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ANTIBIOTIC-ASSOCIATED DIARRHEA: PATHOGENESIS, ACTUAL ASPECTS OF PREVENTION AND TREATMENT

Abstract

The article provides an overview of current Russian and foreign literature on the problem of pathogenesis, treatment and prevention of antibiotic-associated diarrhea. Antibiotic-associated diarrhea is one of the most relevant aspects of modern drug therapy due to the frequent prescription of antibacterial agents. Antibiotic-associated diarrhea (according to WHO) is defined as the presence of three or more episodes of an unformed stool for two or more consecutive days that occurred during or after the end of antibiotic therapy. The risk of this disorder development is high when using aminopenicillins, as well as their combinations with clavulanic acid, cephalosporins, or clindamycin. Despite the presence of a common etiologic factor — the intake of antibacterial agents, the immediate causes and mechanisms of antibiotic-associated diarrhea development in patients may be different. The article describes the main issues of the etiology and pathogenesis of this pathology, the risk factors for the development of antibiotic-associated diarrhea are named, which allows predicting this complication in certain categories of patients. The virulence factors of Clostridium difficile, Klebsiella oxytoca, Candida spp. and the clinical manifestations associated with their effects are highlighted. The clinical variants of this disease are described: 1) pseudomembranous colitis; 2) segmental hemorrhagic colitis; and 3) "mild illness". Contemporary literature data on the possibilities of prevention, as well as effective methods of treatment of antibiotic-associated diarrhea, are presented. For the treatment and prevention of all clinical forms of antibiotic-associated diarrhea, most authors suggest the use of drugs that make up the deficiency of normal intestinal microbiota — probiotics and prebiotics. The problem of the benefits of adjuvant therapy with probiotics during the course of antibiotics for the prevention of antibiotic-associated diarrhea remains controversial, the effectiveness and safety of the use of various probiotic cultures for this purpose is being studied. The information presented in this review is intended to target physicians to the rational use of antibacterial agents, and to early diagnosis of their most frequent side effect, antibiotic-associated diarrhea.

Key words: *antibiotic-associated diarrhea, pseudomembranous colitis, segmental hemorrhagic colitis, intestinal candidiasis, probiotics*

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AAD — antibiotic-associated diarrhea

The history of the existence and use of antibiotics as pharmaceuticals is less than a century, since the discovery of penicillin in 1928 by Alexander Fleming. However, it is impossible to imagine modern medicine without this group of drugs. Doctors of almost all medical specialties in their daily practice are faced with diseases and conditions that require the administration of antibiotic therapy. However,

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in addition to the undoubted benefits for humanity in terms of combating infectious agents, antibiotics have brought new problems and challenges to medical science, namely, a variety of pathologies associated with the violation of the qualitative and quantitative composition of human symbiotic microflora. One of the most common of these problems is antibiotic-associated diarrhea.

Antibiotic-associated diarrhea (AAD) occurs in 5–30% of patients, early — directly during antibiotic therapy, delayed — within two months after its completion.

Antibiotic-associated diarrhea (according to WHO) refers to the presence of three or more episodes of loose stools for two or more consecutive days that occurred during or after antibiotic therapy.

Almost all antibiotics can cause diarrhea, but the risk is highest when using aminopenicillins, as well as their combinations with clavulanic acid, cephalosporins, clindamycin [1, 2, 3]. According to the literature, the following incidence of AAD with administration of antibacterial agents was found: clindamycin — 20–30%, amoxicillin/clavulanate — 10–25%, cefixime — 15–20%, ampicillin — 5–10%, macrolides — 5%, fluoroquinolones — 2% [4] (Figure 1).

Experts from the Russian Gastroenterological Association in the guidelines for the diagnosis and treatment of Clostridium difficile-associated disease (2016) [5] identify the main risk factors for this infection, which include the fact of antibiotic therapy, as well as being treated in a hospital, and proven risk factors: age over 65 years, presence of concurrent diseases, recent surgery on the digestive tract, enteral nutrition, reduced acid production in the stomach, including, as a result of antisecretory therapy, and immunosuppressive therapy. A significant number of studies described in foreign literature are devoted to the study of risk factors for the development of AAD, and in particular AAD caused by Clostridium difficile infection [6–9, 10]. According to the results of meta-analyses of these numerous works, the importance of the following factors is also proven: simultaneous administration of several antibiotics, prior therapy with fluoroquinolones [8], administration of non-steroidal anti-inflammatory drugs, prolonged hospitalizations. Vitamin D deficiency [9] and high level of fecal interleukin-8 [10] were identified as possible risk factors for Clostridium difficile infection. The authors note the need for further research in this area, as the more significant factors of Clostridium difficile infection development will be determined, the more successful its prevention can become.

Despite the presence of a common etiological factor — treatment with antibacterial agents — direct causes and mechanisms of AAD in patients may be different. Different variants of AAD classifications based on AAD etiology and pathogenesis can be found in the literature. The division of AAD into diarrhea caused by Clostridium difficile infection and idiopathic form is most widely used [11]. Idiopathic AAD, in turn, is divided into infectious and non-infectious variants. Infectious idiopathic AAD is a diarrhea developed as a result of excessive growth of opportunistic intestinal flora due to suppression of normal microbiota. The most common etiological factor of this AAD variant is Clostridium difficile (16–20% of cases), as well as Clostridium perfringens, Staphylococcus aureus, Klebsiella oxytoca, and Candida spp. [2, 3]. Non-infectious idiopathic AAD may be due to the chemical effect of the antibiotic itself and/or is a consequence of its side effects on the

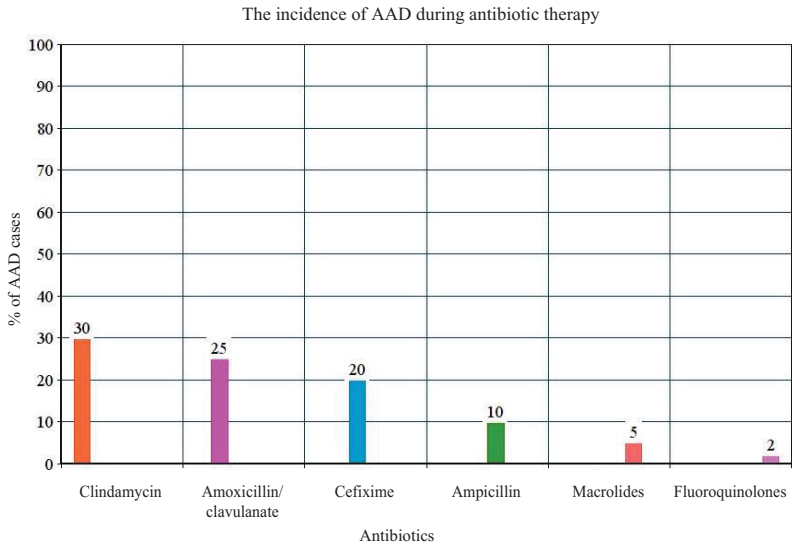

Figure 1. *The incidence of AAD during treatment with various antibiotics*

intestinal wall: for example, macrolides have the ability to stimulate the motilin receptors of the digestive tract and accelerate gastric evacuation and intestinal transit [12]; clavulanic acid enhances the motility of the small intestine; cephalosporin antibiotics stimulate postsynaptic receptors of gamma-aminobutyric acid in the mesenteric plexus and thus stimulate intestinal motility. Non-infectious AAD can also be osmotic or secretory in nature and occur due to impaired metabolism of bile acids and decomposition of carbohydrates in obligate anaerobic microflora [12]. In addition, osmotic pressure in the lumen of the intestine may increase due to incomplete decomposition and absorption of antibiotics themselves (cefixime). Intensification and acceleration of deconjugation and dehydroxylation processes of bile acids disrupts the absorption of fats, resulting in steatorrhea [13]. On the other hand, the suppression of lactobacilli increases the content of non-metabolized bile acids, which provoke the secretion of water and chloride ions in the lumen of the large intestine, which causes the secretory component of diarrhea.

Excessive growth and colonization of the large intestine with Clostridium difficile, an endospore-forming Gram-negative bacterium, causes the development of the most severe type of AAD — pseudomembranous colitis. Clostridium difficile is an obligate anaerobe; its endospores are found in large amounts in soil and water. It is known that up to 6% of healthy individuals have this bacterium in a very small amount in their intestinal microbiota. Due to the fact that Clostridium difficile is resistant to most antibiotics, during antibiotic therapy in the suppression of obligate intestinal flora, it is able to multiply excessively. Clostridium difficile is considered the cause of AAD in 10–25% of cases [3].

Clostridium difficile does not have the ability to invade. Pathological processes in the mucous membrane of the large intestine in pseudomembranous colitis develop under the action of bacterial exotoxins — enterotoxin A and enterotoxin B.

Enterotoxin A has a direct cytotoxic effect on the epithelial cells of the colon, binding to receptors on the apical surface of epithelial cells and reducing the density of the cell connection with each other, which leads to increased fluid secretion in the lumen of the intestine and enterotoxin B penetration into the intestinal wall. Enterotoxin B increases vascular permeability and stimulates the release of proinflammatory cytokines. Along with cytotoxic and cytopathic effects, it also contributes to the development of pronounced general intoxication and, in some cases, encephalopathy [14].

One of the waste products of Clostridium difficile, p-cresol, inhibits beta-dopamine-hydroxylase resulting in impaired formation of norepinephrine from dopamine. Thus, in the human body there is an imbalance of neurotransmitters, which explains the phenomenon of encephalopathy in patients with pseudomembranous colitis. In severe cases, a significant deficiency of norepinephrine and related phenomena of neurogenic orthostatic hypotension are possible [15].

The clinical manifestations of AAD vary from mild spontaneously stopped diarrhea to fulminant pseudomembranous colitis. There are three variants of AAD depending on the etiological agent, symptoms and features of intestinal mucosa lesion [17]: 1) pseudomembranous colitis; 2) segmental hemorrhagic colitis; 3) mild illness.

Pseudomembranous colitisis (AAD, the etiological agent of which is Clostridium difficile) is characterized by a watery stool with possible impurities of blood and mucus with a frequency of defecation from 5 to 30, presence of fever, leukocytosis. In severe pseudomembranous colitis fluid and electrolyte disorders, cardiovascular disorders, possible complications (toxic megacolon, toxic shock syndrome, intestinal perforation) develop.

Segmental hemorrhagic colitis is a variant of AAD, the etiological agent of which is Klebsiella oxytoca, a Gram-negative facultative aerobic bacterium, a representative of human opportunistic microflora. It is known that there is a toxigenic strain of Klebsiella oxytoca that can actively reproduce in the intestine when suppressing a normal microbiota and produces a toxin that has a direct cytotoxic effect on intestinal epithelial cells. As a result, hemorrhagic inflammation develops, which is manifested by diarrhea with blood admixture [16].

Mild illness is the mildest form of AAD, including any symptoms from the intestines occurring due to antibiotic therapy unrelated to any of the above variants of AAD. Thus, this definition includes dysbiosis that occurs when antibiotics are used, including that which is associated with excessive growth of Candida fungi in the intestine [17]. Colonization of

both the large and small intestine by Candida spp. becomes possible due to the suppression of normal intestinal microbiota by broad-spectrum antibiotics with anti-anaerobic activity and/or antibiotics creating a high concentration in the wall of the digestive tract, such as cephalosporins of the third and fourth generations. The presence of risk factors such as hypochlorhydria or achlorhydria, reduced motility, prior mucosal damage as a result of any chronic pathology, nutrient deficiency, chemotherapy or radiation therapy is also significant.

Virulence factors of Candida spp.: capacity for adhesion in almost all human tissues; mycogenic sensitization of the patient's body due to the action of Candida-produced alcohol dehydrogenase and acid P2-protein; ability to synthesize aspartic protease and phospholipase, as well as hemolysin, the presence of various endotoxins that damage human tissues; capacity for rapid adaptive phenotypic variability; immunomodulatory effects that reduce the effectiveness of human antifungal resistance; capacity for suppression of normal human flora.

The growth of Candida fungi in the human digestive tract can have three forms:

1) Silent fungal carriage.
2) Non-invasive enterocolitis (luminal mycopathy) is an inflammation of the mucosa not penetrating beyond the lamina propria of the mucosa; occurs without transformation of fungus in filamentous form; the pathogenesis of this form of intestinal candidiasis is associated with the development and extension of dysbiosis with intoxication due to the products of abnormal fermentation of nutrients and metabolites of fungi, with the development of secondary immunodeficiency and fungal allergy.
3) Invasive damage to the intestinal wall due to the penetration of the filamentous form into the mucous membrane. Most often, these forms of intestinal candidiasis are stages of the pathological process [17].

Treatment of AAD depends on the specific etiological agent. General measures are discontinuation of antibiotic treatment causing AAD, correction of fluid and electrolyte disorders, malabsorption syndrome, correction of immunodeficiency. The use of antidiarrheal agents that reduce motility is absolutely unacceptable, as it increases the time of contact of bacterial or fungal toxins with the intestinal wall.

Vancomycin and/or metronidazole are used for the treatment of pseudomembranous colitis caused by Clostridium difficile. An important condition is the oral administration of vancomycin and metronidazole, intravenous administration of these drugs is much less effective, since this method of administration does not create sufficient concentrations in the intestinal wall [4, 20]. Segmental hemorrhagic colitis caused by Klebsiella oxytoca usually does not require antibiotics, but in some severe cases it is possible to use fluoroquinolones or metronidazole [16].

In the treatment of intestinal candidiasis when choosing antifungal agents, it is important to correctly assess the form of candidiasis: invasive or non-invasive.

Non-invasive candidiasis (luminal mycopathy) does not require the administration of resorbable antifungal agents, and it is enough to use slightly resorbable polyenes: nystatin, natamycin. In invasive candidiasis administration of resorbable azole antifungals in mean therapeutic doses is mandatory [17].

For the treatment and prevention of all clinical AAD forms, most authors suggest the use of drugs that compensate for the deficiency of the normal intestinal microbiota — probiotics and prebiotics [19, 21, 22]. The question of the benefits of concomitant probiotic therapy during the course of antibacterial agents for the prevention of AAD remains debatable to some extent, and efficacy and safety of various probiotic cultures used for this purpose are being studied. It is believed that probiotics restore the resistance of the intestinal mucosa to colonization by pathogenic and opportunistic bacteria, which is reduced due to the suppression of normal intestinal microbiota, and increase local immunity. Also, the contribution of prebiotic strains to the process of intestinal digestion, which also becomes defective secondary to antibiotic therapy due to changes in the composition of the intestinal microflora, is important to prevent the development of diarrhea. It should be taken into account that the efficacy of various probiotics for the treatment and prevention of AAD varies and depends on the resistance of the culture to the action of gastric acid and bile, the ability to colonize the mucous membrane of the colon and sensitivity to antibiotics [22].

Experts from the Global Gastroenterological Association agree that, to date, convincing evidence of the efficacy of therapy with probiotics in the prevention of Clostridium difficile infection has been accumulated. However, they agree with the opinion of USA Food and Drug Administration (FDA) that more information is required which is based on randomized placebo-controlled blind studies in order to be able to name specific probiotics with proven efficacy [23]. On the other hand, in foreign literature in recent years there are more reviews on this issue, as well as meta-analyses of data on the efficacy and safety of probiotics for the prevention of Clostridium difficile infection designed to help the practitioner to form an opinion on this problem [24, 25, 26, 27]. The data presented in these works convincingly show a positive result of early and rational use of probiotics with antibiotic therapy to prevent the development of AAD.

A systematic review and regression meta-analysis conducted by scientists at Cornell University (New York) include 19 published studies with a total of 6,261 patients. The incidence of manifest Clostridium difficile infection was shown to be 1.6% in patients receiving probiotics during antibiotic therapy compared with 3.9% in the control cohort, and this difference was statistically significant ($P < 0.001$). Meta-analysis showed that the efficacy of probiotic therapy for the prevention of AAD was the higher, the faster it was started after the first dose of the antibiotic. There was no increase in the frequency of any side effects in combined therapy with antibiotics and probiotics. The authors concluded that early administration of probiotics reduces the risk of Clostridium difficile infection by more than 50% in inpatients receiving antibiotics [27].

Other meta-analyses have also shown that polycomponent probiotics including up to 16 different strains, as well as monocomponent ones containing Saccharomyces boulardii and Lactobacillus rhamnosus GG have the highest preventive efficacy [28]. For the treatment of severe and recurrent forms of pseudomembranous colitis that are resistant to vancomycin and/or metronidazole, some authors suggest using the method of fecal microbiota transplantation. In Western literature in recent years, a number of studies have been published that report the successful use of this method, including in patients with immunodeficiency [29, 30, 31, 32].

Despite gradually accumulating experience of a successful fight against AAD, many authors recognize that the best way of preventing this condition is a carefully weighed approach to antibiotic therapy in each case.

Based on the given literature data, it can be concluded that antibiotic-associated diarrhea is one of the important problems in modern medicine attracting the attention of scientists and doctors around the world. Risk factors and pathogenetic mechanisms of development of this pathology, as well as the potential of probiotic therapy in terms of preventing the occurrence of AAD require further study.

Conflict of Interests

The authors declare no conflict of interests.

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