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## ANTIBIOTIC-ASSOCIATED DIARRHEA: A MODERN VIEW ON THE PROBLEM.

<https://doi.org/10.5281/zenodo.7830849>

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### **Annotation.**

The article is devoted to the current problems of pediatrics, clinical pharmacology and gastroenterology. The article presents a literary review and covers scientific views on the factors of antibiotic-associated diarrhea in children and hazardous factors that leads in the occurrences of gastrointestinal diseases.

### **Keywords.**

*antibiotic-associated diarrhea(AAD), C.difficile, pseudomembranous colitis, antibiotics, risk factors, diagnostics, complications of AAD.*

Relevance of the problem: Today, the occurrence of antibiotic-associated diarrhea in children is an urgent problem in pediatrics, gastroenterology and clinical pharmacology. This disease is based on various reasons, but the main one is the use of antibiotics and the penetration of infectious agents as a result of disruption of the normal functioning of the intestinal microflora. Untimely diagnosis and the tactics of the treatment of this disease can lead to complications. Accompanied by severe violations of the functions of organ and body systems.

Prevalence: The use of antibiotics has become widespread in pediatric practice as the main tool for the treatment of acute infectious and inflammatory diseases. The use of AB, having an arsenal of chemicals in its composition, can have a toxic effect on the body: dysbiosis, allergic reactions, AAD, etc. According to the current classification, AAD is three or more episodes of unformed stools for two or more consecutive days that appear on against the background of the use of antibacterial agents or within 8 weeks after their cancellation. [1]

According to WHO (2017) more than 1.7 billion children under 5 years of age suffer from diarrhea every year. Antibiotic-associated diarrhea (AAD) accounts for 4,5-7% of cases.

Etiology and pathogenesis: Antibiotic-associated diarrhea (AAD) complicates from 2% to 25% of antibiotic treatment courses, but the incidence varies depending on the antibiotic used; it is more common, for example, during therapy with ampicillin (5% to 10%), amoxicillin-clavulanate (10%-25%), or cefixime (15%-20%) and less common during therapy with fluoroquinolones (1% to 2%) or trimethoprim-sulfamethoxazole (<1%). [2]

The most significant causative agent of antibiotic-associated diarrhea (AAD) is *C. difficile*, with which, according to various data, from 10 to 25% of all AADs and from 90 to 100% of cases of pseudomembranous colitis (PMC) are associated.

*C. difficile* is an obligate anaerobic Gram-positive spore-forming bacterium with natural resistance to most antibiotics, toxin-forming strains of which are the main causative agent of nosocomial colitis, including the most severe PMK with high mortality (up to 15-30% of cases). [1]

In healthcare facilities, the pathogen spreads mainly in the form of spores that are highly resistant to the action of some antiseptics and disinfectants. The main transfer factors are environmental objects (bedding, towels, furniture, tools) and the hands of medical staff. The mechanism of *C. difficile* infection is fecal-oral, realized by ingestion of spores of the pathogen. Patients colonized by *C. difficile*, and especially those with clinical manifestations of clostridium-associated infection (CAI), are a source of pathogen to other patients and contribute to the maintenance of the spread of *C. difficile* in the healthcare facility, which requires the use of contact isolation measures and careful adherence to infection control principles. [3]

The frequency of asymptomatic carriage of *C. difficile* in newborns reaches 50%, among the adult population - 3-15%, increases significantly (up to 15-40%) when taking antibiotics. The role of antibiotics in the pathogenesis of diarrhea is reduced to the suppression of the normal intestinal microflora, in particular, to a sharp decrease in the number of non-toxicogenic clostridia, and to the creation of conditions for the reproduction of *C. difficile* and their transition into toxin-forming forms.

*C. difficile* produces several toxins without invading the intestinal mucosa. Toxin A (enterotoxin) initiates damage to colonocytes and causes diarrhea, has a prosecretory and pro-inflammatory effect, is able to activate pro-inflammatory cells, releasing inflammatory mediators and substance P. Toxin B (cytotoxin) has a damaging effect on colonocytes and mesenchymal cells. The pro-

inflammatory and disaggregating action of toxins A and B leads to a significant increase in the permeability of the intestinal mucosa.

Toxin B is 1000 times more powerful cytotoxin than toxin A, but its cytotoxic effect is due to impaired polymerization of intracellular actin filaments. [1]

Risk factors: Risk factors for AAD- age, type of antibiotic treatment, type of combined treatment, and site of infection-were analyzed.

Results of Dominic Turck et al. research (2003): Of 650 children included, 11% had an episode of AAD, lasting a mean of 4.0 +/- 3.0 days, beginning a mean of 5.3 +/- 3.5 days after the start of antibiotic treatment. No child was hospitalized because of AAD. The incidence of AAD was higher in children less than 2 years (18%) than in those more than 2 years (3%;  $P < 0.0001$ ). The incidence of AAD was particularly high after administration of certain antibiotics (amoxicillin/clavulanate, 23%;  $P = 0.003$  compared with other antibiotics). The type of combined treatment and site of infection did not influence the onset of AAD.[5]

Diagnostics: Hanna Pituch et al. (2007), investigated the prevalence of the Clostridium perfringens enterotoxin (CPent) in stool samples originally submitted for detection of Clostridium difficile toxins. Fifty-two fecal samples from inpatients were screened simultaneously for C. difficile and C. perfringens toxins: 75% of the specimens were positive for TcdA/TcdB toxins, 40% were positive for CPent, and 31% gave positive test results for both. It is interesting to note that only a relatively small number of C. perfringens isolates were positive for the cpe gene. All C. difficile strains were susceptible to metronidazole, but intermediate metronidazole resistance was documented for the C. perfringens isolates, which decreased upon in vitro passaging in the absence of metronidazole. We recommend that CPent detection should be included when diagnosing patients with presumed antibiotic-associated diarrhea. [6]

Complications of AAD: One of the complications of antibiotic-associated diarrhea (AAD) is pseudomembranous colitis, which occurs in 100% of cases of C. difficile associated infection. Manifested by fibrinous inflammation of the colon wall with the formation of superficially located plaques in the area of mucosal necrosis, resulting from the destructive action of toxins released by this bacterium. [4]

Pseudomembranous colitis (PMK) does not depend on the dose of the antibiotic, nor on the multiplicity, nor on the route of administration of the drug. Clinical manifestations of PMK in children are diverse and develop acutely. Young children are characterized by fever, refusal to eat, increased intoxication,