# CLINICAL-PHARMACOLOGICAL APPROACH TO THE CLINICAL USE OF BACTERIOPHAGE DRUGS IN ACUTE INTESTINAL INFECTIONS

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***Abstract.*** *Acute intestinal infections (AI) are a large group of infectious diseases caused by pathogenic, opportunistic bacteria, viruses, protozoa, transmitted through household, water or food, characterized by inflammatory lesions of the gastrointestinal tract. (GIT) of varying degrees, the development of vomiting, diarrhea, intoxication and dehydration. The main causative agents of acute intestinal infections in young children are viruses. In children under one year of age, the etiological agent of acute intestinal infections in 90% of cases is various viruses, in children 1-4 years old - 75%, in children over 5 years old - 40%. The most common cause of diarrhea in children is rotavirus. By the age of 3-5, every child experiences it at least once. Rotaviruses cause 30-50% of cases of gastroenteritis requiring hospitalization and parenteral rehydration. According to various sources, up to 440,000 children die from rotavirus gastroenteritis worldwide each year (1). In addition to rotavirus, the causative agents of viral diarrhea are RNA-containing astroviruses, Norfolk virus, and similar agents belonging to the group of unclassified viruses, which received their names from the places where they were found - Norfolk (Ohio, USA), Hawaii virus, Mount Snow virus, etc. In addition, caliciviruses, adenoviruses, enteroviruses, coronaviruses, and cytomegalovirus are also responsible for viral diarrhea (2).*

***Key words:*** *Salmonella spp., Shigella spp., Escherichia coli, Clostridium botulinum, Yersinia enterocolitica, Yersinia pseudotuberculosis, Vibrio cholerae, Campylobacter spp., Staphylococcus spp.*

## Introduction

The share of bacterial infectious agents in the etiology of acute intestinal infections increases with the age of the child - from 10% in infants to 60% in children aged 5-14 years. Bacterial pathogens of acute intestinal infections are divided into two groups: pathogenic and opportunistic. The first group includes

Opportunistic pathogens that can cause ACI are represented by a wide range of bacteria and include Proteus spp., Klebsiella spp., Pseudomonas spp., Providencia spp., Clostridium perfringens, Clostridium difficile, Citrobacter spp., Morganirat sp, Enterobacter. spp., Hafnia alvei, Edwardsiella tarda, Vibrio spp. (cholera and non-cholera groups O1 and O139).

Pathogenic bacteria cause acute intestinal infections that are specific nosological entities, while the clinical signs of intestinal infections caused by opportunistic bacteria are less specific.

Exceptions are pseudomembranous colitis caused by Clostridium difficile and necrotic enteritis of swine caused by strains of Clostridium perfringens, the causative agent of gas gangrene that produce β-toxin. The development of necrotic enterocolitis in newborns is also associated with the latter pathogen (3). Opportunistic pathogens are so called because they cause infectious diseases under certain conditions (reduced immunity, infancy, and other modifying risk factors for severe disease).

ACI still occupies a leading position in the infectious pathology of childhood, second only to ARVI in terms of incidence. Up to 1.2 billion cases of diarrheal diseases are recorded worldwide annually. Every year, 5 to 8 million children under 5 years of age die from acute respiratory infections in the world. Mortality rates are especially high in developing countries, where acute intestinal infections are the most common cause of dehydration and malnutrition. The incidence and mortality from acute intestinal infections are highest in children under 5 years of age. Natural feeding eliminates infection through food and water and protects the child from intestinal infections. When a child begins to receive complementary foods, the risk of intestinal infections increases sharply. Compared with adults, enterotoxigenic and enteropathogenic escherichiosis and campylobacteriosis are more common in children. Salmonellosis is most common in infants, and dysentery is most common in children over 6 months of age. Up to 4 years (2).

**Pathogenesis**

The entrance gate and the main target organ for ACI is the gastrointestinal tract. The essence of the pathogenesis of bacterial acute intestinal infections is the interaction of various factors of microbial virulence (infectious dose, adhesion, toxin production, invasion) and the host's defense mechanisms (normal microflora, acidic environment of the gastric contents, intestinal motor function, vomiting, diarrhea, specific immunity, breastfeeding). According to the results of electron microscopic studies of the interaction of bacteria with the epithelium of the gastrointestinal tract, 4 types of this interaction have been identified, characterizing the mechanisms of pathogenic action of pathogens of acute intestinal infections.

The pathogenesis of diarrhea due to rotavirus infection is complex and, according to modern concepts, involves both osmotic and secretory mechanisms.

Rotaviruses infect the epithelial cells of the small intestine (more than the proximal two-thirds). The virus multiplies in enterocytes located on the tops of the villi and causes their death.

Dead epithelial cells are replaced by differentiated cells that are unable to absorb carbohydrates, primarily the disaccharide lactose, and other nutrients (amino acids). As a result, the concentration of these substances in the lumen of the small intestine increases, the reabsorption of water and electrolytes is impaired, and osmotic watery diarrhea develops. Entering the small intestine, disaccharides and amino acids become substrates for fermentation by intestinal microflora with the formation of large amounts of organic acids, hydrogen, carbon dioxide, methane, and water. As a result, gas formation in the intestines (flatulence) increases and the pH of the intestinal contents decreases.

The rotavirus-unspecific structural protein NSP4, the first enterotoxin described in viruses, causes secretory diarrhea similar to bacterial enterotoxins. The mechanism of action of this protein has two phases: enterotoxigenic and enteroneurogenic. In the enterotoxigenic phase, intestinal secretion increases, mainly due to the secretion of chlorides, under the influence of NSP4, which interacts with surface membrane proteins and age-dependent (mainly functioning over 6 months) calcium-sensitive ion channels. NSP4 does not change the level of cAMP or cGMP in enterocytes. In the enteroneurogenic phase, as a result of villous ischemia and activation of the enteric nervous system, the production of nitric oxide (NO) increases, under its influence vascular damage increases and neurogenic reactive inflammation develops. As a result of vascular damage, prostaglandin E2 synthesis and cGMP-dependent secretion of anions through adrenergic, non-cholinergic receptors of the enteric nervous system increase.

In acute intestinal infections, flatulence is associated with increased gas formation due to bacterial fermentation and indigestion, osmotic diarrhea. The cause of abdominal pain syndrome is stretching of the intestinal loops and tension of the mesentery, mesenteric inflammation in infections accompanied by invasive cytotoxic transepithelial interaction, mesenteric adenitis, inflammation of the intestinal wall. All this is accompanied by stimulation of pain receptors.

Digestive disorders are the result of morphological and functional changes in the gastrointestinal tract.

**Clinical variants of acute intestinal infections**

By distribution, OCI is divided into local and generalized, and by severity - mild, moderate and severe (4, 5, 6).

With localized infection, the lesion does not extend beyond the gastrointestinal tract and can be detected at various levels (gastritis, enteritis, colitis, combined lesions), the detection of which helps scatological examination of feces. According to its results, patients are prescribed enzyme therapy.

Gastritis - a lesion of the stomach, accompanied by pain and heaviness in the epigastric region, nausea and repeated vomiting against a background of moderate fever and intoxication. Short-term liquefaction of stool with an unpleasant odor is possible. Gastritis is the main manifestation of food poisoning infections. The coprogram reveals a large amount of connective tissue, coarse plant fiber and unchanged transverse striated muscle fibers.

Enteritis - a lesion of the small intestine, manifested by non-local (or localized around the navel), constant (or periodically recurring), independent (or during palpation) abdominal pain; phenomena of flatulence; liquid, abundant, watery, often foamy, with pieces of undigested food, yellow or yellow-green in color with a pungent odor and a small amount of transparent mucus (lumps or flakes). The coprogram contains leukocytes, epithelial cells, a large amount of fatty acids, starch grains (extracellular and intracellular), muscle fibers and soap (fatty acid salts) and soluble proteins.

Gastroenteritis is a combination of gastritis with enteritis, often found with escherichiosis and salmonellosis.

Colitis is an inflammatory lesion of the colon, which is accompanied by independent (or palpable), constant (or periodically recurring) pain along the entire length of the colon and loose, light stools with an unpleasant odor and pathological impurities (cloudy mucus, greens, blood). .

The coprogram contains a lot of indigestible fiber, intracellular starch and iodophilic microflora, leukocytes, erythrocytes.

Enterocolitis - simultaneous damage to the small and large intestine, clinically manifested by the appearance of a large amount of liquid stool with turbid mucus, sometimes with a large amount of greens (feces like "swamp mud") and blood, which is characteristic of salmonellosis.

The coprogram contains undigested cellulose, starch grains, and iodophilic flora.

Gastroenterocolitis - damage to all parts of the digestive tract, accompanied by symptoms of enterocolitis due to repeated vomiting, abdominal pain and intoxication, is more common with salmonellosis.

Distal colitis is a clinical syndrome characteristic mainly of shigellosis, manifested by independent (or during palpation) pain in the left iliac region. The pain can be constant, but intensifies or occurs only before defecation (tenesmus).

The sigmoid colon is spasmodic, painful during palpation, sphincteritis, flexion or dilatation of the anus are noted. The stool is loose, frequent, scanty, with a large amount of turbid mucus, often green and bloody ("hemocolitis"). In severe forms, the stool loses its fecal character and smell and may consist only of pathological impurities ("rectal spitting"). An analogue of tenesmus in young children may be restlessness, crying during or before bowel movements. With distal colitis, the coprogram contains a large number of leukocytes, red blood cells, and mucus.

Common forms of bacterial acute intestinal infections include typhoid-like diseases with bacteremia (characteristic for salmonellosis, typhoid and paratyphoid fever) and septic (with septicopyemic foci). Salmonellosis, Grigoriev-Shiga dysentery, campylobacteriosis, intestinal infections caused by opportunistic microorganisms, often have a generalized course in children with modifiable risk factors.

The criteria for the severity of AEI are the severity of intoxication, gastrointestinal damage, and dehydration.

The mild form of the disease is characterized by moderate intoxication (body temperature not higher than 38-38.5 ° C) and moderate diarrhea (up to 6-7 times a day without significant fluid loss).

The moderate form of the disease, which occurs most often, is manifested by severe intoxication (body temperature up to 39-39.5 ° C, headache, dizziness, lethargy) and a pronounced local syndrome (abdominal pain, flatulence, stool up to 10-12 times a day) , vomiting with fluid loss in the stool and the development of toxicosis with exicosis of I-II degree.

The severe form of ACI is characterized by a pronounced local syndrome (feces "uncountable" with a large loss of fluid and electrolytes) and the development of a number of emergency syndromes (neurotoxicosis, toxicosis with exsicosis of II-III degree , infectious-toxic shock, hemolytic-uremic syndrome, acute renal failure, sepsis).

**Treatment**

The main components of the treatment of acute intestinal infections are presented in Table 2.

The most important component of the treatment of acute intestinal infections is rehydration.

Traditionally, the principles of dehydration are discussed separately, the interested reader will find a detailed description of this method of therapy in the available manuals (6, 7, 8).

Indications for hospitalization of children with acute intestinal infections are as follows:

all severe forms of acute intestinal infections, regardless of the age of the patients;

moderate forms with symptoms lasting more than 5 days and ineffective therapy in the outpatient phase;

OCI with severe abdominal pain syndrome, requiring examination and observation by a surgeon to exclude acute surgical pathology (intussusception, acute appendicitis, etc.);

suspicion of the development of hypo- or hyperosmolar dehydration based on clinical presentation or previous treatment;

children with modifying risk factors for serious illnesses;

lack of necessary conditions for treatment at home;

all children in closed groups (nursing homes, orphanages, shelters, other hospitals, etc.) (6).

**Diet**

Nutrition for children with acute intestinal infections is determined depending on the age of the patient and the severity of the disease. In children under one year old with mild forms of the disease, the amount of food is reduced by 15-20% in the first 3-4 days of the disease, the missing volume is filled with liquid. Optimal nutrition is the use of adapted milk or fermented milk formulas, if there is no breast milk.

The benefits of continuing breastfeeding during ACI include minimizing the loss of protein, other nutrients, electrolytes, water, and energy; reducing nutrient losses in the stool and restoring the intestinal mucosa; providing anti-infective factors and avoiding sensitization to foreign proteins; and maintaining lactation in mothers who continue breastfeeding (8).

Breastfeeding is the most important protective factor against acute intestinal infections in children in the first year of life. In developing countries, the risk of death from acute intestinal infections is 14 times lower for breastfed children than for children who do not receive breast milk.

Breastfeeding is a mechanism that partially compensates for the physiological immune deficiency of children in the first months of life. Breast milk contains many components of immunity, the deficiencies of which are noted in newborns: cells (macrophages - 60%, neutrophils - 25%, lymphocytes, mainly T-lymphocytes - 10%) and soluble components (immunoglobulins, cytokines, chemokines, receptors, growth factors and innate immunity). However, the main mechanism by which breastfeeding protects the child from intestinal pathogens in the first months of life is the presence of a large number of oligosaccharides and glycoconjugates in breast milk.

Breast milk oligosaccharides constitute the third most dense component of breast milk after lactose and fat. Their mass is greater than that of protein, at 3 g/l. The oligosaccharide composition of breast milk varies considerably in quantity and quality among nursing mothers.

Oligosaccharides, glycoconjugates, and glycolipids in breast milk are receptors for pathogens and their toxins, competing for binding to adhesion receptors on epithelial cells, thereby inhibiting their pathogenic effects. Table 3 lists the protective factors of breast milk and their additional pathogens and their toxins.

It is not recommended to include cow's milk, kefir and unadapted milk formulas in the diet of infants with acute intestinal infections due to the risk of sensitization to cow's milk protein and the development of diapedetic bleeding in the gastrointestinal tract, osmotic diarrhea and increased acidosis.

In the diet of children over 6 months, fermented milk mixtures are combined with 5-10% rice and buckwheat porridge (gluten-free) with water and vegetable puree (puree soup), then the diet is gradually expanded depending on the age of the child and the nature of the diet before the disease.

In the first 5 days of the disease, in moderate and severe forms of acute intestinal infections in infants, the daily amount of food is reduced to 1/2-2/3 of the norm with fractional administration (8-10 times a day). In severe forms of acute intestinal infections, protein deficiency can occur due to impaired absorption and loss of amino acids through the intestines during the acute period. This is typical for children with malnutrition, premature birth, and prolonged starvation diets, especially for children with acute intestinal infections accompanied by invasive diarrhea. In such cases, from the 3rd day of the disease, adapted milk formulas enriched with protein are prescribed, used for feeding premature babies, as well as cottage cheese. The general principle of the diet for infants with ACI is to “rejuvenate” the diet: reduce the amount of food, increase the frequency of feeding, and temporarily eliminate complementary foods with gradual expansion.

In children over one year of age with gastroenteritis, foods that increase intestinal motility, fermentation, contain fiber, have an irritating, sensitizing effect, and are high in fat are excluded from the diet.

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