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PRACA ORYGINALNA
ORIGINAL ARTICLE

# PECULIARITIES OF ANTIBIOTIC-ASSOCIATED DIARRHEA DEVELOPMENT IN CHILDRENWITH ACUTE RESPIRATORY INFECTIONS

# ODMIENNOŚCI ROZWOJU BIEGUNKI POANTYBIOTYKOWEJ U DZIECI Z OSTRYMI INFEKCJAMI GÓRNYCH DRÓG ODDECHOWYCH

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## ABSTRACT

**Introduction:** Acute respiratory infections (ARI) are the main cause of morbidity in most countries. The probability of complications and age determine antibiotics administration.

Antibiotic associated diarrhea (AAD) is one of the side effects of antibiotics.

**The aim:** The study of the prevalence rate of AAD and the characteristics of its development in children with ARI.

**Materials and methods:** The study included 75 children aged from 1 to 12 y diagnosed with ARI, who were treated with age-specific doses of antibiotics. The influence of children's anamnesis, parents' health on the development of AAD was studied with odds ratio calculation (OR).

**Results:** In general, AAD incidence was 52%. The highest frequency 59.3% was observed in children under 3 y. AAD most often developed in children treated with amoxicillin – 92%. The greatest dependence of AAD development was connected with breastfeeding less than 6 months – OR was 7.65, preterm birth – 2.9, functional GIT disorders in anamnesis – up to 3.14, allergy – 2.33. The risk of AAD development increased with the age of parents more than 35 y – 5.03, at the age of parents less than 18 and older than 35 y – 4.09, parents' allergies - 3.74 and parents smoking - 2.43.

**Conclusions:** The most important factors of AAD development on antibiotics therapy in children with ARI are breastfeeding less than 6 months, functional GIT disorders and allergic conditions in anamnesis. Suboptimal age and parents' health (GIT disorders, allergic conditions and unhealthy habits) also increase the risk of AAD development.

**KEY WORDS:** Antibiotic associated diarrhea, children

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## INTRODUCTION

Acute respiratory infections (ARI) are the main cause of morbidity and mortality in both developed and developing countries [1; 2]. A child may have up to 6-8 cases of acute respiratory infection during a year. The incidence of acute respiratory infections is recorded throughout the year but more abundantly in the autumn and winter. Around 90% of children have respiratory pathology during flu epidemic. Viruses dominate the etiology of ARI, they are considered to constitute 55-90% of cases [3]. Respiratory syncytial virus is most often revealed. It is pointed out that it is responsible for the development of acute respiratory disease in 60% of children and in 80% of infants at the peak of viral season
[4]. A number of authors emphasize the role of rhinovirus in infants (human rhinovirus, HRV), which can be detected in 38% of infants with ARI. Respiratory syncytial virus is detected less often in children of above mentioned group
– 5-7% of cases. [3]. The frequency of bacterial infection at ARI in infants can reach 10%, however, the frequency of its detection depends on viruses present in the body [3]. In general, the availability of bacteria as etiological factor may be 27% for all age groups of children [1].

The probability of bacteria presence, ARI severity, du-ration, age and other factors condition antibiotics admin-istration. Unfortunately, despite the high probability of complications of antibiotic therapy, the frequency of their use at acute respiratory infection is rather high. It is pointed out that it constitutes 52-66% depending on the type of ARI [1]. The number of side effects of antibiotic therapy is large and includes the development of allergic condi-tions, the formation of pathogenic microflora resistance, the formation of intestinal microbiome disorders and the development of antibiotic associated diarrhea (AAD).

## THE AIM

The research aim is to study the prevalence rate of AAD and the characteristics of its development in children with ARI.

## MATERIALS AND METHODS

We have examined 75 children aged from 1 to 12 years old diagnosed with of ARI bacterial etiology treated in in-pa-tient department. All of them were treated with age-spe-

**Table I.** Prevalence antibiotic-associated diarrhea

| | Group 1 | Group 2 | Group 3 | Total |
|---|---|---|---|---|
| Antibiotic-associated diarrhea, n/N/% | 16/27/59,3 | 14/29/48,3 | 9/19/47,4 | 39/75/52 |

Note: n - number of cases; N - total number in groups; % - percent.

**Table II.** Characteristics of study groups.

| | Group 1d | Group 1 | Group 2d | Group 2 | Group 3d | Group 3 |
|---|---|---|---|---|---|---|
| | 16 | 11 | 14 | 15 | 9 | 10 |
| Boys, abs/% | 10/62,5 | 6/54,5 | 8/57,1 | 6/40,0 | 4/44,4 | 5/50,0 |
| Age, y, M±м | 1,01±0,16 | 1,29±0,23 | 4,64±0,34 | 4,33±0,33 | 10,11±1,03 | 10,9±0,85 |
| Weight, kg, M±м | 9,29±0,58 | 10,57±0,76 | 16,44±1,25 | 17,63±0,65 | 29,23±4,59 | 32,9±3,55 |
| Height, cm, M±м | 69,50±3,37 | 77,09±2,95 | 106,57±2,54 | 105,47±2,50 | 138,11±5,76 | 147,5±5,28 |

Note: M±м – Mean and Mean Error, abs/% - absolute value of the characteristic/percent of the characteristic.

cific doses of antibiotics. The children were divided into 3 groups depending on age, group 1 – children aged from 2 months to 3 years old, group 2 – children aged from 4 to 6 years old, group 3 – children aged from 7 to 12 years. Each group was divided into 2 subgroups depending on the presence or absence of AAD signs. Antibiotic-associated diarrhea was defined as 3 or more cases of loose stool after antibiotic administration [5].

The influence of some factors of children's anamnesis, the peculiarities of parents' health, their age and some habits on AAD development in a child on the background of ARI and antibiotic therapy were studied.

The obtained results were processed by descriptive statistics methods calculating average error share, mean, its error, obtaining of odds ratio (OR), calculation of significance test $\chi 2$, F-test (F), Student's t-test (r).

## RESULTS

The incidence rate of antibiotic-associated diarrhea was 52% for all examined patients (Table I). There was a ten-dency to large values in infants, although there was no significant difference in the study groups. The highest frequency - 59.3% was noted in the children of group 1 under the age of 3 years old. The lowest value was recorded in the patients of group 3 - 47.4%. The further analysis of OR value showed that the age-dependent value less than 1 year and AAD development in group 1 was 1.75 at p = 0.69. The calculation of analogous dependence for three groups revealed the value of OR as 2.17 at p = 0.34.

AAD most often developed in children who were treated with antibiotics of penicillin line. We have treated 92% of patients with amoxicillin, who later developed symptoms of antibiotic-associated diarrhea. We have detected 86% of ADD cases in children who were treated with third generation cephalosporins. The incidence rate of AAD at macrolides therapy was the lowest – 25% of patients who took these antimicrobial drugs.

The assessment of gender composition showed a tenden-cy for boys to prevail in groups 1 and 2 among children with antibiotic-associated diarrhea (Table II). At the same time, these differences were not significant. The maximum number of boys was in the group 1d, where they constituted 62.5%. The group 2d included less number of boys – 57.1%. At the same time, the girls predominated in the group 3d. The indices of physical development did not have signifi-cant differences in the study groups either depending on age or presence or absence of diarrhea. Nevertheless, there was a tendency to large values of mass and height in the groups of AAD children.

The value of odds ratio was studied to determine the dependence of some anamnesis features and development of antibiotic-associated diarrhea (Fig. 1) . The values of OR were determined for preterm birth, previous signs of functional diarrhea and/or vomiting, intestinal colic, allergy and also breastfeeding less than 6 months. The highest value of OR was obtained for a pair of breastfeeding less than 6 months and AAD development – 7.65. The influence value of preterm birth on AAD development was 2.9. The presence of functional disorders in anamnesis also increased the risk of AAD development from 2.7 to 3.14 units. The value of dependence of AAD development on allergy was somewhat less – 2.33. All these values were significant.

The next group of indices included the hereditary history peculiarities, age and lifestyle of the parents of the studied children (Fig. 2). The greatest value of OR was determined for pairs of parents' age and AAD development. At the parents' age over 35 years old the frequency of AAD in-creased by 5.03 units. Odds ratio at the age of less than 18 years old was 2.91, but its value was not significant. The indices combination of parents' age less than 18 years old and older than 35 years old increased the risk of AAD development by 4.09 times. The presence of allergic con-ditions also increased the probability of AAD. In this case, OR was 3.74 units. In fact, the risk of AAD in children in the study groups increased by the same value at periodic bowel disorder in parents' anamnesis.

The influence of parents' smoking and alcohol on the risk AAD development in children of the study groups was

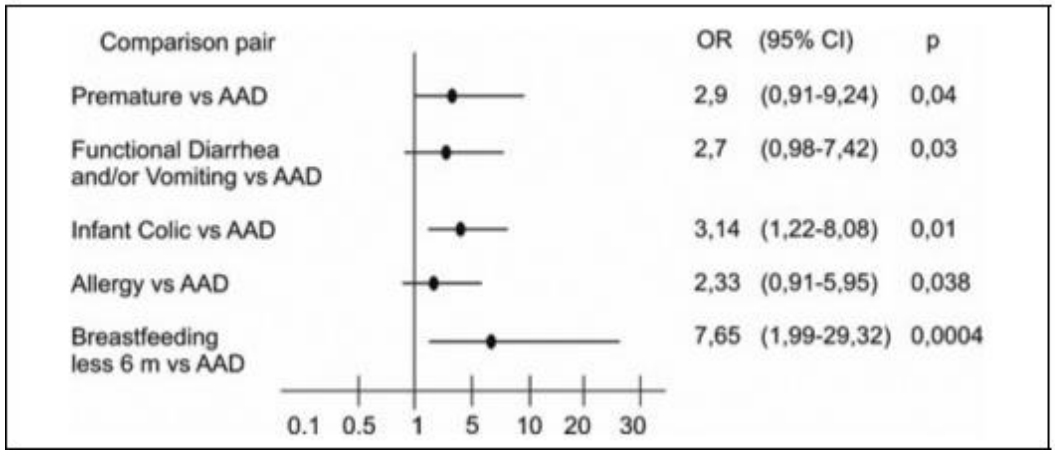


**Fig. 1.** Effect of selected anamnesis characteristics on development of the antibiotic associated diarrhea

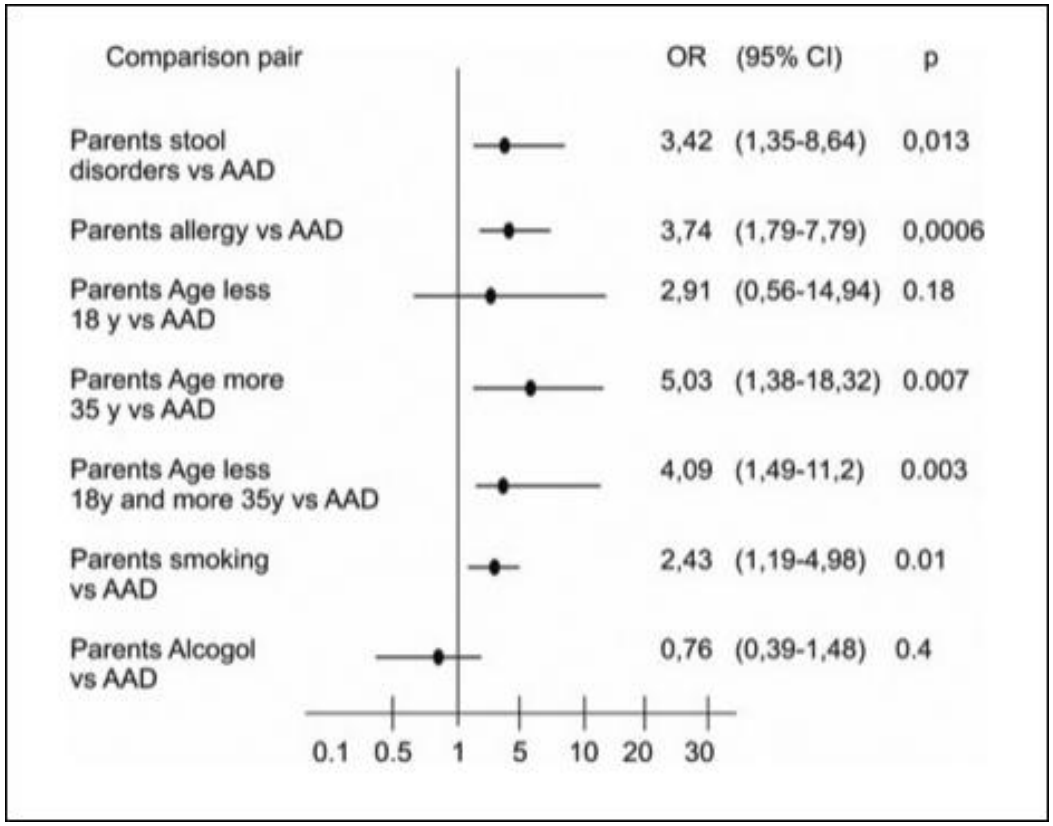


**Fig. 2.** Effect of selected parents' anamnesis characteristics on development of the antibiotic associated diarrhea

studied. The index in the pair of smoking – AAD appeared to be 2.43, while OR for the pair alcohol consumption – AAD was only 0.76 units.

## DISCUSSION

Our data showed that the incidence rate of antibiotic-associated diarrhea was 52% in all examined children. This complies with the data of other researchers. The literature indicates that AAD frequency can be from 5 to 60% [5, 6, 7, 8]. The dependence of AAD development on age is also mentioned by some authors [9] for 2-year-old children and younger. At the same time, other researchers deny the existence of such connection [10]. Our data did not show any significant differences as to age, although such trend existed, especially for children under 1 year old according to odds ratio. The possibility of such influence can be determined by the formation of intestinal microflora, which is modulated by breastfeeding, mother's diet and introduction of complementary feeding in infants [11, 12, 13].

Among the antibiotics, amoxicillin most often caused the development of AAD, less often – cephalosporins and macrolides. The literature also indicates that amoxicillin with clavulanic acid often caused the development of AAD which is confirmed by our data [7, 9, 10].

The most significant increase in risk of AAD develop-ment was observed at breastfeeding less than 6 months. The role of breastfeeding in the development of microbiome and immune system is extremely important and crucial [14, 15]. It has been established that breast milk has its own microbiota [16]. Not only its direct transfer to a child is pos-sible, but also the indirect influence of other factors on the microflora formation of a child such as pro- and prebiotics, oligosaccharides, immunoglobulin, immunomodulation

factors. Moreover, the effect of breastfeeding can be traced up to the age of 3 [11]. In this regard, the composition of microflora in children at breast and formula feeding is different [17, 18], which can determine the probability of antibiotic-associated diarrhea development.

An important factor in AAD development was preterm birth, OR was 2.9 units. Some scientists suggest that the peculiar features of a baby's intestinal microbiome are formed during intrauterine growth under the influence of microflora composition of uterine cavity, amniotic fluid, in some cases having an influence on preterm birth.[19, 20, 21, 22]. The peculiarities of condition, care, diseases and feeding of premature babies influence the mechanisms of microflora formation, which, possibly, leads to its greater sensitivity to antibiotics.

The duration of breastfeeding and preterm birth could affect the indices of physical development in children with antibiotic-associated diarrhea. They did not differ significantly from those in children without AAD, although there was a tendency to higher weight and height in all study groups.

A number of events of a child's life were identified, the presence of which increased the risk of antibiotic-associated diarrhea development. The presence of functional disorders such as diarrhea and vomiting increased the risk of AAD development. The cases of intestinal colic in anamnesis increased the risk of AAD development to greater degree. The pathogenesis of functional disorders development is connected not only with the dissociation "brain-intestine" relationship, but also with the changes in CNS activity, microbiota composition and immune status [23]. It is indicated that microbiota regulates and participates in the metabolism of micro- and macronutrients [24]. In addition, it is a virtual endocrine organ [25]. Thus, the features of formation and composition of microflora determine the level and characteristics of gastrointestinal tract functioning, including the development of pathological conditions. This also proves our finding that allergic conditions have significant influence on AAD development in children. It is indicated that differences in microbiota composition during neonatal period may precede the development of allergic conditions [26, 27] and, in fact, determine their development.

The parents' health, the peculiarities of life style also influenced AAD development. The significant relationship was observed between parents' allergic conditions and bowel disorders with the probable development of antibi-otic associated diarrhea in a child. The role of hereditary factors in the formation of diseases is widely recognized. The results of human microbiota studies show its significant genetic predetermination, especially at initial stages, but also throughout life, which is realized through inflamma-tory reactions and immune response condition [27, 28]. The role of hereditary factors could be confirmed by the influence of age factor of parents on AAD development. At the age less than 18 and over 35 years old of both par-ents at child's birth, the probability of AAD development increased.

The presence of bowel disorders in a child and parents and their connection with AAD may indicate the role of hereditary factors in disorders formation of axis connection "brain-intestine" [23, 29]. Probably, preterm birth also plays a certain role in dissociation of this connection.

Also, the dependence of some parents' unhealthy habits on the risk of AAD development in a child was found. In particular, the influence of alcohol and smoking was studied. Smoking increased by 2 times the probability of antibiotic associated di-arrhea in a child. Perhaps, this influence was mediated through the duration of feeding in socially disadvantaged families.

## CONCLUSIONS

The most important factors of antibiotic-associated diar-rhea development in children with ARI are breastfeeding less than 6 months as well as signs of previous functional disorders and allergic conditions.

A number of features of parents' health – bowel disor-ders, allergic conditions, suboptimal age of parents at child's birth, unhealthy habits – increase the risk of developing antibiotic associated diarrhea in children with ARI.

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