

## Is protracted bacterial bronchitis a new nosological group or an old problem of differential diagnosis of chronic cough in children?

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

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cough, bronchitis, chronic bronchitis, child.

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**The purpose** is to study the clinical-anamnestic and microbiological features of the protracted bacterial bronchitis (PBB), recurrent bronchitis (RB), chronic bronchitis (CB) in children and to determine the risk factors for the development of chronic bronchitis.

**Materials and methods.** A total of 89 children were examined, among them 21 children with PBB, 27 children with RB and 41 children with CB. The study included the collection of anamnesis, objective examination, chest X-ray, bronchoscopy and microbiological examination of the bronchial mucosa and upper respiratory tract composition.

**Results.** An analysis of PBB clinical features showed that their total duration was  $4.1 \pm 0.3$  weeks. In children with RB, the duration of exacerbations did not differ significantly and was  $3.8 \pm 0.4$  weeks. In patients with CB, the annual number of bronchitis and the total duration of cough were two times higher than in patients with RB. Bacteriological analysis showed that *Streptococcus pneumoniae* was the most frequent causative agent of the disease in children with PBB and RB. In children with exacerbation of CB, *Haemophilus influenzae* was more commonly identified. At the same time, such a representative of the normal bronchial microbiome as *Aerococcus viridans*, was identified in 81.0 % of PBB patients, in 33.3 % of RB patients, and in 8.7 % of CB patients.

**Conclusions.** The study showed that risk factors for CB development in children with PBB and RB are the lower respiratory tract *H. influenzae* colonization and decreased activity or absence of the normal airway microbiota (*Aerococcus viridans*).

### Ключові слова:

кашель, зятяжний бактеріальний бронхіт, рецидивний бронхіт, хронічний бронхіт, діти.

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### Зятяжні бактеріальні бронхіти – нова нозологічна група або старі проблеми диференційної діагностики хронічного кашлю в дітей?

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**Мета роботи** – вивчити клініко-анамнестичні та мікробіологічні особливості зятяжних бактеріальних бронхітів (ЗББ), рецидивного бронхіту (РБ), хронічного бронхіту (ХБ) у дітей і встановити фактори ризику розвитку ХБ.

**Матеріали та методи.** Обстежили 89 дітей: 21 хворого на ЗББ, 27 дітей із РБ і 41 пацієнта з ХБ. Дослідження включало детальний збір анамнезу, об'єктивне обстеження дітей, рентгенографію органів грудної клітки, бронхоскопію та мікробіологічне дослідження складу слизової оболонки бронхів і верхніх дихальних шляхів.

**Результати.** Аналіз особливостей клінічного перебігу ЗББ показав, що загальна тривалість становила  $4,1 \pm 0,3$  тижня. У дітей із РБ тривалість загострень вірогідно не відрізнялася та становила  $3,8 \pm 0,4$  тижня. У хворих на ХБ кількість бронхітів на рік і загальна тривалість кашлю були вдвічі більшими, ніж у хворих на РБ. Бактеріологічний аналіз показав, що найчастішим збудником захворювання в дітей із ЗББ і РБ був *Streptococcus pneumoniae*. У дітей із клінікою загострення ХБ частіше визначали *Haemophilus influenzae*. Такий представник нормальної мікрофлори бронхів, як *Aerococcus viridans* ідентифікували у 81,0 % пацієнтів із ЗББ, у 33,3 % дітей із РБ, у 8,7 % хворих на ХБ.

**Висновки.** Дослідження показало, що факторами ризику розвитку ХБ у дітей із ЗББ і РБ є колонізація нижніх дихальних шляхів *H. influenzae* та зниження активності або відсутність нормальної мікрофлори бронхів (*Aerococcus viridans*).

### Ключевые слова:

кашель, бронхит, хронический бронхит, дети.

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### Зятяжные бактериальные бронхиты – новая нозологическая группа или старые проблемы дифференциальной диагностики хронического кашля у детей?

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**Цель работы** – изучить клиничко-анамнестические и микробиологические особенности зятяжных бактериальных бронхитов (ЗББ), рецидивирующего бронхита (РБ), хронического бронхита (ХБ) у детей и определить факторы риска развития ХБ.

**Материалы и методы.** Обследовали 89 детей: 21 пациента с ЗББ, 27 детей с РБ, 41 больного ХБ. Исследование включало детальную сбор анамнеза, объективное обследование детей, рентгенографию органов грудной клетки, бронхоскопию и микробиологическое исследование состава слизистой оболочки бронхов и верхних дыхательных путей.

**Результаты.** Анализ особенностей клинического течения ЗББ показал, что общая их продолжительность составила  $4,1 \pm 0,3$  недели. У детей с РБ продолжительность обострений достоверно не отличалась и составляла  $3,8 \pm 0,4$  недели. У больных ХБ количество бронхитов в году и общая продолжительность кашля были вдвое больше, чем у больных РБ. Бактериологический анализ мокроты показал, что наиболее частым возбудителем заболевания у детей с ЗББ и РБ был *Streptococcus pneumoniae*. У детей с клиникой обострения ХБ чаще определяли *Haemophilus influenzae*. Такой предста-

витель нормальной микрофлоры бронхов, как *Aerococcus viridans* идентифицирован у 81,0 % пациентов с ЗББ, у 33,3 % больных РБ, у 8,7 % детей с ХБ.

**Выводы.** Исследование показало, что факторами риска развития ХБ у детей с ЗББ и РБ являются колонизация их нижних дыхательных путей *H. influenzae* и снижение активности или отсутствие нормальной микрофлоры бронхов (*Aerococcus viridans*).

## Introduction

Cough is one of the most common symptoms of bronchitis in childhood. In most foreign recommendations on the classification of cough in children, for example, the British Thoracic Society, it is recommended to use the concepts "acute cough" is cough lasting 3 weeks, "chronic cough" is cough lasting 8 weeks. Prolonged acute cough is a "grey" area between acute and chronic cough, sometimes called "subacute cough" [1]. In domestic pulmonary practice in both children and adults, chronic cough is defined as a daily cough lasting more than 8 weeks [2]. While in the modern guidelines of the United States, Australia and New Zealand, chronic cough in children is defined as one that lasts more than 4 weeks [3].

For comparison, the duration of cough and the course of various forms of bronchitis according to International Classification of Diseases, 10th Revision (ICD-10), cough in children more than 8 weeks can be a symptom of only chronic bronchitis (J41), and long-lasting acute cough (4–8 weeks) – subacute bronchitis (J20). In the domestic pediatric pulmonary medicine, there is a problem of inconsistency between the national clinical classification of bronchitis in children and ICD-10. Thus, in the new clinical classification of bronchitis in children, which was adopted at the XIII Congress of Pediatricians of Ukraine (2016), there are acute, recurrent (there is no such form in ICD-10) and chronic bronchitis. According to the definition of this classification, "recurrent bronchitis (RB) is a bronchial disease with the recurrence of acute bronchitis episodes (2–3 times a year) for 1-2 years on the background of acute respiratory viral infections without signs of bronchial obstruction, characterized by a prolonged exacerbation (3–4 weeks and longer)". Chronic bronchitis (CB) is characterized by "the presence of productive cough for several months within two years, persistent moist rale, 2–3 exacerbations a year within two years". Thus, chronic cough, according to its course duration, can be both in case of RB and CB.

Today, the relatively new clinical nosology in children – protracted bacterial bronchitis (PBB) – is being actively studied and discussed in the world. The PBB was first described in the study conducted in Australia in 2006 and is now included in the international cough guidelines [4]. PBB is characterized by an isolated chronic (lasting >4 weeks) wet or productive cough without signs of another cause, and usually responds to 2 weeks of an appropriate oral antibiotic [5]. Foreign studies show that PBB may be the most common cause for chronic wet cough in preschool children (0–6 years old) [6].

The prevalence of PBB among children with chronic wet cough in Ukraine is unknown, but many foreign studies report that its prevalence ranges from 10 to 40 % in the population [7,8]. In the study by Gedik et al., which included 563 children with chronic cough, the most common final diagnosis among all the participants were: asthma (24.9 %), asthma-like symptoms (19.0 %), protracted bacterial bron-

chitis (PBB) (11.9 %), and upper airway cough syndrome (9.1 %) [9]. In an Australian multicenter study, 41 % of 346 children who had a chronic wet cough, after a thorough examination, were diagnosed with PBB [8].

The persistent bacterial infection of the lower respiratory tract is the basis of PBB pathogenesis. The most common cause of PBB is atypical *H. influenzae* (47–81 %), *S. pneumoniae* (24–39 %), *M. catarrhalis* (19–43 %), which were isolated from the bronchoalveolar lavage samples [10,11]. The occurrence of PBB is associated with the violation of mucociliary clearance, immune deficiency, airway abnormalities and bacterial biofilms formation in the respiratory tract [12].

PBB is often misdiagnosed (for example, as asthma) or inadequately treated, which leads to symptoms persistence and potential structural damage to the respiratory system [13,14].

PBB require complex differential diagnostics. They need to be differentiated with acute bronchitis of viral etiology. Other reasons which should be considered are foreign body in respiratory tract and cough due to adenotonsillar hypertrophy. Cystic fibrosis, bronchiectasis, primary ciliary dyskinesia, pulmonary aspiration and immunodeficiency are rare but important differential diagnoses [15].

Due to the fact that protracted bacterial bronchitis today remains an understudied problem in Ukraine, it is relevant to study its clinical, anamnestic and microbiological features, as well as their role in the development of CB in children.

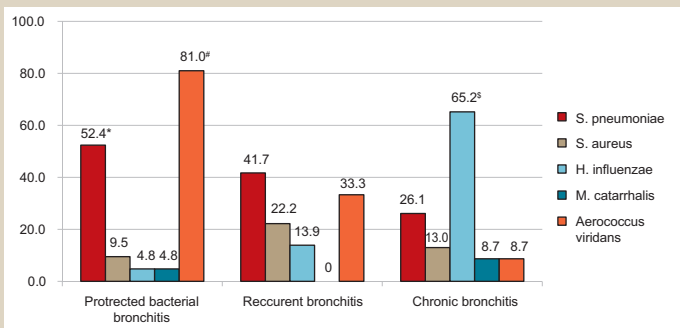
## The purpose

The purpose is to study the clinical-anamnestic and microbiological features of PBB, RB and CB in children and to determine the risk factors for CB development.

## Materials and methods

To achieve the goal, a comprehensive survey was conducted including 89 children aged from 6 months to 18 years, who had complaints of prolonged wet cough (more than 4 weeks). Among the examined children, the groups of patients with RB and CB (according to diagnoses already documented earlier in the primary medical documentation) and a group of children with the first episode of bronchitis with a protracted course (that is, possibly PBB) were identified. Exclusion criteria were: the presence of hereditary or congenital bronchopulmonary pathology (bronchial asthma, cystic fibrosis, primary ciliary dyskinesia, deficiency of alpha-1-antitrypsin, congenital malformations of bronchus and lungs), microaspiration syndrome, immunodeficiency, congenital heart disease, tobacco smoking.

After selection, all the examined children were divided into 3 groups. The first group consisted of 21 children with PBB (average age –  $3.8 \pm 0.6$  years), the second group – 27 children with RB (average age –  $13.2 \pm 2.1$  years) and



\*: significance of differences compared with the third group (P < 0.05); #: significance of differences compared with the second and the third group (P < 0.05); \$: significance of differences compared with the first and the second group (P < 0.05).

Fig. 1. The structure of the identified microflora (%) in the bronchoalveolar lavage fluid of patients.

the third group – 41 child with CB (average age – 14.7 ± 2.6 years).

Parents of patients received complete information on the scope of diagnostic measures and signed a written consent to participate in the study.

Instrumental methods of examination included chest X-ray and bronchoscopy. The study of qualitative and quantitative microbial composition of bronchial mucosa was performed in bronchoalveolar lavage fluid obtained during diagnostic and therapeutic bronchoscopy according to the standard method. In addition, the microbial spectrum of the upper respiratory tract obtained by oropharyngeal deep swabbing was studied. The conclusion was made based on a staining reaction presence on plates. The museum strain *Aerococcus viridans* № 167 was used as a control strain.

All statistical calculations were performed by means of Statistica v 6.1 (license number – AGAR909E415822FA). Quantitative and qualitative indicators were evaluated. Descriptive statistics were presented in the form of average and standard error of mean (M ± m) for values with normal distribution. Statistical significance was defined at P < 0.05.

## Results

Analysis of PBB clinical features showed that their total duration was 4.1 ± 0.3 weeks in the 1st group children; the duration of exacerbations did not differ significantly and was 3.8 ± 0.6 weeks (P > 0.05) in the 2nd group children. In patients with CB, the annual number of bronchitis and the total duration of cough were two times higher than in patients with RB (4.5 ± 0.2 vs 2.6 ± 0.3 times; 4.3 ± 0.3 vs 2.2 ± 0.2 months, respectively, P < 0.001). There were found significant differences in repeated bronchitis duration in patients with RB and CB (3.2 ± 0.8 vs 6.2 ± 1.1 years, P < 0.05).

According to X-ray data, all patients including PBB demonstrated an increase in vascular pattern and pulmonary hilum enlargement was revealed in 19.0 % of patients. In CB patients as compared to RB patients, the following signs were more common: increased vascular pattern (73.2 % vs 40.7 %, P < 0.01), pulmonary hilum enlargement and consolidation (65.9 % vs 11.1 %, P < 0.001). Deformation of the vascular pattern was inherent in CB patients and was found in all the patients of this group without any

exception (100 %), while it was revealed in only one child (P < 0.001) among RB patients. Emphysematosis, attenuation differences, pulmonary tissues infiltration were found in children with CB (24.4 %, 17.1 %, 7.3 %, respectively) and were absent in children with RB. In the first two cases, the differences were significant with P < 0.01 and P < 0.05, respectively.

The results of endobronchial examination showed visual signs of hypotension of the trachea and bronchi in half of CB patients (51.2 %), which is one of the risk factors for the drainage function of the bronchi disturbance. Endobronchitis was mostly diffuse (in 61.0 % of the subjects) and catarrhal-purulent (58.5 %), catarrhal (26.8 %) and purulent (14.6 %) by the nature in this study group. In assessing the bronchial epithelial layer condition, the moderate signs of the mucous membrane atrophy were noted in 34.1 % of cases and the bronchial epithelial dysplasia was noted in 46.3 %. In patients with RB, visual signs of the bronchial mucous membrane atrophy or dysplasia were not recorded in any case.

Comparison of bronchial signs in patients with CB and RB showed a difference in the frequency of tracheal and bronchial mobility reduction (51.2 % vs 18.5 %, P < 0.01), the bronchial wall hypertrophy (19.5 % vs 3.7 %, P < 0.05), the nature of endobronchitis (catarrhal purulent 58.5 % vs 33.3 %, P < 0.05, purulent 14.6 % in the absence of it in children with RB, P < 0.05, catarrhal – 26.8 % vs 66.7 %, P < 0.05). There was no significant difference (P > 0.05) between the frequency of bilateral (65.9 % vs 74.1 %) and left sided endobronchitis (17.1 % vs 25.9 %), bronchial edema (22.0 % vs 14.8 %).

The analysis of the cytomorphological studies results of brush biopsy material from the bronchial mucous membrane of RB and CB patients in the remission period confirmed the infiltration of inflammatory cells into bronchial mucosa. A comparative analysis of the brush biopsy specimens for cellular structure from the bronchial mucosa of the examined children also confirmed that the features of CB inflammation in the clinical remission period were mainly lymphocytic-macrophage infiltration and RB – neutrophilic-macrophage infiltration.

The bacteriological analysis of sputum showed that the most frequent cause of the disease in children with PBB and exacerbation of RB was *Streptococcus pneumoniae* (52.4 % and 41.7 %, respectively). *Staphylococcus aureus* was detected in 9.5 % of PBB patients and in 22.2 % of RB patients, *Haemophilus influenzae* was found in 4.8 % and 13.9 % of sick children, respectively. In children with CB exacerbation, *Haemophilus influenzae* was identified significantly more frequently (in 65.2 % of cases, P < 0.05), *Streptococcus pneumoniae* was detected in 26.1 % of patients, *Staphylococcus aureus* and *Moraxella catarrhalis* were identified in 13.0 % and 8.7 % of patients, respectively (Fig. 1).

At the same time, monocultures of *Haemophilus influenzae* were defined approximately in 70 %, *Streptococcus pneumoniae* and *Moraxella catarrhalis* – in about 50 % of cases.

*Aerococcus viridans*, as a representative of the normal bronchial microbiome, was identified in 81.0 % of PBB patients, only in one third of RB children (33.3 %) and in 8.7 % of CB (P < 0.05) in the clinical remission periods

(Fig. 2). In the period of exacerbation, there was no case of the microorganism identification.

An association between dysbiotic disorders in the bronchi (in the form of the normal microflora decreased activity or none at all) and such anamnestic data as the beginning of RB in preschool age ( $r = 0.39$ ,  $P < 0.01$ ) and repeated courses of antibiotic therapy ( $r = 0.53$ ,  $P < 0.001$ ) was established.

## Discussion

Thus, today, in different international guidelines, there is a mixed approach to the term “chronic cough” in children. In our opinion, it would be rational to use the classification of cough taking into account the age of patients, because age-related anatomical and functional features influence the pathological changes in the bronchi.

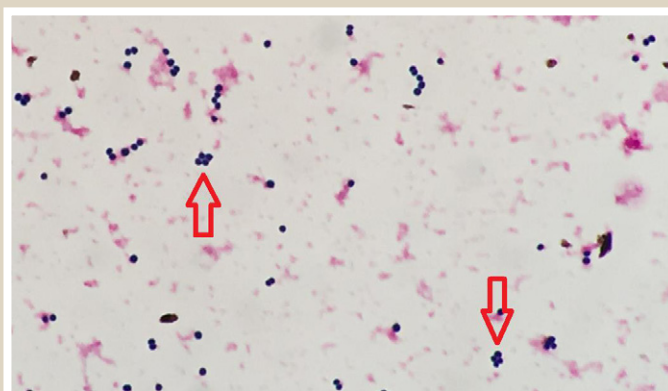
The existence of PBB as a new nosological group is also a debatable issue. This is due to the fact that PBB, as a separate nosological form, is not in the ICD-10. In addition, its diagnostic criteria do not correspond to any forms of bronchitis, presented in the domestic clinical classification of bronchopulmonary diseases in children. It should be foreseen that until there are unified approaches to PBB diagnosis, there will be no reliable statistics for the disease among children, in particular in Ukraine. In our opinion, one way to overcome this problem could be to register children under 6 years of age with a subacute course of bronchitis (corresponding to ICD-10 J20) as patients with PBB (it must be taken into account as the terms of bronchitis course and bacterial etiology as well as the age of a patient).

Our study confirmed that children of pre-school age mainly suffer from protracted bacterial bronchitis (the average age of children was  $3.8 \pm 0.6$  years). The duration of bronchitis was  $4.1 \pm 0.3$  weeks corresponding to the literature data [5,7].

It is assumed that PBA is the predictor of chronic purulent bronchitis [16]. Ukrainian scientists believe that the risk group for chronic bronchitis development are children with recurrent lower respiratory tract infection, namely with recurrent bronchitis [17]. Studies conducted by Yu. G. Antipkin, K. D. Duka et al. allowed to identify a group of children with “transitional forms” of recurrent bronchitis, which require the same treatment approaches as chronic bronchitis [17,18]. Perhaps in this group there are children with recurring PBB. Danielle F. Wurzel has shown that recurrent PBB in children and Haemophilus influenzae persistence in the respiratory tract are the risk factors for bronchiectasis [19]. Bronchiectasis, as a variant of acquired pathology, should be considered as signs of chronic deforming endobronchitis.

Regarding Haemophilus influenzae presence in the microbiota of the respiratory tract in children, our study shows that this pathogen was significantly more common among children with chronic bronchitis enabling it to be considered as one of the risk factors for chronic inflammation.

In addition, normal microbiota of the lower respiratory tract mucous membrane, in particular Aerococcus viridans, plays a very important role in chronic bronchopulmonary inflammation in RB children that was confirmed in our previous studies [15,17]. The characteristics identification of such bronchitis course in the absence of Aerococcus



**Fig. 2.** Aerococcus viridans are gram-positive, arranged in pairs and tetrads (photo, contrast microscopy,  $\times 400$ ).

viridans in bronchial secretion is of significant importance as it is accompanied by frequent and prolonged exacerbations and intoxication syndrome.

## Conclusions

1. Protracted bacterial bronchitis in modern conditions should be considered as a variant of the subacute course of bronchitis, due to specific microbiotic disorders in the bronchi and age-related anatomical and functional characteristics of preschool children.

2. Protracted bacterial bronchitis is predominantly typical for preschool children with average duration of  $4.1 \pm 0.3$  weeks. In children with recurrent bronchitis, the duration of exacerbations does not differ significantly and lasts for  $3.8 \pm 0.6$  weeks. Streptococcus pneumoniae is the most frequent causative agent of protracted bacterial and recurrent bronchitis and Haemophilus influenzae – of chronic bronchitis.

3. The risk factors for chronic bronchitis development in children with protracted bacterial and recurrent bronchitis are the lower respiratory tract H. influenzae colonization and decreased activity or absence of normal airway microbiota (Aerococcus viridans).

**The perspective for further scientific research** is to develop personalized preventive programs for patients with high risk for chronic bronchopulmonary pathology.

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