



Research article

## ADOLESCENT SMOKING AS RISK FACTOR OF DECREASE IN ADAPTATION RESOURCES OF NEUTROPHIL METABOLISM IN ORAL CAVITY AND PROGRESSIVE RECURRENT BRONCHITIS

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*High prevalence of smoking among children and its early onset is an urgent problem in modern pediatrics. For proper health risk quantification, it is extremely important to understand and parameterize relationships between effects of adverse factors and physiological processes in the body, including the cellular level.*

*The aim of this study was to analyze how tobacco smoking influences maladaptive changes in the mucosal immunity system of the oral cavity in adolescents and to assess kinetic trends in the clinical course of recurrent bronchitis (RB) in long-term outlook.*

*The study included 92 patients with RB aged  $16.8 \pm 3.1$  years. Two groups were created of them; the observation group was made of 64 patients, who admitted smoking as a habit, and the reference group included 28 people without nicotine addiction. The control group was made of 23 adolescents of the same age without any signs of the analyzed disease. Oral neutrophils (N) were selected as basic research material. N oxygen metabolism was registered by luminol-dependent chemiluminescence (LDCL) in spontaneous (sLDCL) and induced (iLDCL) variants. Functional N probing was performed using opsonized zymosan ( $\Sigma$ ) and peptidoglycan from *S. aureus* strain Cowan. Concentrations of antibodies (AT) to glycolipid (GLP) (Re-mutant *Salmonella* Minnesota), *Candida albicans* and *S. aureus* were determined by ELISA tests.*

*The analyses made it possible to detect a close relationship between levels of ROS generation by neutrophilic granulocytes and the immune components of anti-endotoxin immunity. Immune changes were not established to be universal in the groups of examined patients and were shown to reflect the specificity of destabilizing effects produced by tobacco smoke. A direct moderate correlation was established in the observation group between sLDCL indicators and the concentration of anti-candidosis antibodies ( $r = +0.59$ ,  $p = 0.0382$ ), which reflects the level of bacterial stimulation involving dysbiotic shifts in gut microbiota. A direct correlation was detected between levels of biocidal parameters of neutrophil granulocytes and anti-glycolipid levels ( $r = +0.64$ ,  $p = 0.0417$ ).*

*Integral assessment of specific humoral immunity to glycolipid and the phagocytic link of the mucosal protection in the oral cavity reflects the degree of endogenous intoxication and kinetic trends in the RB clinical course in adolescents in subsequent years of life. These relationships may provide solid grounds for 'exposure – response' stage in the risk assessment procedure for assessing risks of respiratory diseases in smoking adolescents.*

**Keywords:** adolescents, smoking, recurrent bronchitis, mucosal immunity, oral neutrophilic granulocytes, endotoxin aggression, anti-endotoxin immunity, prediction.

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Environmental instability, deterioration of the economic and social situation, and acceleration of technological progress have created a qualitatively new environment around humans that places increased demands on the body [1–4]. In this regard, the load on the adaptive capabilities of the body has increased, leading to frequent disruptions of homeostatic balance. Published works emphasize the increasing frequency of tobacco smoking among children and the early onset of tobacco use [5–7]. While the prevalence of smoking among adults has stabilized in recent years, it continues to increase among adolescents and has increased 3-fold over the past 10 years [7–10].

The impact of tobacco smoke on the child's body is aggravated by deep neuropsychiatric and hormonal changes characteristic of puberty, morphofunctional rearrangement of the main regulatory systems and mechanisms, and new social loads [11, 12]. All this causes increased vulnerability and susceptibility of adolescents to occurrence of diseases, with diseases of the respiratory system occupying one of the leading places in their structure. Among them, acute diseases of the bronchopulmonary system, which have their own medical and statistical characteristics, prevail in quantitative terms. According to the recent literature, the inflammatory process in the bronchial tree is increasingly becoming recurrent with a tendency to a prolonged course [13].

Exposure to tobacco smoke has an irritating and damaging effect on the oral mucosa and causes dystrophic changes in the epithelial layer [6, 8]. Smoking can induce the development of secondary dysfunction of mucosal immunity of the oropharynx. Cigarette smoke contains free radicals that trigger oxidative stress and lipid peroxidation; it also inhibits endogenous antioxidants and dysergic shifts in immune homeostasis. Nicotine is an anthropogenic pathogenetic factor in the progression of the inflammatory process in the respiratory system and determines the formation of chronic pathology of the bronchopulmonary system [2].

In the cascade of integrated mucosal defense mechanisms, the priority role belongs to

the function of the phagocytic barrier, which is carried out by neutrophil granulocytes that migrate from the vascular bed to the oral cavity [14–20]. Functionally, as effector and inducer cells, neutrophilic granulocytes closely cooperate with the coordinating role of the epithelial cover, including buccal epithelial cells [21]. They are closely interrelated with the process of colonization of bacterial pathogens, being a trigger for disrupting the integrated activity of the body in the external environment, its adaptive stability [22]. This allows us to consider neutrophilic granulocytes as cascade and network interactions that determine the development and regulation of inflammatory and immune processes [23–25].

From this point of view, great clinical and practical importance is to be found in studies that reveal the nature of maladaptation shifts on the part of the first barrier of pathogens entering the patient's body and the negative contribution of smoking to functional shifts on the part of mucosal immunity in adolescents with recurrent respiratory pathology [6, 26]. Today, the problem of high levels of smoking among children that leads to structural and functional disorders in the respiratory system is in the focus of attention of medical professionals and causes concern among health authorities both in our country and abroad [26–39]. Information on the effects of tobacco smoke in relapsing bronchitis (RB) in adolescents is extremely limited. At the same time, quantitative risk assessment requires understanding and parameterizing dependencies of the influence of hazardous factors on physiological processes in the body, including those at the cellular level. This prompted us to study this issue from the point of view of mucosal protection of the oral cavity as the first obstacle to aerogenic pathogens, with an analysis of the body adaptive resistance to the infectious process in adolescents with RB.

**The goal of the study** was to analyze how tobacco smoking influences maladaptive changes in the mucosal immunity system of the oral cavity in adolescents and to assess kinetic trends in the clinical course of recurrent bronchitis (RB) in long-term outlook.

**Materials and methods.** The study included 92 patients with RB aged 15–18 ( $16.8 \pm 3.1$ ) years. The examination and treatment were conducted at the children's hospital of the State Medical Institution of the Central Clinical Hospital No. 18 in Kazan, Russia. All patients signed a voluntary informed consent form before starting the study. Clinical and diagnostic measures were carried out in accordance with Russian recommendations<sup>1</sup>. Two groups were formed: the main group included 64 patients who confirmed their smoking habit, and the comparison group included 28 peers without nicotine addiction. The obtained data were recorded in a specially designed card and in an extract from the hospital patient's medical history. The control group consisted of 23 adolescents of the same age without signs of disease and nicotine addiction.

Criteria for including a patient:

1. A patient's age is from 15 to 18 years.
2. Informed consent signed by a patient's legal representatives.
3. Acceptable concomitant treatment: medicines used for the treatment of background diseases, except for respiratory organs.

Exclusion criteria: the presence of severe background somatic diseases in patients, including atopy, bronchial asthma, autoimmune diseases (lupus erythematosus, scleroderma), blood diseases, or hypertension.

The material for the study was oral neutrophils (N) that migrated from the vascular bed to the oral cavity. Oxygen metabolism of N was recorded by luminol-dependent chemiluminescence (LDChL). We studied spontaneous LDChL (sLDChL), which allows us to assess the endogenous activation of polymorphonuclear leukocytes in the patient's body and signs of destabilization of their functional activity, and induced LDChL (iLDChL). iLDChL was registered using two stimulants: opsonized zymosan ( $\Sigma$ ) and *S. aureus* peptidoglycan of the *Cowan* strain. Registration of sLDChL and iLDChL was assessed by taking

into account the light flux for 1 minute. To unify the iLDChL indicators, we recalculated them to 1000 neutrophilic granulocytes. The results were expressed in pulses-minute (imp/min).

Venous blood samples were collected from all patients with RB upon admission to the hospital, and anti-endotoxin immunity indicators were recorded by enzyme-linked immunosorbent assay (ELISA). Glycolipid was used as an antigen, which is a structural unit of endotoxin (Re-mutant *Salmonella* Minnesota) and determines the entire spectrum of general biological properties of endotoxin (E). The concentration of antibodies (AB) was expressed in micrograms/ml. In addition, the intensity of specific antibacterial immunity to *Candida albicans* and *S. aureus* antigens (AG) was evaluated.

Statistical analysis methods using the standard software package STATISTICA 12.0 and visualization methods based on the EXCEL package were used to interpret the study results in the observed groups of children. Methods of variation statistics were used for statistical data analysis (relative indicators were calculated with the determination of confidence limits for fluctuations in indicators with an error-free forecast probability of 95 %). To obtain objective results, an individual analysis of digital data as a percentage was applied. When analyzing quantitative indicators, we calculated arithmetic mean values and mean square deviations (M (SD)). The significance of differences in the initial values of dependent samples (i.e., within groups) was evaluated using the nonparametric Wilcoxon test, and the significance of differences in the average values of independent samples (i.e., between two groups) was evaluated using the nonparametric Mann – Whitney test.

**Results and discussion.** Analysis of clinical and anamnestic data of adolescents in the compared groups showed high frequency of risk factors for the development of RB that

<sup>1</sup> Klinicheskie rekomendatsii – Bronkhit – Deti – 2021-2022-2023 (28.09.2021), utv. Minzdravom RF [Clinical recommendations – Bronchitis – Children – 2021-2022-2023 (September 28, 2021), approved by the RF Ministry of Health]. BU «Pokachevskaya gorodskaya bol'nitsa». Available at: <https://gbpokachi.ru/upload/medialibrary/2c1/jei4lfgwtm7l2lsl2m456zjjcs30iw.pdf> (April 27, 2024) (in Russian).

initiate repeated episodes of the disease: hereditary anamnesis burdened by bronchopulmonary pathology in 39.13 %, passive smoking in 45.65 %, incomplete family in 27.17 %, early addiction of adolescents to smoking (from 14 years) in 68.47 %. In the course of the study, it was noted that almost 28.26 % of the surveyed children who use nicotine-containing cigarettes did not have a seasonal increase in the disease. The duration of each episode ranged from 10 to 14 days or more, and patients were repeatedly admitted to the hospital. Most of them (83.69 %) complained of coughing, increased fatigue, decreased activity, emotional lability, loss of appetite, and susceptibility to ENT diseases.

Analysis of physical development showed that, deviations were 32.81 % in the main group and 28.57 % in the comparison group. According to the Quetelet index, 46.74 % of the patients in the compared groups had a lack of nutrition and 8.69 % were overweight.

We studied the indicators of mucosal immunity of the oral cavity as markers of adaptive resistance of the body and assessment of the negative effects of smoking. The phagocytic barrier function plays a priority role in the cascade of integrated mechanisms of mucosal immunity. In our research, we focused on recording the effector function of neutrophilic granulocytes and their biocidity. Tables 1 and 2 show indicators of the functional state of neutrophilic granulocyte metabolism according to the sLDChL and iLDChL reactivity tests.

The sLDChL indicators in the acute period of RB were significantly higher as opposed to the control group and significantly exceeded the examination results obtained for the children in the comparison group:  $1904.64 \pm 72.30$  uti/min ( $p = 0.0059$ ) and  $1152.37 \pm 49.47$  uti/min ( $p = 0.0486$ ), respectively. Taking into account the obtained data, it can be assumed that the high level of endogenous

Table 1  
sLDChL indicators given comparatively in the groups of examined patients

	Groups of examined patients		
	Main group (N = 64), M (SD)	Comparison group (N = 28), M (SD)	Control group (N = 23), M (SD)
sLDChL, imp/min	1904.64 ± 72.30	1152.37 ± 49.47	625.27 ± 44.08
<i>p</i> **	0.0059	0.0357	
<i>p</i> *	0.0486		

Note: *p*\*\* means against the control group, *p*\* means against the comparison group.

Table 2  
The effect of cigarettes on the iLDChL indicators given comparatively in the groups examined with different methods of stimulation

Variant of functional neutrophil probing	Groups of examined patients		
	Main group (N = 64)	Comparison group (N = 28)	Control group (N = 23)
Oposonized zymosan (imp/min), M (SD)	104.12 ± 12.11	124.07 ± 14.8	118.72 ± 12.51
<i>p</i> **	0.0413	0.0587	
<i>p</i> *	0.0159		
Staphylococcus aureus (imp/min), M (SD)	87.43 ± 5.40	107.91 ± 8.6	114.90 ± 11.50
<i>p</i> **	0.0041	0.0368	
<i>p</i> *	0.0072		
<i>p</i> ***	0.0107	0.0214	0.0723

Note: *p*\*\*\* means comparison between the stimulation variant, *p*\*\* means against the control group, *p*\* means against the comparison group.

activity of neutrophilic granulocytes, in addition to bacterial stimulation, was associated with the direct effect of tobacco smoke on neutrophil reactivity. Cigarette smoke is known to contain hazardous chemical compounds that initiate oxidative stress and synthesis of nitric oxide, which inhibits endogenous antioxidants in the adolescent body.

In the analysis of iLDChL (Table 2), attention was paid to the statistically significant difference in the indicators in the groups of examined patients. This was mostly observed when neutrophilic granulocytes were stimulated using *S. aureus*.

The production of reactive oxygen species in the zymosan-induced chemiluminescence (CL) test was less pronounced in the main group of adolescents and the indicators in the acute period of RB were  $104.12 \pm 12.11$  imp/min, while in the comparison group –  $124.07 \pm 14.8$  imp/min. In other words, in smokers, pronounced depression in the generation of reactive oxygen species was noticed, indicating a decrease in the potential resources of antimicrobial protection of neutrophilic granulocytes.

It should be noted that while the iLDChL values with two stimulants were almost equal to each other in healthy children, a significant decrease in them was recorded in adolescents with RB of the main group when *S. aureus* was stimulated in comparison with opsonized zymosan ( $p = 0.0107$ ). Low response values were detected when using the *S. aureus* stimu-

lator and amounted to  $87.43 \pm 5.40$  uti/min ( $p = 0.0041$ ) in the main group and they were significantly different from patients without bad habits,  $107.91 \pm 8.6$  uti/min ( $p = 0.0072$ ). Since the *S. aureus* iLDChL reaction requires the indispensable participation of serum opsonins for the process to progress and zymosan was already used in its opsonized form, the obtained results allow us to judge the deficiency of opsonic blood factors, which is more pronounced in RB in adolescents of the main group. The obtained results should be considered as a decrease in the antimicrobial reserve of phagocyte protection in relation to *S. aureus*, one of the most significant etiological factors of the purulent-inflammatory process.

Taking into account the fact that neutrophilic granulocytes are the main effector blood cells that emphasize endotoxin, it seemed reasonable to analyze the relationship between the indicators of antimicrobial function of granulocytes and anti-endotoxin protection (Table 3).

When analyzing the parameters of anti-glycolipid antibodies, a significant decrease in their concentration in patients of the main group ( $5.02 \pm 0.29$   $\mu\text{g/ml}$ ) was noted not only against the control group ( $p = 0.0216$ ), but also the comparison group ( $p = 0.0471$ ). It is necessary to note the objective intensity of humoral antibacterial immunity to *Candida albicans* antigens, which exceeds the indicators in the comparison group by 1.5 times ( $7.28 \pm 0.94$   $\mu\text{g/ml}$  vs.  $4.55 \pm 0.52$   $\mu\text{g/ml}$ ). In addition, the

Table 3

Concentration of AB to glycolipid, *Candida albicans*, *S. aureus* AG in adolescents with RB of the main group and comparison group ( $\mu\text{g/ml}$ )

Groups of examined patients	Glycolipids, M (SD)	<i>C. albicans</i> , M (SD)	<i>S. aureus</i> , M (SD)
Main page ( $N = 64$ )	$5.02 \pm 0.29$	$7.28 \pm 0.94$	$11.28 \pm 2.12$
Comparison Group ( $N = 28$ )	$6.21 \pm 0.11$	$4.55 \pm 0.52$	$6.35 \pm 1.39$
Control Group ( $N = 23$ )	$7.86 \pm 0.23$	$3.17 \pm 0.20$	$4.02 \pm 0.37$
$p^{***}$	0.0216	0.0326	0.0061
$p^{**}$	0.0395	0.0475	0.0317
$p^*$	0.0471	0.0383	0.0328

Note:  $p^{***}$  means between the main group and the control,  $p^{**}$  means between the comparison group and the control,  $p^*$  means between the examined patients.

intensity of humoral immunity to *S. aureus* was noticed, as evidenced by the high concentration of AB to this AG.

Taking into account the high titer of anti-*Candida albicans* antibodies, a marker of deep intestinal dysbiosis, and, consequently, colonization of gram-negative microbiota in the intestine (a source of lipopolysaccharides), we can talk about a significant deficiency of anti-endotoxin protection and signs of endotoxin aggression in the main group of patients. Registration of the intensity of humoral specific immunity to the intestinal microbiota and the phagocytic link of mucosal protection of the oral cavity expands the possibilities to assess the negative role of smoking on the adolescent body in a broader aspect.

Biological effects of nicotine are provided by a cumulative signal that includes rapid responses when nicotine cholinergic centers are activated in nerve cells. This lipophilic xenobiotic is proven to exert the effect of chronic cellular stress by penetrating into cells and reprogramming them under prolonged exposure [5, 12]. Being an anthropogenic pathogenetic factor in the progression of the inflammatory process in the respiratory organs, smoking determines the RB progression with a chronic outcome in subsequent years of life.

Neutrophilic granulocytes of the oral cavity in cooperation with buccal epithelial cells of the mucosa are known to play a leading role in regulating the functioning of colonization resistance [21, 23]. The antigenic load on colonization resistance increases initially upon exposure to smoking. At the same time, harm of smoking is manifested, on the one hand, due to the direct influence on the mucous membrane of the respiratory tract, and, on the other hand, due to the toxic effect on the functional and metabolic activity of oral neutrophils.

The analysis made it possible to test the close relationship between the indicators of generation of reactive oxygen species by neutrophilic granulocytes and immune links of anti-endotoxic immunity. The nature of immune shifts in the groups of examined patients was found to be not universal and re-

flect the specifics of the destabilizing effect produced by tobacco smoke. We registered a different profile of immunological protection. In smokers, a pronounced depletion of the balance of antimicrobial immunity is recorded, which is associated with dysbiotic shifts in the digestive system and proliferation of gram-negative microbiota (a source of endotoxin), *Candida albicans* and *S. aureus* fungi. Individual analysis revealed a low level of antibodies to glycolipids in the main group of subjects and a significant increase in the concentration of antibodies to *Candida albicans* and *S. aureus*.

**Conclusion.** From a clinical point of view, it is important to emphasize the effectiveness of using two stimulators as different methods of functional probing of neutrophilic granulocytes. In the main group, a decrease in the functional reserve of the phagocytosis system was found and a deficiency of opsonic blood factors was detected, which predisposes to a decrease in the elimination of endotoxin, its entry into the bloodstream in increasing amounts, the development of endotoxin aggression and the progressive course of the disease relapses. In the main group, a direct correlation of average strength was established between the sLDChL indicators and the concentration of anti-candida antibodies ( $r = +0.59$ ,  $p = 0.0382$ ), which reflects the degree of bacterial stimulation involving dysbiotic shifts of the microbiota in the intestine. A direct relationship was registered between the indicators of neutrophilic granulocyte biocidity and the concentration of anti-glycolipid ( $r = +0.64$   $p = 0.0417$ ).

The conducted analysis allows us to take a deeper approach to the problem of smoking among adolescents with RB as a risk factor that further determines the formation of chronic pathology in the bronchopulmonary system and a decrease in the quality of life.

**Key points:**

1. Smoking depletes the adaptive resources of oxygen-dependent metabolism of oral neutrophils, which initiates susceptibility to a prolonged, progressive course of recurrent bronchitis in adolescents.

2. An integral assessment of specific humoral immunity to GLP and the phagocytic link of oral mucosal protection reflects the degree of endogenous intoxication and the kinetic trends in the RB course in adolescents in subsequent years of life.

These relationships may provide solid grounds for 'exposure – response' stage in

the risk assessment procedure for assessing risks of respiratory diseases in smoking adolescents.

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