

The use of antibacterial drugs in the treatment of coronavirus infection in children in real outpatient clinic practice

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Abstract

Introduction. In light of the available data on the unjustified use of antibiotics in children with acute respiratory viral infections, the frequency of prescribing antibacterial drugs to children with a new coronavirus infection in real clinical practice is of great practical and scientific interest.

The objective of the study was to study the frequency of antibiotic therapy and identify factors that increase the risk of needing antibiotics in children with coronavirus infection at the outpatient stage.

Materials and methods. A retrospective cross-sectional study was conducted on the basis of children's polyclinics in Samara from November 2021 to July 2022, which included a survey of parents and an analysis of outpatient records of 100 children who were under outpatient observation and treatment for COVID-19. An analysis was made of the frequency of prescribing antibiotics to them and potential factors predisposing to their prescribing to children with COVID-19. The obtained data were subjected to statistical processing using the IBM SPSS Statistics 25 program and a comparative analysis.

Results. The frequency of use of antibiotic therapy according to the results of the study was 11% and did not exceed the Russian average data (14.3%). When analyzing the factors influencing the doctor's decision to prescribe an antibiotic to a child with coronavirus infection, the most important were a history of recurrent respiratory infections (children from the FIC group), as well as the presence of concomitant diseases and background conditions in children, primarily chronic bronchopulmonary diseases and nervous system.

Discussion. The prescription of antibiotics for children with a new coronavirus infection at the outpatient stage remains empirical due to the limitations of the use of laboratory and instrumental methods for additional examination of the child, which objectifies the likelihood of a secondary bacterial infection. Despite this, the frequency of antibiotic use according to the results of the study was 11% and did not exceed the Russian average data (14.3%), as well as the average frequency of antibiotic use for acute respiratory viral infections in children in the Russian Federation (21.5–23.3%).

Keywords: children, COVID-19, coronavirus infection, antibiotic therapy, antibiotics.

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Применение антибактериальных препаратов в лечении коронавирусной инфекции у детей в реальной амбулаторно-поликлинической практике

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Аннотация

Введение. В свете имеющихся данных о необоснованном применении антибиотиков у детей при острых респираторных вирусных инфекциях частота назначения антибактериальных препаратов детям с новой коронавирусной инфекцией в реальной клинической практике представляет большой практический и научный интерес.

Целью проведенного исследования стало изучение частоты применения антибактериальной терапии и выявление факторов, повышающих риск необходимости в антибиотиках, у детей с коронавирусной инфекцией на амбулаторно-поликлиническом этапе.

Материалы и методы. Проведено ретроспективное одномоментное исследование на базе детских поликлиник г. Самары в период с ноября 2021 года по июль 2022 года, включившее анкетирование родителей и анализ амбулаторных карт 100 детей, находившихся на амбулаторном наблюдении и лечении по поводу COVID-19. Проведен анализ частоты назначения им антибиотиков и потенциальных факторов, предрасполагающих к их назначению детям с COVID-19. Полученные данные были подвергнуты статистической обработке с использованием программы IBM SPSS Statistics 25 и проведением сравнительного анализа.

Результаты. Частота применения антибиотикотерапии по результатам проведенного исследования составила 11 % и не превысила российских среднестатистических данных (14,3 %). При анализе факторов, влияющих на принятие решения врача о назначении ребенку с коронавирусной инфекцией антибиотика, наиболее важными оказались рецидивирующие респираторные инфекции в анамнезе (дети из группы ЧБД), а также наличие сопутствующих заболеваний и фоновых состояний у детей, в первую очередь хронических заболеваний бронхолегочной и нервной системы.

Обсуждение. Назначение антибиотиков детям с новой коронавирусной инфекцией на амбулаторном этапе остается эмпирическим в связи с ограничениями использования лабораторных и инструментальных методов дополнительного обследования ребенка, объективизирующих вероятность присоединения вторичной бактериальной инфекции. Несмотря на это, частота применения антибиотикотерапии по результатам проведенного исследования составила 11 % и не превысила российских среднестатистических данных (14,3 %), а также средней частоты применения антибиотиков при ОРВИ у детей в Российской Федерации (21,5–23,3 %).

Ключевые слова: дети, COVID-19, коронавирусная инфекция, острая респираторная вирусная инфекция, антибактериальная терапия, антибиотики.

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INTRODUCTION

Coronaviruses have long been known as pathogens of acute respiratory diseases, though that virus was not associated with dangerous infections until the beginning of the XXI century. Coronaviruses SARS-CoV and MERS-CoV, which became

pathogens of atypical pneumonia and differed from predecessors in higher pathogenicity [1] were studied from 2002 to 2012. At the end of 2019 humanity faced a new coronavirus — SARS-CoV-2 that managed to erase the borders between countries and continents and led to the pandemic

which the medical community has been fighting with for the past 3 years. In the early stage of the pandemic the low incidence of COVID-19 was recorded in children compared to adults. It was also noted that the clinic in children was mainly characterized by a mild or asymptomatic course, also, children were considered to be an important element in the infection spread [2–5]. However afterwards, the incidence of children showed the growth tendency and by early 2022 the specific weight of the age group 0-17 reached 13 % [6], moderate and severe courses were registered more often [7].

In COVID-19 pandemic the problem of irrational administration of antibiotics became especially relevant. According to clinical guidelines, the administration of antibiotics is justified when attaching a bacterial infection [8], however, the frequency of bacterial complications in the course of COVID-19 was known to be not that high. In particular, a meta-analysis of 24 studies, involving 3 338 patients, showed that the frequency of bacterial co-infection at the moment of seeking medical care was 3,5 %; secondary bacterial infections complicated the course of COVID-19 in 14,3 % of patients [1, 9]. Despite the fact that the administration of antibiotic therapy in viral infections is not justified and is not recommended in the early stages of the disease, the use of antibiotics in COVID-19 at the start of the pandemic reached 80–90 % [7, 10, 11] in Russia and 70–80 %, according to foreign studies [12, 13]. this tendency was observed both in outpatient practice and hospitals, and the presence of bacterial complication and their possible sources often remained uncertain [14].

Unjustified antibiotic administration in children with acute respiratory viral infections (ARVI) has long been an urgent problem of pediatrics. In 79,6 % of cases with such complaints an acute viral infection (rhinopharyngitis, nasopharyngitis, rhinitis, ICD-10 J06.9 code) is diagnosed in children; moreover, systemic antibiotics are administered in 23 % of cases. In addition, the study results of ARVI treatment practices in children in outpatient clinics of Russia shows that in 84 % of cases such administrations can be considered as unjustified. Over the past few years, the frequency of prescribing children antibacterial drugs for ARI in outpatient care has not changed significantly,

but there is a tendency of its decrease: for instance, in 2017 antibiotic therapy was administered to 23,3 % of children with ARI, in 2018 – 22,9 %, in 2019 – 22,7 % and in 2020 – 21,5 % [15]. According to other results that cover 18 cities of Russia, the frequency of systemic antibacterial therapy in uncomplicated ARVI reached an average of 59,6 % [16].

In accordance with temporary guidelines for treating children with the new coronavirus infection, principals of first aid include: home lock down, the lack of objective patient monitoring, limitation to apply additional research [1]. The pediatrician's decision on administrating antibiotic therapy may be the key point in COVID-19 outpatient treatment tactics in children that, as a rule, is necessary with moderate and severe disease and may require hospitalization of the child. Thus, relevant is the question of administration frequency in an actual outpatient practice of antibiotic therapy in children with coronavirus infection and reasons for its use.

OBJECTIVE of the study is to examine the frequency of antibiotic therapy and to identify factors that increase the risk of needing antibiotics in children with coronavirus infection at the outpatient stage.

METHODS

To achieve the objective, a retrospective cross-sectional study of the coronavirus infection (SARS-CoV-2) in children was conducted. The patient's monitoring was held on the basis of children's polyclinics in Samara Kuibyshevsky, Samarsky and Industrial Districts from November 2021 to July 2022. Inclusion criteria in the study were: confirmed case of COVID-19 (диагноз по МКБ U07.1) in the anamnesis, no hospitalization for coronavirus infection, voluntary consent of the child's legal representative to the participation and processing of personal information. The data were collected through a survey of parents, questionnaires and an analysis of outpatient records of children. The study involved 100 children aged 3 months to 17 years. In the course of the data obtained there was an analysis of the frequency of antibiotic administration in children with coronavirus infection at the outpatient stage and potential factors, predisposing the prescription

of antibiotics to children with COVID-19. For this purpose, all the children were divided into 2 groups, depending on the use of antibiotic therapy in treating coronavirus infection: the 1st group included the children with received course of antibiotic treatment, the 2nd group consisted of the children with no administered antibiotics.

The obtained data were subjected to statistical processing using the IBM SPSS Statistics 25 program and a comparative analysis. The results of nominal values are expressed in absolute terms with percentages (%). Pearson's criterion χ^2 was used to evaluate differences in nominal values (percentage). Due to the skewed form distribution, the quantitative characteristics are presented as median and quartiles: Me [Q1; Q3], the group comparison was made by the Mann-Whitney test. The results were considered statistically significant at $p < 0,05$.

RESULTS

Of 100 children, included in the final analysis, the 1st (main) group of 11 patients (11 %) received antibiotic treatment, the second group consisted of 89 children (89 %) with no antibiotic therapy. The children's age was 5,8 [1,4; 11,6] years (the girls — 6,3 [2,6; 12,8] years old, the boys — 4,6 [1,8; 11,0] years old).

The separation by gender in the group was similar: the 1st group included 54,5 % of boys and 45,5 % of girls, the second group — 57,3 % and 42,7 %, respectively. The children's age with administered antibiotics was 6,9 [5,4; 11,5] years that is a little higher than the age of the children with no antibiotic treatment, being 5,0 [1,7; 11,6] years ($p > 0,05$), though the difference seems to be unreliable.

When analyzing the course of coronavirus infection and the development of complications in the children of the groups under study, 59 % of patients turned out to experience a mild course and 41 % had a moderate case; no severe course was found. When prescribing antibiotics, a moderate course was stated in the majority of cases: the 1st group recorded 10 (90,9 %) cases of moderate coronavirus infection and 1 (9,1 %) mild one. The second group, on the contrary, often had a mild course— in 58 children (65,2 %), and a moderate one was diagnosed in 31 children (34,9 %) ($p < 0,05$). Overall, the frequency of administrat-

ing antibiotic therapy with a moderate course is 24,4 % and a mild one — 1,7 %. Nevertheless, due to a small total number of cases of prescribing antibiotic therapy, the difference of its use in children with various severity of the disease turned out to be unreliable.

Of 11 children with administered antibiotics, 3 patients diagnosed complications in the form of otitis media, sinusitis and urinary tract infection (UTI). 8 patients received antibiotic therapy due to more severe clinical manifestations in the form of severe intoxication, febrile fever, with the presence of related background diseases (5 children with allergic diseases, 2 children with a disease of the nervous system, 1 child with bronchial asthma).

4 children started receiving antibiotics at an early stage (on the 2–3 day of the disease): 1 — with the concomitant diagnosis of bronchial asthma, severe intoxication syndrome and febrile fever, 2 — with the clinic of laryngotracheitis, 1 — with a laboratory confirmed complication (UTI). Yet, early administration of antibiotic therapy in 3 children with no complications can be considered premature and unjustified. Antibiotic therapy was prescribed to 3 children from the 4th day of the disease, and the other 3 patients — from the 5th day. In these cases antibiotics were administered due to severe intoxication, febrile fever, catarrhal syndrome and complication development (otitis media and sinusitis). Another child received antibiotic therapy from the 9th day of the disease due to a longer fever period, though the results of further laboratory and instrumental studies (general clinical blood test and a CT scan of lungs) did not reveal any pathological changes and signs of bacterial complications.

The analysis of clinical COVID-19 manifestations in the examined patients showed that all 11 children with administered antibiotics (100 %) had intoxication symptoms, the second group experienced them more seldom — in 76 children (85,4 %) ($p < 0,05$). Catarrhal syndrome was diagnosed in both groups equally often — 90,9 % and 93,3 %, respectively. The clinical picture of laryngotracheitis was recorded in the 1st group slightly more often than in the second one — in 5 (35,5 %) and 22 (24,7 %) children, respectively ($p > 0,05$). As a result, out of 27 children with laryngotracheitis, 5 (18,5 %) re-

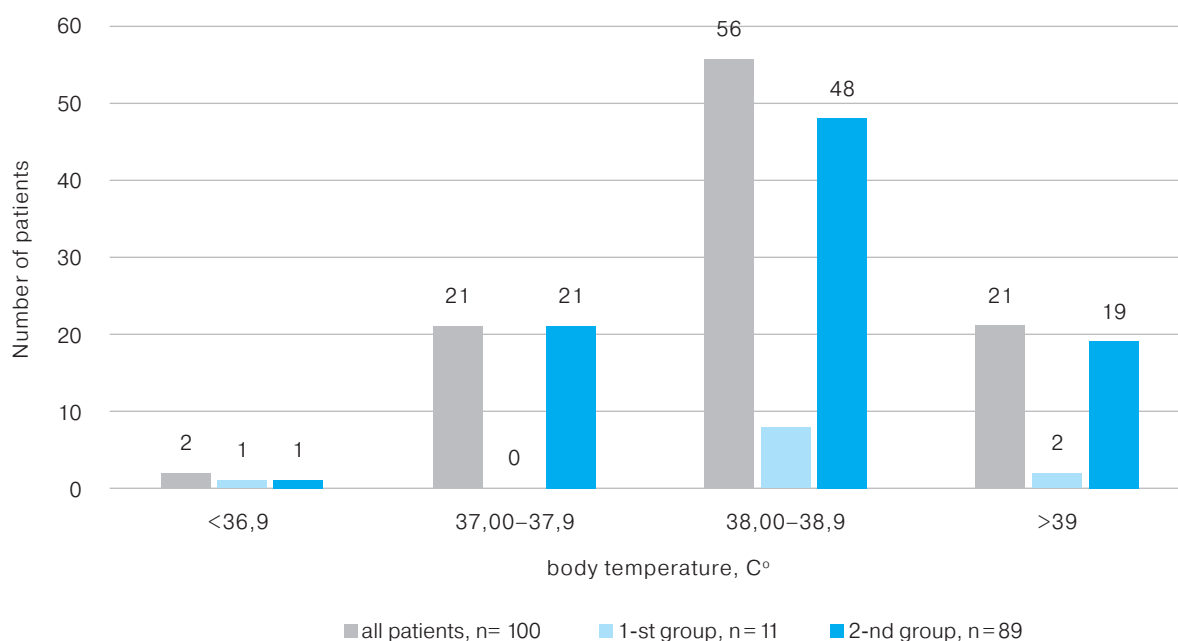


Fig. 1. **Distribution of children of the studied groups according to the degree of increase in body temperature**
 Рис. 1. **Распределение детей изучаемых групп по степени повышения температуры тела**

ceived treatment with the antibacterial drug. In 2 children COVID-19 proceeded with the clinic of obstructive bronchitis; one of them got antibiotics, the other did not. Thus, the 1st group has a higher frequency of bronchial obstruction syndrome (BO), their percentage is 9 %, and in the second group – 1,1 % ($p > 0,05$).

An increase in body temperature was noted in almost all children – in 10 (90,9 %) in the 1st group and in (98,9 %) – in the 2nd one. As the nature of fever often plays a crucial role in administrating antibiotic therapy with ARI in outpatient practice, we analyzed the characteristics of the fever course in the examined children. In both groups the temperature turned out to rise up to febrile numbers, the maximum increase was recorded in a child of 2nd group; also, the temperature was higher in the children of the 1st group than the 2nd one (38,7 [38,5; 38,8] and 38,0 [37,9; 38,7] °C, respectively, $p < 0,05$). The duration of fever was twice as long in the 1st group than in the 2nd one (3,0 [2,0; 5,0] and 2,0 [2,0; 3,0] days, respectively, $p < 0,05$); besides, the percentage of children with long-lasting fever in the 1st group was statistically more significant than in the 2nd one (9,1 % and 2,2 %, respectively, $p < 0,05$). Thus, the children with administered antibiotics had more often cas-

es of fever, characterized by a higher intensity and duration that became the primary indication for prescribing antibiotic therapy. Data on the children distribution of the studied groups by the degree of increase in body temperature are presented in Figure 1.

Considering that children with recurrent respiratory infections, related to the dispensary group “often and long-term ill” (OIC) are frequently administered antibiotic therapy in viral infections unreasonably, we evaluated the anamnesis of our patients, particularly, the frequency of respiratory infections for the previous year and also the frequency of previous use of antiviral and immunotropic drugs. It turned out that the average number of ARVI in both groups was almost the same – 4,9 and 4,2 in the 1st and 2nd groups, respectively. The children in 1st group experienced a little more often cases of severe and complicated ARVI in their history – 7 patients (63,6 %) and 43 patients (48,3 %) in the 1st and 2nd groups, respectively, however, statistically significant difference was not found ($p > 0,05$). The frequency of antibiotic administration during the previous year before coronavirus infection was slightly higher in the 1st group than in the 2nd one – 6 (54,6 %) and 41 (46,1 %), respectively ($p < 0,05$). Moreover, al-

Table 1. **The presence of concomitant diseases in groups of children who received and did not receive antibiotic therapy in the treatment of coronavirus infection**
 Таблица 1. **Наличие сопутствующих заболеваний в группах детей, получавших и не получавших антибиотикотерапию при лечении коронавирусной инфекции**

	1 group		2 group		
Background pathology:	n = 11	%	n = 89	%	p
Allergic diseases	8	72,7	22	24,7	0,04
Bronchopulmonary system	3	27,3	4	4,5	0,05
Nervous system	5	45,5	13	14,6	0,05
ENT organs	3	27,3	12	13,5	0,27
Circulatory system	3	27,3	8	9,0	0,14
Digestive tract	2	18,2	8	9,0	0,33
Musculoskeletal system	2	18,2	8	9,0	0,33
Visual analyzer	2	18,2	7	7,9	0,29

most all the children of the 1st group (90,9 %) received treatment with antiviral and immunomodulatory drugs during the year before coronavirus infection; in the 2nd group the children received the drugs of this group less often, in 78,7 % of cases ($p < 0,05$). However, as we see, the factor of more frequent use of antiviral and immunomodulatory drugs in the children of the 1st group did not influence on the decrease in the need of antibiotic therapy in these children when treating coronavirus infection.

As a result, of 44 children, assigned to the group of frequently ill children, 7 (15,9 %) received antibiotic in COVID-19 treatment. Moreover, in the 1st group 7 children (63,6 %) are assigned to OIC, in the 2nd group — 37 children (41,6 %) ($p < 0,05$). Thus, as we see, burdened anamnesis in the children of OIC group probably turned out to be an important factor in deciding to administer them antibiotics in the treatment of coronavirus infection. At the same time, although the presence of recurrent respiratory infections in the child's history is not an indication for prescribing him antibiotics in ARI, due diligence must be exercised towards such children as they have a higher risk of attaching a bacterial infection and complication development.

To clarify the role of concomitant diseases in deciding to administer antibiotic therapy to children with coronavirus infection, we investigated the presence of concomitant (background) diseases

in the children of the studied group; the results are presented in the table (Table 1).

8 people of the 1st group had allergic diseases (72,7 %), in the 2nd group — 22 people that is only 24,7 %. Despite this, most children with allergic diseases did not receive antibiotic therapy in treating coronavirus infection: only 8 children (26,7 %) out of 30 with allergic diseases were administered antibiotics.

Pathology of the bronchopulmonary system (bronchial asthma or recurrent bronchitis) in the children of the 1st group was diagnosed in 3 (27,3 %) children, in the 2nd group — in 4 (4,5 %) children. It turned out that out of 7 children with pathology of the bronchopulmonary system almost half was administered antibiotics in the treatment of coronavirus infection — 3 (42,9 %) children.

In the 1st group 5 children (45,5 %) had neurological diseases, in the second group — 13 children (14,6 %) are observed by a neurologist; the frequency of nervous diseases in the 1st group exceeds twice the incidence rate in the 2nd group.

Differences in the frequency of detecting pathology in ENT organs, digestive tract, circulatory system, musculoskeletal system and visual analyzer при by comparing the 2nd group turned out statistically insignificant.

The observation results showed that additional research methods were applied quite rarely in treating children with coronavirus infection, only the method of pulse oximetry became rou-

tine, which was used in all 100 children (100 %). Different laboratory and instrumental studies were conducted in 8 cases (8 %). 3 children (3 %) got clinical blood test, none of these children had confirmed laboratory signs of bacterial infection; however, 1 child was administered antibiotic due to clinic sinusitis. Additional studies were undertaken with 4 patients to detect extent of lung lesions: 2 – chest X-ray and 2 – computed tomography of lungs; pneumonia was not found in all the cases. However, an antibiotic was administered to 1 of these patients due to prolonged fever and the development of obstructive syndrome, which in itself, is not an obvious indication for antibiotic therapy. 3 children got general urine analysis, 1 patient got confirmed UTI and was administered antibiotics.

One of the important issues of the study was to investigate the influence of administering antiviral drugs to treat coronavirus infection in children on the disease course and frequency of antibiotic prescription. It turned out that all the children of the 1st group received antiviral drugs (100 %) before administering antibiotic therapy. The frequency of using antiviral drugs in the 2nd group was a bit rarer (93,3 %). Thus, statistically significant differences in the frequency of antibiotic administration to children, depending on the use of antiviral drugs, were not found.

Another significant factor affecting the course of coronavirus infection and the risk of complication development in children is adequate intake of vitamin D, its important role in anti-infective protection is currently well studied [17–20]. So, we analyzed if there were any preventive measure of vitamin D deficiency among the children before the case of new coronavirus infection. It turned out that the children who constantly received prophylactic doses of vitamin D had rare cases of administering antibiotic treatment – of 32 children only 1 child (9 %) required antibiotic therapy. At the same time, the frequency of using antibiotics among the children with no vitamin D prophylaxis was higher – of 68 children 10 people (14,7 %) received antibiotics. Thus, only 1 child from the 1st group (9 %) got vitamin D, in the 2nd group 31 children (34,8 %) regularly received vitamin D. Nevertheless, a statistically significant difference in the data analysis was not found that may be associated with the fact that taking

prophylactic doses of vitamin D does not exclude its deficiency the child's body, and determination of vitamin D level in the blood of the examined children was not held.

DISCUSSION

The study found that antibiotic therapy for children with coronavirus infection was not often administered – in 11 % cases, both due to complications and empirically with no objective signs of bacterial infection. Meanwhile, the revealed frequency of using antibiotic therapy in children with new coronavirus infection at the outpatient stage did not exceed the average frequency of administering antibiotics in children with ARVI as a whole. However, with the exception of single complication cases, most children of the studied group received antibiotic therapy to “secure” them against adverse outcomes of a viral infection and to prevent bacterial complications.

Moderate severity of new coronavirus infection was diagnosed in 90,9 % of patients with administered antibiotics that was certainly considered in prescribing antibiotic therapy. In all these cases the use of antibiotics can be justified by the combination of clinical data: moderate severity of the condition, fever severity (high and long febrile body temperature), the presence of intoxication and pronounced catarrhal syndrome. At the same time, the frequency of prescribed additional tests for estimating the risk of secondary bacterial infection, remains rather low in real clinical practice and it was only 8 % in our study.

In the analysis of the factors influencing the doctor's decision-making on administering antibiotics to a child with coronavirus infection, we discovered that recurrent respiratory infections turned out to be most important in the child's anamnesis (children from OIC group) as well as the presence of concomitant diseases and background conditions, first of all, chronic diseases of bronchopulmonary and nervous system.

Interestingly, our analysis did not reveal any significant effect on coronavirus infection in children, the frequency of prescribing antibiotic therapy, the use of antiviral drugs for treating this disease or previous experience of using antiviral and immunotropic drugs within 1 year before the infection. This may be due to the limited number of cases observed as well as preferential inclusion

of patients with mild and moderate disease course in the group.

CONCLUSION

Antibiotic administration to children with new coronavirus infection at the outpatient stage remains empirical due to the limited use of laboratory and instrumental methods in the child's additional examination, objectifying the probability of secondary bacterial infection. Despite this, the frequency of using antibiotic therapy based on the study was 11 % and did not exceed the Russian average data (14,3 %) as well as an average frequency of antibiotic prescription for ARVI in children in Russia (21,5–23,3 %).

When deciding whether to use antibiotics for COVID-19, the pediatrician should be primarily guided by objective evidence — the development of obvious clinical manifestations of bacterial

complications and (or) laboratory signs of bacterial infection. Early administration of antibiotic therapy to children in the first 3 days of illness only on the basis of high fever and intoxication syndrome with no signs of complications, identified in the study, should be considered premature and unjustified.

Children with chronic diseases, frequent and severe recurrent respiratory infections in the anamnesis, certainly constitute a risk group for developing complications and require increased attention of the pediatrician in terms of timely administering antibiotic therapy. However, unjustified early inclusion of antibiotics in the complex treatment of such patients along with the use of a number of other drugs, prescribed for antiviral and immunomodulatory purposes as well as concomitant diseases, may lead to polypharmacy and adversely affect children's health.

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AUTHORS' CONTRIBUTION:

Ginzburg Anna Sergeevna — contribution to the study, analysis of the results, statistical processing and interpretation of the data, the article writing.

Kiryutkina Anastasia Petrovna — study management, material collection, filling the information cards, analysis and editing of literature data, study material.

Migacheva Natalia Begievna — development of the study design, monitoring the study progress, editing of the study text.