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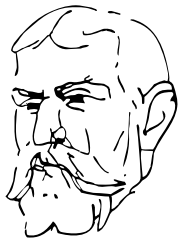

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CONTENTS

ORIGINAL ARTICLES

ORIGINAL ARTICLE

ANTIBIOTIC ASSOCIATIVE DISORDERS OF THE MICROBIOCENOSIS OF THE COLON IN INFANTS WITH ACUTE RESPIRATORY DISEASES

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ABSTRACT

The aim: Study the effect of antibiotics of different groups on the condition of the colon microflora in infants with acute respiratory pathology

Materials and methods: 140 infants with acute respiratory pathology were examined. Clinical, laboratory and instrumental examination, assessment of the functional state of all organs and systems, chest x ray, clinical signs of the colon microbiocenosis violation, analysis of bacteriological examination and immunological studies of local colon immunity (immunoglobulin concentration (sIgA, IgA, IgG, IgM) in coprofiltrates) were done.

Results: The negative effect of antibiotics of different pharmacological groups on the colon microflora state in infants with acute respiratory diseases has been established. The indigenous microflora of the colon is most inhibited by drugs from the group of 3rd generation cephalosporins, aminoglycosides and their combination. While cephalosporins 1-2nd generations, penicillins and macrolides to a lesser extent affect the state of the microbiocenosis of the colon. The use of two courses of antibacterial therapy to a greater extent disrupts the microbiocenosis of the colon in the examined children, compared with one course of therapy. In commune acquired pneumonia and acute complicated bronchiolitis in infants on the background of antibiotic therapy there is a probable decrease in secretory immunoglobulin in coprofiltrate (sIgA), compared with healthy children ($p < 0.05$).

Conclusions: The analysis of the obtained results showed that antibiotic therapy negatively affects not only the condition of the colon microflora in the examined children, but also suppresses humoral factors of local immunity of the colonic mucosa. Key words: digestive tract microbiocenosis, antibiotic therapy, children.

KEY WORDS: children, antibacterial therapy, gastrointestinal tract microbiocenosis

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INTRODUCTION

The human gastrointestinal tract (GIT) is a relatively open biological system through which the macroorganism actively interacts with the microbial world of the environment. The number of microorganisms in the GIT increases in the distal direction, reaching a maximum in the colon (1011 - 1012 bacterial cells per 1 g of content) [1, 2]. That is why most of the scientific work on the study of human microbial ecology is devoted to the study of the composition and functions of the biocenosis of the colon, which is the most densely populated microflora biotope of the GIT. Representatives of 17 famalies, 45 genuses and more than 400 species of microorganisms were found in the colon biotope [2-5].

There are dominated "characteristic" groups of microorganisms in each biocenosis. In many literary sources they are called differently - obligate, dominant, main, indigenous, resident microflora [3]. It is assigned a leading role in maintaining the symbiotic relationship between the macroorganism and its microbiota. Obligatory microflora performs a regulatory function, counteracts the population of the habitat by random microorganisms and excessive growth of populations of opportunistic pathogens, actively participates in the processes of fermentation, synthesis, detoxification and immunostimulation [3-6].

The causes of the disorder in the microbial status of the body are extremely diverse. It is known that the microecology of the intestine can be influenced by the nature of food, age, season, state of the environment. Unfortunately, the evolution of medicine and pharmacy does not always pay attantion to maintain a friendly symbiosis of human with his microflora. Most modern treatments adversely affect the physiological characteristics of the biocenosis, primarily by inhibiting the beneficial saccharolytic microflora and increasing the population level and aggressive properties of opportunistic pathogens [1, 2, 7, 8]. However, the strongest negative effect on the human microbial ecosystem is manifested by the use of massive, inadequate antibiotic therapy. Unfortunately, there are no antibacterial agents that act exclusively on pathogenic bacteria without affecting the indigenous flora. This requires a rational, reasonable and adequate approach to the use of antibacterial therapy. In addition, there is a need to study the effect of antibiotic therapy on the normal microflora of the colon.

THE AIM

The aim of the research was to study the effect of different antibiotics groups on the state of the colon microflora in infants with acute respiratory diseases.

MATERIALS AND METHODS

There were examined 140 infants with commune acquired pneumonia (CAP) and acute complicated bronchiolitis (ACB). All children were hospitalized in the infants department of Vinnitsa Regional Children's Clinical Hospital. The study included infants who received antibiotic therapy prior to admission to the hospital without using probiotics. Children were divided into two groups: the first group included 80 infants (57.1%) with CAP and the second group consisted of 60 children (42.9%) with ACB. There was a control group consisted of 30 healthy infants.

The work began after obtaining the consent of the patient and his parents to participate in the study in compliance with the provisions of the UN Convention on the Child Rights. The research materials do not contradict the International Code of Medical Ethics (1983) and the laws of Ukraine, meet the basic bioethical norms of the Helsinki Declaration, adopted by the General Assembly of the World Medical Association, the Council of Europe Convention on Human Rights and Biomedicine (1977).

For the diagnosis and treatment of CAP we used British Thoracic Society guidelines for the management of community acquired pneumonia in children (2011) and Clinical practice guidelines of the management of community-acquired pneumonia in infants and children older than 3 months of age of the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America (2011). For the diagnosis and treatment of ACB we used The American Academy of Pediatrics guidelines on the diagnosis, treatment, and prevention of bronchiolitis in children aged 1 to 23 months (2016) and NICE recommendations for *diagnosis and management of bronchiolitis in children (2015).*

All children who were involved in the study underwent thorough clinical, laboratory and instrumental examination, assessment of the functional status of all organs and systems, chest radiography. In addition, an assessment of the clinical picture of the violation of the microbiocenosis of the colon, analysis of bacteriological examination to determine the microbiological landscape and analysis of immunological studies of local immunity of the colon in the study groups. The state of local immunity of the colon in the examined children was determined using the immunological method. The concentration of immunoglobulins (sIgA, IgA, IgG, IgM) in coprofiltrates was determined.

Statistical processing of the study results was performed by conventional methods of variation statistics using IBM SPSS statistic (12th edition).

One of the leading places in the treatment of CAP and ACB is occupied by etiologic therapy with antibiotics, taking into account the age of the child and the conditions of its infection. The analysis of previous antibiotic therapy in the examined patients on admission to the hospital showed that 30 children (37.5%) with CAP received the 3rd generation cephalosporins. Penicillins and penicillin with clavulanic acid were given to 11 children of the first group (13.8%). However, aminoglycosides and the combination of cephalosporins with aminoglycosides were given to the same number of children in this group - respectively 9 patients (11.2%). Also, the same number of children in this group (10.0%) received 1st generation and 2nd generation cephalosporins. Only 5 children of the first group (6.3%) received macrolides.

We also analyzed antibiotic therapy in children of the second group. Thus, almost the same number of children in this group were used 3rd generation cephalosporins - 11 children (18.3%), penicillins - 10 children (16.7%) and macrolides - 10 children (16.7%). At the same time, 9 (15.0%) children in this group received 1st generation cephalosporins and 8 children (13.3%) – 2nd generation cephalosporins. Also 7 children in second group (11.7%) used aminoglycosides and 5 children (8.3%) used the combination of cephalosporins and aminoglycosides.

RESULTS

Since, as mentioned above, the most common cause of colonic dysbiosis in infants with CAP and ACB is antibiotic therapy, the clinical manifestations of impaired colonic microbiocenosis depending on the pharmacological group of drugs were further studied.

Thus, we found that dyspeptic and pain syndromes occurred in all patients treated for the underlying disease with 3rd generation cephalosporins, aminoglycosides, and a combination of cephalosporins and aminoglycosides. There was a significant difference with children used penicillins, macrolides and cephalosporins 1st and 2nd generations ($p < 0,05$) in the incidence of these syndromes.

According to stool character, diarrhea was probably more often diagnosed in children receiving aminoglycosides than in those treated with penicillins, macrolides and 1st generation cephalosporins ($p < 0.05$). At the same time, normal stool was observed with a significantly higher frequency in children who had macrolides, compared with patients treated with penicillins and 3rd generation cephalosporins ($p < 0.05$). In addition, constipation was diagnosed with a significantly higher frequency in children treated with penicillins, cephalosporins 1st and 2nd generations, compared with children who received aminoglycosides ($p < 0.05$).

Dermato-intestinal syndrome was diagnosed with a significantly higher frequency in children treated with macrolides and 1st generation cephalosporins compared with children who had combination antibiotic therapy ($p < 0.05$). Estimation of the frequency of bowel movements during the day in the examined children did not reveal a significant difference between groups with different antibiotic therapy ($p > 0.05$).

Analysis of the nature of stool consistency revealed that liquid stools were diagnosed in patients receiving combination antibacterial therapy for the underlying disease with a significantly higher frequency ($p < 0.05$). At the same time, soft stools were significantly more frequent in children used macrolides and 3rd generation cephalosporins, compared with children treated with 2nd generation cephalosporins ($p < 0.05$).

Subsequently, the results of microbiological examination of feces in the examined children were analyzed, taking into account the obtained antibiotics or their combinations (Fig. 1). The level of bifidobacteria was significantly lower in

Table I. The concentration of immunoglobulins in coprofiltrates in the examined children depending on the pharmacological group of antibacterial therapy

Immunoglobulin	Immunoglobulin concentration in serum, M±m							
	Control group	Penicillin	Macrolide	Cephalosporin 1st generation	Cephalosporin 2nd generation	Cephalosporin 3rd generation	Aminoglycoside	Combination of Cephalosporin and aminoglicoside b
	g/l	g/l	g/l	g/l	g/l	g/l	g/l	g/l
sIgA	0,79±0,04	0,19±0,11*	0,06±0,01*4	0,18±0,09*	0,27±0,10*	0,28±0,18*	0,06±0,02*4	0,09±0,03*
IgA	0,05±0,01	0,07±0,03	0,09±0,04	0,09±0,04	0,06±0,02	0,09±0,03	0,05±0,03	0,05±0,02
IgG	0,59±0,05	0,27±0,08*	0,16±0,02*	0,15±0,03*	0,15±0,03*	0,17±0,04*	-	0,13±0,01*
IgM	-	0,02±0,01	0,02±0,01	0,03±0,01	0,03±0,01	0,08±0,021234	0,08±0,011234	0,07±0,011234

Notes: * - probable differences in the indicators of the control group (p <0,05). 1 - probable differences in the indicators of children receiving penicillins (p <0,05). 2 - probable differences in the indicators of children received macrolides (p <0,05). 3 - probable differences in the indicators of children received cephalosporins of the 1st generation (p <0,05). 4 - probable differences in the indicators of children received cephalosporins of the 2nd generation (p <0,05).

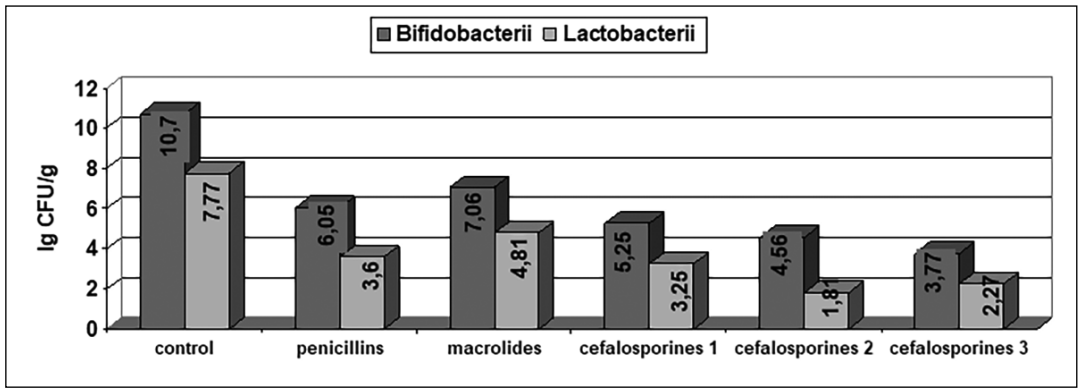

Fig. 1. Results of microbiological examination

children received 3rd generation cephalosporins and a combination of cephalosporins and aminoglycosides, compared with infants used penicillins and macrolides (p <0.05). In addition, the concentration of bifidobacteria was significantly lower in children received 2nd generation cephalosporins, compared with those treated with macrolides (p <0.05).

Analysis of the lactobacilli amount in the colon showed a probable decrease of their level in children received 2nd and 3rd generation cephalosporins, combination antibacterial therapy, compared with those treated with penicillins, macrolides and aminoglycosides (p <0.05). In addition, the concentration of lactobacilli was significantly lower in children received combination antibacterial therapy compared with infants treated with 1st generation cephalosporins (p <0.05).

The study of the *Escherichia coli* level in the examined infants depending on the antibacterial therapy showed a probable decrease only in those who used 2nd and 3rd generation cephalosporins and combination antibacterial therapy, compared with the control group (p <0.05). Analysis of the opportunistic pathogens amount did not reveal a significant difference depending on antibacterial therapy (p> 0.05). Only in children treated with 3rd generation cephalosporins, the amount of Citrobacter was significantly higher than in infants treated with combination antibacterial therapy (p <0.05).

The next part of our research was to analyze the clinical presentation of the colon microbiocenosis disorders in infants with CAP and ACB, depending on the number of antibacterial therapy courses. Analysis of the obtained data indicates that dyspeptic and dermatointestinal syndromes were diagnosed with almost the same frequency in both groups of the study (p> 0.05). However, the frequency of individual clinical manifestations of dyspeptic syndrome probably differed between children with a different number of antibiotic therapy courses. Thus, constipation was observed more often in children received one course of antibiotic therapy, compared with those who received two courses of such treatment (p <0.05). In addition, fecal mucus was observed with a significantly higher frequency in children received two courses of antibiotic therapy (p <0.05).

The pain syndrome was also diagnosed with a higher frequency in infants after two courses of antibiotic therapy (p <0.05), compared with those who had only one course. Analysis of the frequency of bowel movements showed that children who underwent one course of antibiotic therapy, in most cases (p <0.05) were diagnosed with stool frequency 0-1 times a day, compared with those who received two courses (p <0.05). After assessing of the consistency of feces were found that solid stools observed more often in

children after one course of antibiotic therapy ($p < 0.05$). The frequency of other clinical symptoms did not have a significant difference between children with different number of antibiotic therapy courses ($p > 0.05$).

Subsequently, during a microbiological study of feces in the examined children, depending on the number of courses of antibacterial therapy, was found that two courses of antibacterial therapy is more likely suppress the amount of bifidobacterias than in children received one course of antibiotic therapy ($p < 0.05$). At the same time, the amount of lactobacilli and *Escherichia coli* probably did not depend on the number of antibacterial therapy courses ($p > 0.05$). Hemolytic type of *Escherichia coli* was sown in higher concentrations in children received two courses of antibacterial therapy, compared with the infants after one course of such treatment ($p < 0.05$).

One of the parts of our study was to analyze local immunity humoral factors of colon depending on the pharmacological group of antibacterial therapy. Probable decrease of the sIgA concentration in coprofiltrate in both groups compared with the control group ($p < 0.05$) were found. In addition, the level of sIgA in the coprofiltrate was significantly higher in children received 2nd generation cephalosporins, compared with the infants treated with macrolides and aminoglycosides ($p < 0.05$). However, the sIgA level in the examined children coprofiltrate probably did not depend on the pharmacological group of antibacterial therapy they treated with ($p > 0.05$) (Table I).

The concentration of IgG in the coprofiltrate was probably reduced in both groups of the study, compared with the control group ($p < 0,05$). However, IgG was not detected in the coprofiltrate of children treated with aminoglycosides. At the same time, the level of IgM in the coprofiltrate was significantly lower in children treated with penicillins, macrolides, 1st and 2nd generation cephalosporins, compared with infants treated with 3rd generation cephalosporins, aminoglycosides and combination antibacterial therapy ($p < 0.05$).

DISCUSSION

The intestinal microflora relative to the influence of various factors of the external environment, but its compensatory capabilities is not immiscible. There are many etiological factors that can cause a microbiocenosis of the colon. But the leading role in the development of microbiocenosis disorders of the large intestine belongs to antibacterial therapy (antibiotic violations) [9-12]. Most antibiotics used for therapeutic purposes are violated in the process of evolution associative relations between intestinal microorganisms [9, 12]. As numerous studies show, the number of antibiotics accumulated in the contents of the colon, many times exceeds the minimum inhibitory concentrations for a large number of representatives of indigenous microflora [10, 13].

The evaluation of the large intestine microbiocenosis was based not only on the results of the study of feces microflora, but also on the peculiarities of its clinical manifestations. An overview of modern literary sources showed that the most inherent clinical characteristics of antibiotic-sized violations of the large intestine may be dyspeptic, pain and dermatinestinal syndromes [10, 12].

The obtained results of our work show the occurrence of not only diarrhea but also constipation and alternation of diarrhea and constipation on the background of antibiotic therapy. At the same time, constipation was diagnosed with a significantly higher frequency in children on the background of treatment with penicillins and 1st and 2nd generations cephalosporins.

The analysis of modern literature sources demonstrates the development of antibiotic-associated diarrhea (AAD) against the background of antibacterial therapy. The incidence of AAD in the population varies between 5–35% of cases and depends on the patient's age and type of antibiotics [14]. AAD is considered to be predominantly nosocomial pathology (20–25%), which in some cases can reach 60% [1]. However, recently there has been a tendency to increase the frequency of this complication among outpatients [6, 15, 16]. The use of any antibiotics can cause diarrhea, especially those that affect anaerobes. However, more frequent intake of aminopenicillins, cephalosporins of II and III generations is associated with a high risk of developing AAD [3].

The development of dyspeptic phenomenon in violation of the colon microbiocenosis depends on the number of courses of antibacterial therapy. However, the symptoms of pain are more common in children received two courses of antibiotic therapy.

The gastrointestinal tract microflora plays an important role in the functioning of the immune system of the body [7, 17, 18]. The secretory form of IgA dominates over immunoglobulins of other classes in the external secretions of our body [9]. sIgA antibodies inhibit bacterial adhesion to the mucosa, neutralize viruses and participate in immune exclusion [9, 19]. In addition, in almost all secretions of the digestive tract, as well as in coprofiltrates, the same immunoglobulins are found as in serum (IgA, IgG, IgM). However, their concentration in the secretions is slightly lower than in the serum under the influence of local factors. These immunoglobulins enter the secretions of the digestive tract as a result of transudation from serum [2]. Normal sIgA synthesis contributes to the resistance of children to diseases whose pathogenesis is associated with the attachment of pathogens to mucous membranes [9]. Therefore, reducing the concentration of sIgA in coprofiltrates may contribute to the development of various pathologies.

The state of local immunity of the mucous membrane of the colon in examined children was evaluated by humoral factors, namely at the levels of secretory immunoglobulin A and general immunoglobulins (IgA, IgG, IgM) in faces.

The analysis of the obtained results showed that antibiotic therapy has a negative effect not only on the condition of the colon microflora in the examined children, but also suppresses humoral factors of local immunity of the colon mucosa. This fact completely coincides with the clinical observations of modern scientists, where it is indicated that the suppression of the microflora of the colon by antibacterial drugs is a significant increase in the activity of intestinal enzymes. Activation of intestinal enzymes leads to degradation of labile immunoglobulins and loss of antibody activity.

Further in-depth study of the impact of multicomponent probiotics on the state of microbiocenoses of the child's body will help optimize treatment and prevention approaches in the prevention and treatment of antibiotic-associated disorders in pediatrics.

CONCLUSIONS

There are clinical (dyspeptic, pain and dermatointestinal syndromes) and microbiological signs of violation of the microbiocenosis of the colon in infants with CAP and ACB on the background of antibiotic therapy.

The negative effect of antibiotics of different pharmacological groups on the state of the colon microflora in infants with acute respiratory diseases is present. The indigenous colon microflora is mostly inhibited by antibacterial drugs from 3rd generation cephalosporins, aminoglycosides groups and their combination. The using of two courses of antibiotic therapy greater extent disrupts the colon microbiocenosis in the examined children.

There is a probable decrease in secretory immunoglobulin in coprofiltrate (sIgA) in infants with CAP and ACB on the background of antibiotic therapy compared with healthy children ($p < 0.05$).

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The Authors declare no conflict of interest.

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