Muffled heart sounds, tachycardia, decreased blood pressure. Reduced urine output. Convulsions are possible.

In the gastroenterocolitis variant, on the 2nd-3rd day of the disease, symptoms of colitis in the form of a decrease in the volume of feces, an admixture of mucus, sometimes blood, tenesmus, and false urges are added to the signs of gastroenteritis (see above). When palpating the abdomen, spasm and soreness of the sigmoid colon are noted.

The enteric variant of salmonellosis develops more often in young children with household contact. The disease begins acutely, with the appearance of abdominal pain, toxic symptoms (loss of appetite, vomiting, fever). The stool is loose, frequent, watery, there may be a slight admixture of mucus. The abdomen is moderately swollen, rumbling is noted throughout the abdomen upon palpation. Dehydration may develop (toxicosis with exsicosis in children).

Enterocolitis variant of salmonellosis also develops with household infection, also more often in young children in hospital. This variant is accompanied by a pronounced toxic syndrome (high fever for 5–7 days, anxiety or lethargy of the patient, loss of appetite and sleep disturbance, vomiting is possible). There is pain in the abdomen, frequent liquid stool of a dark green color ("swamp mud"), with an admixture of turbid mucus and blood. An enlargement of the liver and spleen is often observed. This variant of salmonellosis is characterized by a protracted course with the formation of a carrier state.

The colitis variant of salmonellosis is rare, clinically it resembles shigellosis – with pronounced symptoms of intoxication and colitis syndrome (cramping abdominal pain, tenesmus, spasmodic sigmoid,

gaping anus). The stool is not abundant, liquid with an admixture of turbid mucus and blood.

Atypical generalized types of salmonellosis are usually preceded by gastrointestinal variants. In the typhoid-like variant, the fever becomes constant or wave-like. Headache, weakness, and insomnia increase. Physical findings are characterized by pale skin, by the 6th–7th day of illness, roseola rash appears on the skin of the abdomen, bradycardia, dry wheezing is detected in the lungs, the abdomen is swollen. By the end of the first week of illness, an enlargement of the liver and spleen is noted. The duration of fever is 1–3 weeks.

The septic variant of atypical types of salmonellosis in the first days of the disease is similar to the typhoid-like variant. Later, the condition of patients worsens. Fluctuations in body temperature become irregular, with large daily differences, repeated chills and profuse sweating, tachycardia, myalgia. Purulent foci form in the lungs, heart, kidneys, liver and other organs. The disease lasts a long time and can end fatally. After the disease, some patients become carriers of the bacteria.

In *latent salmonellosis*, there are no symptoms, and the diagnosis of this variant of infection is made when the pathogen is isolated from the faeces of contacts during outbreaks.

Complications

1) Vascular collapse, hypovolemic shock, acute cardiac and renal failure;
2) Septic complications – purulent arthritis, osteomyelitis, endocarditis. Abscess of the brain, spleen, liver and kidneys, meningitis, peritonitis, appendicitis, pneumonia, urinary infection (cystitis, pyelitis);
3) Infectious toxic shock.

Diagnosis

1) Clinical and epidemiological data (combination of toxic and gastrointestinal syndromes). Consumption of food prepared and stored in violation of sanitary standards, consumption of raw eggs;
2) The CBC reveals leukocytosis, neutrophilia with a shift to band cells, and an accelerated ESR.;
3) Bacteriological testing of feces, vomit, blood, urine, bile, gastric lavage, and remains of suspicious products.
4) Serological diagnosis is performed on the 7^{th}–8^{th} day of illness by the agglutination test (AT) and more often by the indirect hemagglutination test (IHT) with H-, O- and Vi-antigen. In both tests, the test result is positive if the serum is diluted in ratio 1:200;
5) Polymerase chain reaction (PCR).

Treatment

1) Hospitalization of patients with salmonellosis is carried out according to severity and epidemiological indications;
2) The treatment regime for severe intoxication and dehydration is bed rest;
3) Drink plenty of fluids. Diet with the exclusion of foods that irritate the stomach and intestines such as milk, raw fruits and vegetables;
4) For gastrointestinal types of salmonellosis, gastric lavage is recommended in the first hours of the disease.
5) Antibacterial therapy.

✓ In the gastritis variant, antibiotics are not prescribed.
✓ For moderate and severe gastrointestinal types, fluoroquinolones are used:
   - ciprofloxacin 1.0–1.5 g/day (divided into 2 doses), or ofloxacin 0.4–0.8 g/day (divided into 2 doses) orally or parenterally for 5–7 days or

- third generation cephalosporins (ceftriaxone) 2 g/day (divided into 2 doses) from 5–7 days to 10–14 days in severe cases;

✓ In case of generalized salmonellosis, fluoroquinolones (ciprofloxacin) and/or 3rd-generation cephalosporins (ceftriaxone) are used according to the antibacterial therapy regimen for patients with typhoid fever (see Typhoid fever);

6) In case of carriage, salmonella bacteriophage is recommended at 2 tablets*3 times a day or 50 ml*2 times a day 30 minutes before meals for 5–7 days;
7) Oral rehydration therapy;
8) In the development of exsicosis of II–III degrees, parenteral solutions are indicated (Ringer's solution, Hemosol, etc.). In the development of dehydration shock, resuscitation therapy is carried out, as in severe Cholera.
9) In the absence of intoxication, it is possible to use antidiarrheal drugs that stimulate the absorption of sodium ions from the intestinal lumen, inhibiting intestinal peristalsis – loperamide, imodium.

Prevention

Non-specific prevention of salmonellosis consists of veterinary and sanitary supervision of the slaughter of livestock and poultry, carcass processing technology, preparation and storage of meat dishes. Compliance with sanitary standards in food trade and public catering units.

There is *no specific prevention.*

SHIGELLOSIS

Definition

Shigellosis (Dysentery) is an acute intestinal infection caused by bacteria of the genus Shigella and characterized by toxic and gastrointestinal syndromes (mainly distal colitis syndrome).

Etiology

Shigellosis (dysentery) is caused by bacteria of the genus Shigella from the family Enterobacteriaceae. These are rod-shaped, gram-negative, non-motile microbes with rounded ends. They are facultative aerobes and do not form spores or capsules. Bacteria have a complex antigen structure. Their cell walls contain O-somatic antigen, and in some species (Shigella Flexneri) K-antigens. When bacteria are destroyed, endotoxin is released, which causes intoxication syndrome and also has neurotoxicity. The heat-stable part of the Shigella endotoxin (enterotoxin) causes intestinal disorders.

The genus Shigella is divided into 4 species (groups):

1) Group A is Sh. Dysenteriae, which includes 15 serovars;
2) Group B is Sh. Flexneri with 19 serovars;
3) Group C is Sh. Boydii, containing serovars 1–18;
4) Group D is Sh. Sonnei.

Morphologically, all Shigella are similar to each other.

The virulence of Shigella is determined by three main factors, namely the ability to adhere to the membranes of epithelial cells, invasion into them and toxin production.

The survival rate of Shigella varies from several days to months. Food products are a favorable environment for them. Shigellosis pathogens quickly die under the influence of direct sunlight and heating (at 60^0C they die in 30 minutes, 100^0C – almost instantly). Disinfectants

(hypochlorites, chloramines, lysol, etc.) destroy dysentery bacteria within a few minutes.

Epidemiology

The source of infection are patients with acute or chronic dysentery, convalescents and bacteria excretors. Epidemiologically, the most dangerous are patients with acute dysentery, releasing a huge number of bacteria into the environment during the peak of the disease. The mechanism of transmission is fecal-oral, this mechanism occurs through water, food, household contact. The main route of transmission of Grigoriev-Shiga bacteria is through household means, Flexner bacteria is through water, and Sonne bacteria are transmitted through food (especially milk).

Susceptibility to dysentery bacteria varies among people of different age groups. The leading age group among patients with dysentery are preschool children. Dysentery is characterized by a pronounced summer-autumn seasonality.

Pathogenesis

Shigella enter the stomach through the mouth, where, under the influence of an acidic environment, some of them die, releasing endotoxin, which causes toxic syndrome. The surviving portion of shigella enters the small intestine. In the small intestine, pancreatic enzymes protect enterocytes from adhesion and invasion of shigella, so long-term colonization of enterocytes does not occur. However, some bacteria penetrate the enterocytes of the ileum and multiply in them. Endotoxin, formed as a result of the destruction of shigella in the foci of primary invasion in the epithelium of the small intestine, enters the blood and causes fever.

The main place of reproduction of shigella is the epithelium of the large intestine. When shigella invades the mucous membrane of the large intestine, epithelial cells are rejected, which leads to the appearance of superficial microerosions, this is facilitated

by the cytotoxin secreted by shigella. Shigella toxins are fixed by the tissues of the central nervous system and affect the centers of the autonomic nervous system. Disruption of intestinal innervation, inflammatory changes in its mucous membrane are clinically manifested by spastic abdominal pain. Spasms and uneven contractions of different segments of the intestine lead to retention of intestinal contents in its upper sections. This explains the scanty non-fecal appearance of stool, consisting of inflammatory exudate. Spasmodic contraction of the muscles of the sigmoid and rectum causes painful false urges to defecate and tenesmus (a burning or sore feeling in the anus and a sensation of incomplete defecation).

In severe cases, toxicosis and exsicosis may occur.

Clinical classification

I. According to the type:
   1) Typical type.
   2) Atypical type:
   ✓ Hypertoxic;
   ✓ Food poisoning-like;
   ✓ Dyspeptic type (mainly in infants);
   ✓ Inapparent;
   ✓ Latent (carrier).

II. According to the severity:
   1) Mild;
   2) Moderate;
   3) Severe.

III. According to the course:
   1) Acute (up to 1.5 months).
   2) Progressive (up to 3 months).
   3) Chronic (more than 3 months).
   ✓ Uncomplicated.
   ✓ Complicated.

Clinical manifestations

The incubation period usually lasts 1–4 days, but can extend up to 8 days.

The onset of the disease is often acute with fever, vomiting, anorexia and severe abdominal pain, imperative urges and painful defecation. Diarrhea may be watery and voluminous in the initial period of the disease, turning into frequent, small-volume, bloody-mucous stools. Manifestations are usually pronounced in children, with a temperature of up to 40–41^{0}C and more severe anorexia and watery diarrhea. Unlike most diarrheal infections, dysenteric diarrhea does not have dehydration as a main symptom and is characterized by small volumes of bloody mucopurulent stools with tenesmus and abdominal cramps. Shigellosis is characterized by damage mainly to the distal colon and rectum. Patients complain of cutting, cramping abdominal pain localized in the iliac regions, more on the left. Abdominal pain usually precedes each bowel movement and is superimposed on it. The urges are often "false", accompanied by excruciating pulling pains in the rectum – tenesmus. Palpation of the abdominal organs reveals a spasmodic, tonically tense colon, in milder cases only its distal section – the sigmoid colon. It is palpated as a dense, infiltrated, slightly mobile, sharply painful cord. Palpation often intensifies the spasm of the intestinal muscles and provokes the urge to defecate. Rectal prolapse may occur, especially in debilitated patients.

Infection with Sh. dysenteriae serotype 1 is usually complicated by hemolytic uremic syndrome. This syndrome is caused by Shiga toxin-mediated vascular endothelial damage. Bacteremia is rare and is most often reported in severely malnourished children, HIV-infected patients, and patients with defects in innate immunity.

The hypertoxic type of dysentery is characterized by a sudden, violent onset with fever up to 40°C and higher. Expressed symptoms of intoxication are characteristic, neurotoxicosis often develops, and intestinal syndrome (colitis) is delayed.

The dyspeptic type of dysentery is observed in infants, occurs with normal or subfebrile fever, without any disturbance of the condition. It is characterized by the development of unstable stool in the absence of colitic syndrome.

The inapparent type is characterized by the absence of intoxication symptoms with mild and short-term intestinal dysfunction. Infrequent loose stools with a small admixture of mucus are noted. Laboratory tests play a major role in establishing the diagnosis.

The latent type (carrier) of dysentery is characterized by the absence of symptoms of the disease. It is diagnosed based on the isolation of shigella from feces during bacteriological examination.

Complications

- ✓ Toxic megacolon;
- ✓ Intestinal perforations;
- ✓ Rectal prolapse;
- ✓ Toxic shock;
- ✓ Hemolytic uremic syndrome (HUS).

Diagnosis

In typical cases, the diagnosis of dysentery does not cause difficulties, except for atypical course of the disease. The diagnosis is based on the epidemiological history, clinical manifestations, physical and laboratory findings.

Laboratory findings:

1) Coprological findings include mucus, accumulation of leukocytes with a predominance of neutrophils (more than 30–50 in the microscopic field), erythrocytes and various amounts of altered epithelial cells.
2) The gold standard for diagnosing shigellosis is isolation and identification of the bacterium from stool. One of the major

difficulties, particularly in endemic areas where laboratory facilities are poor, is the fragility of Shigella and its loss during transport, particularly with rapid changes in temperature and pH. In the absence of a reliable enrichment medium, buffered glycerol saline or Cary-Blair medium can be used as a storage medium, but rapid inoculation onto the culture medium is necessary.

3) Along with bacteriological methods, methods such as enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) can be used to diagnose dysentery.

Treatment

1) Hospitalization of patients is carried out according to clinical and epidemiological indications.
2) In the acute phase with significant intestinal disorders, the diet should be mechanically and chemically gentle. The transition to normal nutrition should occur gradually over 1–2 months after the disappearance of symptoms.
3) Etiotropic therapy. In *mild and moderate cases* of infection, fluoroquinolones are prescribed:
   - ✓ Ciprofloxacin is recommended as first-line therapy at a dose of 500 mg twice a day (bid per os) for adults and 20–30 mg/kg/day in 2 doses for children; or
   - ✓ Ofloxacin 0.2 g twice a day or ciprofloxacin 0.5 g 2 twice a day; or
   - ✓ Trimethoprim/sulfamethoxazole 480 mg 2 twice a day;

In *severe cases* of dysentery:

- ✓ Ofloxacin 0,4 g twice a day; or
- ✓ Ciprofloxacin 0,75 g twice a day; or fluoroquinolones in combination with aminoglycosides;
- ✓ aminoglycosides in combination with cephalosporins. In the first 2–3 days of treatment, the drugs are administered parenterally, followed by enteral administration.

The duration of antibiotic therapy is determined by the patient's condition. In moderate cases, antibiotics can be taken for 3–4 days, in severe cases – 5–7 days.

4) Supportive therapy.
   - ✓ Oral rehydration.
   - ✓ Infusion detoxification.
   - ✓ To correct the intestinal microbiome, probiotics are indicated for 2–4 weeks.
   - ✓ Enzyme therapy.
   - ✓ Antispasmodic: drotaverine 2% – 2.0 IM;

The use of antiperistaltic drugs such as loperamide and imodium is contraindicated because they can worsen the course of the disease and prolong the period of bacterial excretion.

Prevention

Non-specific prevention of shigellosis is:

- ✓ Early detection and isolation of the source of infection (patient);
- ✓ In the outbreak of dysentery, ongoing disinfection is carried out, and after the patient is hospitalized, final disinfection is carried out.
- ✓ Sanitary control of water supply sources, food blocks, sanitary education of the population.

There is no *specific prevention* due to the lack of effective vaccines.

TYPHOID FEVER

Definition

Typhoid fever is an acute anthropozoonotic infection caused by S. Typhi, manifested by toxic, gastrointestinal and exanthematic syndromes, hepatosplenomegaly and neuropsychiatric disorders.

Etiology

The causative agent of typhoid fever is Salmonella Typhi, which belongs to the genus Salmonella (serogroup D) of the Enterobacteriaceae family. These are Gram-negative small rod-shaped bacteria surrounded by a microcapsule, mobile due to peritrichous flagella, do not form spores and capsules. S. Typhi vegetate on bile-containing media and, when the bacterial cell is destroyed, release endotoxin.

S. Typhi antigens:

- ✓ O-somatic (thermostable);
- ✓ Vi-somatic (thermolabile capsular polysaccharide that protects them from phagocytosis);
- ✓ H-flagellar (thermolabile) antigens.

S. Typhi persist in the external environment and on food products, including water, are relatively resistant to physical and chemical factors, and persist for a long time at low temperatures (in ice for several months). Bacterium die instantly when boiled.

Epidemiology

Typhoid fever is widespread, but it is more common in areas with poor water supply and sanitation. The most endemic regions for typhoid fever are developing countries in Africa, Southeast Asia, and the Western Pacific.

The source of infection is only a person (patient or carrier), who excretes the pathogen into the external environment with urine, feces and saliva starting from the 7th day of clinical manifestations and stops during the recovery period. Bacterial excretion can be extended up to 3 months (acute carriage) or lifelong (chronic carriage).

The mechanism of transmission of infection is faecal-oral, this mechanism is realized through water, food and household routes.

In endemic regions, children are most often affected, in non-endemic regions – people aged 15–45 years. Typhoid fever is characterized by a summer-autumn seasonality.

Pathogenesis

In typhoid fever, pathogenetic phases can be traced.

Infection phase. Entering the human body through the mouth, S.typhi overcomes the acidic barrier of the upper gastrointestinal tract and adheres to the epithelium of the small intestine.

Primary regional infection phase. After adhesion to the epithelium of the small intestine, pathogens penetrate into the regional lymph nodes (mesenteric) through lymphoid formations (solitary follicles and their clusters), where they intensively multiply, leading to inflammation. These two pathogenetic phases correspond to the incubation period.

Bacteremia and toxinemia phase. As a result of inflammation of the mesenteric lymph nodes, the hematolymphatic barrier is disrupted, which leads to the penetration of pathogens into the blood circulation with the development of bacteremia. In the bloodstream, bacteria are destroyed, releasing endotoxin. This phase marks the beginning of the febrile period of the disease. Endotoxin has neurotropic properties, which causes a disorder of the central nervous system with the development of “typhoid status” (status typhosus), has a vagotonic effect, causing flatulence, abdominal pain and intestinal disorders.

Parenchymal dissemination phase. With blood circulation, the surviving portion of microbes disseminates into parenchymatous organs, leading to manifestations of damage to internal organs and rashes.

Excretory-allergic phase. Further multiplying in the liver, S. Typhi re-enters the intestine with bile, leading to a local anaphylactic reaction in the form of necrosis of the intestinal lymphoid formations. Such hepatic-intestinal recirculation of the microbe leads to characteristic anatomical disorders in the intestinal wall.

Pathomorphological changes in the lymphoid formations of the small intestinal epithelium also have a pattern and cyclicity, which also explain the mechanisms of infection and possible complications. There are 5 periods:

1) *The swelling period* approximately corresponds to the first week of the disease. The lymphatic follicles of the intestinal epithelium are enlarged and protrude above the level of the mucous membrane;
2) *Necrotic period* (2nd week of illness). During this period, necrosis of the central part of the swollen follicle occurs, their surface is dirty gray or greenish-yellow;
3) *The period of ulcer formation* is observed around the 3rd week and is characterized by the rejection of necrotic tissue, leading to necrosis of the deep layers of the intestinal mucosa and submucosal layer;
4) *The period of clean ulcers* occurs on the 4th week as a result of the rejection of necrotic tissue and the formation of ulcers with a clean smooth bottom with slightly swollen edges. This period is considered the most dangerous in the development of perforation and intestinal bleeding;
5) *The period of ulcer healing* occurs at 5–6 weeks of the disease and is characterized by healing of ulcers without scarring, but with some pigmentation of a slate-gray color.

From the moment the symptoms of the disease appear, the immune response of the macroorganism is activated with the production of specific antibodies and an increase in the phagocytic activity of macrophages. On the 4th week of the disease, the intensity of bacteremia decreases, granulomas in the organs regress, fever decreases, and the acute phase of the disease ends. However, due to the imperfection of phagocytosis, the pathogen can persist in macrophages, which leads to exacerbations and relapses of the disease or to chronic carriage.

Clinical classification

I. According to the type:
   1) Typical type.
   2) Atypical type:
   ✓ inapparent, abortive;
   ✓ rare types: (pneumotyphus, meningo-typhus, nephrotyphus, colotyphus, typhoid gastroenteritis).

II. According to the severity:
   1) Mild;
   2) Moderate;
   3) Severe.

III. According to the course:
   1) Uncomplicated.
   2) Complicated:
   ✓ specific complications (intestinal bleeding, intestinal perforation, toxic shock);
   ✓ nonspecific (pneumonia, cholecystitis, thrombophlebitis, otitis, etc.).

Clinical manifestations

The clinical manifestation of typhoid fever has the following periods:

1) *The incubation period* lasts from 7 to 25 days. On average, with a typical course, its duration is 9–14 days.

2) *The initial period* is characterized by a gradual or acute onset of intoxication symptoms. Patients complain of fatigue, increasing weakness, chills, increasing headaches, loss or lack of appetite. The temperature rises stepwise and by the 5–7th day of illness reaches 39–40°C. Physical findings during this period are some lethargy and adynamia. Cough or nasal congestion, hyperemia of the pharynx, enlargement and hyperemia of the tonsils are possible, the tongue is thickened, with teeth marks on the lateral surfaces. The tongue is thickly coated, the edges and tip of the tongue are free of plaque, have a rich pink or red color. Auscultation may reveal harsh breathing and scattered dry rales over the lungs. The abdomen is moderately distended, rumbling and soreness are detected on palpation of the right iliac region, shortening of the percussion sound in the right iliac region (Padalka's symptom), the liver and spleen are enlarged, constipation is possible. On average, the duration of the initial period is 5–7 days.

3) *The peak period* begins on the 2nd week of the disease. Fever and neuropsychiatric disorders increase with the development of typhoid status, which is rare in the modern course. Small ulcers on the anterior palatine arches are possible – Duguet's angina, a roseolous rash appears on the skin, located mainly on the skin of the abdomen and lower chest. Some patients have Filippovich's symptom – a yellowish coloration of the skin of the palms and soles of the feet. Heart sounds are muffled, bradycardia, a decrease in blood pressure with the development of acute vascular insufficiency, bronchitis, and sometimes pneumonia is possible. Changes in the digestive system are maximally pronounced. The lips are dry, often covered with crusts, with cracks. The tongue is thickened, with a thick gray-brown coating. The abdomen is bloated, stool retention, in some cases greenish diarrhea develops, sometimes like "pea soup". Rumbling and soreness of the ileum, positive Padalka's symptom. The liver and spleen are enlarged. Sometimes cholecystitis occurs, diuresis decreases, proteinuria, micro-

hematuria, and cylindruria are possible. Bacteriuria occurs, which sometimes leads to pyelitis and cystitis. In some cases, mastitis, orchitis, epididymitis, dysmenorrhea may develop, premature births or abortions have been noted in pregnant women. During the peak of the disease, dangerous complications such as perforation and intestinal bleeding may occur. The peak period lasts from several days to 2–3 weeks and is the most severe and critical period.

4) *The resolution period* does not exceed one week and is characterized by a decrease in fever and a gradual disappearance of signs of toxic and gastrointestinal syndromes. During this period, there may be late complications such as thrombophlebitis, cholecystitis.

5) During *the recovery period*, the impaired functions are restored, the pathogen is eliminated from the body. This period is characterized by asthenic syndrome for 2–4 weeks.

Complications

1) *Intestinal bleeding* often occurs in the 3rd week of illness, sometimes after the fever has disappeared. Bleeding is promoted by flatulence and increased intestinal peristalsis. A direct sign of bleeding is melena (tarry stool). Sometimes scarlet blood is noted in the stool. Common signs of internal bleeding are pale skin, a drop in blood pressure, increased heart rate, a critical drop in temperature, which is accompanied by a clearing of consciousness, activation of the patient and creates the illusion that his condition has improved. With massive bleeding, hemorrhagic shock may develop, which has a serious prognosis.

2) *Perforation of the intestine* most often occurs in the terminal ileum at a distance of approximately 20–40 cm from the place where it passes into the cecum (ileocecal valve). Clinical manifestations of perforation are acute abdominal pain localized in the epigastric region slightly to the right of

the midline, abdominal muscle tension, a positive Shchetkin-Blumberg symptom. The pulse is rapid, weak, the face turns pale, the skin is covered with cold sweat, breathing is rapid, in some cases severe collapse is noted. Perforation of the intestine is facilitated by flatulence, increased peristalsis, abdominal trauma. Manifestations of perforation and peritonitis against the background of antibiotic therapy are often unnoticeable, so even mild abdominal pain should attract the attention of a physician.

3) *Infectious toxic shock* may develop during the peak of the disease and is characterized by a sharp deterioration in the condition, chills, hyperthermia, confusion, hypotension, leuko- and neutropenia. The skin becomes pale, moist, cold, cyanosis and tachycardia increase, respiratory failure ("shock lung") and oliguria develop. Azotemia is noted in the blood (the concentration of urea and creatinine increases).

Diagnosis

- ✓ Clinical and epidemiological data;
- ✓ In the CBC in adults there are signs of depression of the white blood cell (leukopenia, aneosinophilia, thrombocytopenia) and in children – leukocytosis;
- ✓ Isolation of S. Typhi from blood (hemoculture), from feces (coproculture), urine (urino-) and bile (biliculture).
- ✓ Serological diagnostics is performed by the agglutination reaction (AR) (Widal reaction), as well as a more sensitive and specific indirect hemagglutination reaction (IHR) with H-, O- and Vi-antigen. The study is performed upon admission and after 7–10 days. A fourfold increase in the O-antibody titer or a titer of 1:200 or higher is of diagnostic value.
- ✓ ELISA.
- ✓ Polymerase chain reaction (PCR).

Treatment

1) Hospitalization of patients is mandatory;
2) Regime – strict bed rest until the 6–7th day of normal temperature; from the 7–8th day, sitting is allowed, and from the 10th day of normal temperature, in the absence of contraindications, walking is allowed;
3) The diet should be mechanically and chemically as gentle as possible on the intestines, reducing fermentation and putrefactive processes and at the same time be sufficiently caloric;
4) Antibacterial therapy is carried out until the 10th day after normalization of body temperature.

   a) First-line antibiotics (fluoroquinolones):
   ✓ ciprofloxacin 0.5–0.75 g twice a day after meals; or
   ✓ ofloxacin 0,2–0,4 rorally or intravenously twice a day; or
   ✓ pefloxacin 0.4 g twice a day orally or intravenously.

   b) Second-line antibiotics (3rd generation cephalosporins):
   ✓ ceftriaxone or cefotaxime 1.0–2.0 g intravenously once a day.
5) Symptomatic therapy (if indicated):
   ✓ Infusion detoxification with polyionic solutions or 0.9% NaCl or 5–10% glucose solution, Ringer's solution, rheopolyglucin, etc.;
   ✓ In case of intestinal bleeding, strict bed rest, fasting for 12 hours, then taking liquid cold food in small portions are indicated. Intramuscular administration of 3 ml of 1% vitamin K solution, intravenous drip of 100 ml of 5% aminocaproic acid solution.
   ✓ In case of intestinal perforation, urgent surgery is required.

Prevention

Non-specific prevention includes monitoring of water supply, disinfection of wastewater, compliance with the rules for

the preparation, storage and sale of food products, personal hygiene, health education of the population, and improvement of residential areas.

In the typhoid fever outbreak, an epidemiological survey is conducted to identify the source of infection and transmission factors. Patients are hospitalized. Contact persons are monitored for 21 days and examined for bacterial carriage.

Specific prevention of typhoid fever is carried out by vaccination. Vaccination is carried out according to epidemiological indications – when the incidence rate reaches 25 per 100,000 populations, travel to endemic countries, in conditions of constant contact with the carrier of bacteria. Several countries have introduced large-scale vaccination strategies. Several types of vaccines have been developed, the use of which is carried out according to the manufacturer's instructions:

- ✓ Oral live attenuated preparation of S. Typhi strain Ty21a;
- ✓ Parenteral preparation containing capsular polysaccharide Vi;
- ✓ Parenteral dry lyophilized preparation of the Ty2 strain of S. Typhi.

VIRAL DIARRHEA

Definition

Viral diarrhea is an acute intestinal infection caused by various viruses, characterized by predominant damage to the upper gastrointestinal tract (gastrointestinal syndrome) and often in combination with toxic and abdominal (pain) syndrome.

Etiology

There are about 120 types of viruses that can cause loose stools in children and adults, high fever, vomiting and catarrhal symptoms. Most of them are rotaviruses, astroviruses, caliciviruses (in particular the Norwalk virus), enteroviruses, and adenoviruses.

Rotaviruses are RNA-containing viruses of the Reoviridae family of the Rotavirus genus. Rotavirus got its name due to its characteristic ring structure (Latin rota – wheel). The rotavirus genome consists of 11 segments of double-stranded RNA, each of which encodes the structural proteins of the virion (VP) and non-structural proteins. The viral particle has a three-layer icosahedral capsid with a diameter of about 70 nm. Rotaviruses are divided into 7 serogroups (A, B, C, D, E, F, G).

Serogroups A, B, and C are pathogenic for humans. Serogroup A is the most common cause of rotavirus gastroenteritis in humans, causing endemic outbreaks of severe diarrhea in young children in both developed and developing countries. Serogroup B is more common in Asia, particularly China; rotaviruses of serogroups B and C most often cause diarrhea in adults and older children. Rotavirus replication in humans occurs in the epithelial cells of the small intestine.

Rotaviruses are stable in the external environment: they survive for several months in drinking water, open water bodies and wastewater;

on vegetables - 25-30 days; on cotton and wool – up to 15–45 days; on the surface of furniture and on the floor – up to 7–15 days. Rotaviruses are not destroyed by repeated freezing. They die when boiled.

Astroviruses are RNA-containing viruses of the family Astroviridae, 28–30 nm in size with a characteristic shape of a central 5- or 6-pointed star when viewed with an electron microscope. They contain single-stranded RNA. The capsid consists of 3 structural proteins. There are 8 known human serotypes of which serotype 1 is the most common. Astroviruses are primarily childhood pathogens, causing approximately 2–10% of cases of mild to moderate gastroenteritis in young children, with a high incidence in both developing and developed countries.

Caliciviruses, which make up the Caliciviridae family, are small viruses measuring 27–35 nm that are the most common cause of gastroenteritis outbreaks in older children and adults. They are RNA-containing viruses with one structural protein. Human caliciviruses are divided into 2 genera: Noroviruses and Sapoviruses. Noroviruses remain viable in the environment for a long time (up to a month), including in chlorinated drinking water; they are resistant to heating and freezing, ultraviolet radiation, and the action of disinfectants (ethanol, ether, fat solvents). They are inactivated in an acidic environment.

Enteroviruses are the causative agents of enteroviral gastroenteritis. This is a group of intestinal viruses (reproduce in the intestine and are excreted from the body with feces) RNA-containing viruses of the genus Enterovirus, family Picornaviridae (pico – small). The most common cause of diarrhea is Coxsackie A (24 serovars), Coxsackie B (6 serovars) and ECHO (34 serovars), as well as 5 human enteroviruses. Enterovirus virions are 15–35 nm in size, stable in the environment, resistant to low temperatures, resistant to freezing and thawing (in feces at low temperatures they remain viable for more than six months). In wastewater, small reservoirs can

persist for up to 1.5–2 months. Viruses are sensitive to drying, at room temperature they persist for up to 15 days. At a temperature of 33–35^{0}C they die within 3 hours, at a temperature of 50–55°C – within a few minutes and instantly – when boiling and autoclaving. They quickly die under the influence of disinfectants.

Epidemiology

The source of infection in viral diarrhea for humans is a sick person and/or asymptomatic carriers of viruses. Viruses are excreted in stool in very high concentrations before and for several days after clinical manifestation. The infectious dose of the virus varies depending on the type of pathogen – from 10 to 10^{10} viral particles in 1 g of feces.

The mechanism of transmission of the infection is faecal-oral, through water, food, household, and also airborne.

Viral diarrhea pathogens are ubiquitous. Children are particularly susceptible. Outbreaks are common in children's hospitals and day care centers. Infants younger than 3 months are relatively protected by transplacental antibodies and possibly breastfeeding. Infections in neonates and adults in close contact with infected children are usually asymptomatic. Astroviruses are a common cause of mild to moderate watery winter diarrhea in children and infants and a rare pathogen in adults. Outbreaks in hospitals are common. Calicivirus is best known for causing large, explosive outbreaks among older children and adults, especially in settings such as schools, cruise ships, and hospitals. A specific food item, such as shellfish or water used for cooking, is often identified as the source.

The incidence of viral diarrhea increases in the cold season, i.e. winter-spring seasonality is typical. Adenoviral gastroenteritis occurs year-round.

Pathogenesis

The pathogen's entry point is the digestive system. Within 30 minutes of entering the body, the virus penetrates the apical cells

of the small intestine villi, where it replicates. Viruses selectively infect and destroy villus cells in the small intestine. The gastric mucosa is not affected. The mechanism of diarrhea development in rotavirus gastroenteritis has been studied best. Having penetrated the cell, rotaviruses cause the death of mature epithelial cells of the small intestine and their rejection from the villi. The cells replacing the villous epithelium are functionally defective and are not able to adequately absorb carbohydrates and monosaccharides. The occurrence of disaccharidase (mainly lactase) deficiency leads to the accumulation of undigested disaccharides with high osmotic activity in the intestine, which causes a violation of the reabsorption of water, electrolytes and the development of watery diarrhea, often leading to dehydration. Entering the large intestine, these substances become substrates for fermentation by intestinal microflora with the formation of a large amount of organic acids, carbon dioxide, methane and water. Intracellular metabolism of cAMP and guanosine monophosphate in epithelial cells with this infection remains virtually unchanged.

The body is cleansed of viruses by replacing desquamated enterocytes with immature enterocytes that do not have receptors for viruses and by producing antibodies (IgM, IgG).

Clinical manifestations

The incubation period varies from 14–16 hours to 7 days (usually 1–5 days).

The disease most often has an acute onset, with fever, symptoms of intoxication, diarrhea and repeated vomiting - DFV syndrome (diarrhea, fever, vomiting). These symptoms are noted in 90% of patients; they occur almost simultaneously on the first day of the disease, reaching maximum severity within 12–24 hours.

Intestinal dysfunction occurs mainly as gastroenteritis or enteritis, characterized by liquid, watery, foamy stools of yellow or yellow-green color without pathological impurities with a sharp sour odor.

The frequency of bowel movements often corresponds to the severity of the disease. With abundant liquid stool, dehydration may develop, usually I–II degree. Only in some cases is severe dehydration of III degree with the development of dehydration shock observed. Abdominal pain may be observed, most often they are moderate, constant, localized in the upper half of the abdomen, in rare cases the pain is cramping, severe. When palpating the abdomen, pain is noted in the epigastric and umbilical regions. Signs of damage to the digestive system persist for 3–6 days.

The severity and duration of fever fluctuates within 37–39°C for 2–4 days, often accompanied by symptoms of intoxication (lethargy, weakness, loss of appetite, up to anorexia). In some patients, mainly in young children, catarrhal symptoms develop: coughing, runny nose or nasal congestion, rarely - conjunctivitis, catarrhal otitis. Physical findings are hyperemia of the pharynx; hepatosplenomegaly is noted in adenovirus infection.

Complications

1) dehydration shock;
2) acute cardiovascular failure;
3) acute renal failure;
4) secondary disaccharidase deficiency;
5) intestinal dysbiosis;
6) secondary bacterial infection.

Diagnosis

1. In most cases, the diagnosis of viral diarrhea can be made based on clinical and epidemiological features;
2. Laboratory findings:

- ✓ In the CBC, at the onset of the disease there may be leukocytosis with neutrophilia without a left shift, during the peak of infection – leukopenia with lymphocytosis; ESR is normal.
- ✓ In coprology, signs of an inflammatory process are not detected, but at the same time, starch, undigested fiber, neutral fat, signs of lactase deficiency, namely acidic pH of feces, are present.

- ✓ ELISA provides >90% specificity and sensitivity, is available for detection of rotavirus group A, caliciviruses and enteric adenovirus in stool samples.
- ✓ PCR for detection of viral genome

Treatment

The disease is self-limiting, and oral rehydration therapy is usually sufficient. If severe dehydration develops, intravenous fluid therapy is indicated. There is no specific antiviral therapy.

1. Hospitalization for viral diarrhea is carried out according to clinical and epidemiological indications;
2. Diet. In the acute period, milk and dairy products are excluded from the diet, carbohydrate consumption is limited (vegetables, fruits and juices, legumes). Food should be complete, mechanically and chemically gentle, with sufficient content of protein, fat, mineral salts and vitamins. It is necessary to increase the frequency of meals.
3. Supportive care is aimed at treating dehydration and intoxication and is carried out by introducing polyionic crystalloid solutions, intravenously or orally, taking into account the degree of dehydration and the patient's weight. For infusion therapy, solutions such as Trisol, Quartasol, Acesol are used.

- ✓ Considering the enzymatic deficiency, the use of enzyme preparations is indicated.
- ✓ It is advisable to include probiotics and prebiotics taking into account age-related indications and contraindications.

Prevention

Non-specific prevention is:

- ✓ Conducting disinfection with virucidal agents in the source of infection. In case of epidemic outbreaks, increased supervision of the water supply system, organization of food,

maintenance of the territory, compliance with the regime of childcare units and medical institutions is introduced.

Specific prevention is.

Vaccination is developed only for rotavirus infection. Two types of rotavirus vaccine have been developed:

1) Monovalent attenuated oral rotavirus vaccine (RV1), RotaRix (GSK Biologicals, Belgium). The vaccination course consists of 2 vaccinations with an interval of at least 4 weeks between the two vaccinations. The first dose is administered to children starting at 6 weeks of age. Vaccination should be completed by the 24th week of the child's life. To create full immunity, 2 vaccinations are required. The vaccine strain replicates in the small intestine. Since 2006, the RotaRix vaccine has been registered in more than 70 countries in Latin America, Africa, Asia and the European Union.

2) Live oral pentavalent reassortant rotavirus vaccine (RV5), RotaTeq (Merck&Co., USA) contains 5 reassortant (G1, G2, G3, G4, P1A) viruses obtained on the basis of bovine and human parental strains. The bovine strain of the virus used in the creation of the vaccine is nonpathogenic for humans. The vaccination course consists of 3 doses of the vaccine for the prevention of rotavirus infection, with an interval between administrations from 4 to 10 weeks. The first dose of the drug is administered to children aged 6 to 12 weeks. All 3 doses are recommended to be administered before the child reaches 32 weeks of age. It can be used simultaneously with other vaccines (DPT vaccine, inactivated poliovirus vaccine, Haemophilus influenzae type b conjugate vaccine, vaccine for the prevention of viral hepatitis B, vaccine for the prevention of pneumococcal infections. This vaccine can also be used in premature babies.

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SUMMARIES OF LECTURES
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Manual

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