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CLINICAL IMMUNOLOGICAL FEATURES OF OBSTRUCTIVE BRONCHITIS IN CHILDREN WITH ATYPICAL MICROFLORA

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The monograph summarises literature data and long-term research of the Samarkand State Medical University team devoted to the issues of diagnosis, clinic, treatment tactics of acute obstructive bronchitis in children with atypical microflora. The monograph is intended for paediatricians, general practitioners, masters, clinical residents and students of medical institutes.

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Contents

LIST OF ABBREVIATIONS

ACC – acetylcysteine
BO – bronchobstruction
WHO – World Health Organisation
CNS – central nervous system
RS virus – respiratory syncytial virus
OB – obstructive bronchitis
AOB – acute obstructive bronchitis.
ARVI – acute respiratory viral infection
ECG – electrocardiography
IFA – ezyme-linked immunosorbent assay
mAbs – monoclonal antibodies
pAB – polyclonal antibodies
PCNSD – perinatal central nervous system damage
RF – respiratory failure
ESR – erythrocyte sedimentation rate
SamSMU – Samarkand State Medical University
SBRSCEMC – Samarkand branch of the Republican Scientific Centre for Emergency Medical Care
USE – ultrasound examination
ARD – acute respiratory diseases
PCR – polymerase chain reaction
ELISA – enzyme-linked immunosorbent assay
PI – positivity index
OD – optical density
ChI – Chlamydiainfection
MI – mycoplasmainfection
INF – interferon
IgA – immunoglobulin A
IgM – immunoglobulin E

INTRODUCTION

Today, the steady increase in the number of respiratory system diseases is the most relevant area of modern paediatrics. Lower respiratory tract diseases are characterised by various clinical and morphological manifestations, often leading to bronchial obstruction. According to recent studies '….bronchobstructive syndrome is the initial manifestation of various pathological conditions of respiratory organs, in 30–50% of cases determines the severity of the course of the underlying disease and its prognosis' [1]. At present, early diagnosis of acute obstructive bronchitis of atypical aetiology in children, identification of risk factors, prescription of etiopathogenetic therapy for the prevention of relapses taking into account the peculiarities of clinical and laboratory manifestations and prevention of the disease are among the tasks that need to be solved in medicine.

A number of scientific studies are being conducted worldwide to apply modern diagnostic methods to determine the etiological factors of acute obstructive bronchitis in children and to improve the methods of etiological treatment. In this regard, conducting scientific research on the timely identification of the etiological factor of acute obstructive bronchitis in children, characterisation of anamnestic and data features of the clinical course, indicators of cytokines and humoral immunity, determining their relationship, development of etiopathogenetic methods of treatment, as well as improving the set of measures to implement effective methods of treatment is important. The country is implementing comprehensive measures aimed at the development of the medical sphere, in particular early diagnosis of bronchopulmonary pathology, improvement of methods of treatment and prevention of the disease, and certain results have been achieved. In this regard, tasks such as '…increasing the level of accessibility of quality medical services for mothers and children, providing them with specialised and high-tech medical care, implementing comprehensive measures to reduce infant and child mortality' [1].

Based on these objectives, it is necessary to determine the frequency of atypical microflora in acute obstructive bronchitis of atypical etiology in children, to analyse the diseases occurring in their mothers during pregnancy, to determine the peculiarities of the clinical course of the disease, identify disorders in the immune system (immunoglobulins IgA, IgE and

pro-inflammatory cytokines IL-1ß, IL-6, IL-8 and INF-γ), the developed diagnostic algorithm and treatment schemes will prevent disability and relapse of the disease caused by complications of the disease.

Chapter 1. CURRENT UNDERSTANDING OF ACUTE OBSTRUCTIVE BRONCHITIS IN CHILDREN

1.1 Etiological structure of acute obstructive bronchitis in children at the present stage

To date, respiratory diseases occupy the first place in the pathology of childhood, having a significant impact on infant mortality and the formation of persistent deviations in the state of health of children [5, 7, 59, 80], among which a significant role is given to acute obstructive bronchitis frequency of which depends on the period of the year, place of residence, epidemiological situation [3, 34, 61].

Diseases of the lower respiratory tract are characterised by various clinical and morphological manifestations, which is caused by anatomo-physiological features of the child's body, often leading to bronchial obstruction and the etiological agent of the disease. Often bronchoobstructive syndrome is the initial manifestation of various pathological conditions of respiratory organs, at the same time determines both the severity of the course of the underlying disease and its prognosis [19, 67, 69, 101].

According to a number of researchers, the pre-morbid background has a significant impact on the development of APS: allergic diseases, perinatal CNS pathology, rickets, nutritional disorders, irrational feeding, frequent colds, hereditary pathology of the bronchopulmonary system [99, 107].

According to Achilova D. N. (2019) and other researchers, unfavourable environmental situation and parental smoking in the family contribute to the development of AOB. Under the influence of tobacco smoke there is an increase in hypersecretion of bronchial glands of bronchial mucosa, as a result of which the mucociliary clearance is disturbed, as a result of which there is a slowdown in the outflow of mucus through the bronchi and the destruction of bronchial epithelium develops [3, 120, 121].

Currently, unfavourable ecological environment is a rather important etiological factor in the formation of AOB in children [80, 104].

There are works that prove that children whose parents abused alcohol can develop alcoholic fetopathy, in which bronchial tone decreases or disappears altogether, mucociliary clearance is disturbed, the development

of protective immunological reactions slows down, which contributes to the development of bronchobstructive syndrome. Organic and inorganic environmental substances have a toxic, sensitising effect on the mucous membrane of the respiratory tract, contributing to respiratory tract pathology. In young children, the high incidence of respiratory tract infections is due to the degree of development of the immune system, high contagiousness with viral agents, unformed and unstable immunity to them [3, 62, 64, 118].

It is generally accepted that respiratory viral infection is the main etiological factor in the development of AOB in children [6, 23, 68].

Acute obstructive bronchitis is a multifactorial disease, mainly caused by pathogenic microorganisms as well as chemical and physical factors [7, 44, 57, 59].

Many authors in their scientific works point out that during epidemic outbreaks of acute respiratory viral infections the incidence of acute obstructive bronchitis in children reaches peak values [50, 69, 79, 83, 96].

In the majority of preschool children after AOB, subsequent acute respiratory viral infections are followed by bronchoobstructive syndrome, i.e. the disease often becomes recurrent in nature [109].

Recently, 30–50% of AOB cases develop into a recurrent form and 15––30% develop bronchial asthma [71, 110, 116, 119].

The term 'atypical pathogens' first appeared in pulmonology, and over time has been introduced into other areas of medicine. Diseases caused by atypical microflora in particular Chl. Pneumoniae and Myc. Pneumoniae manifested by an atypical course of clinical symptoms, with insignificantly expressed clinical, auscultatory, radiological and laboratory indicators, not amenable to therapy with penicillin and cephalosporin antibiotics [75, 76, 110, 113].

The aetiological role of atypical microflora in the development of AOB is to a certain extent due to the intracellular nature of the existence of these pathogens [11, 16, 20, 26, 32, 33, 41].

As a result of numerous studies, the structure and morphology of atypical pathogens were revealed, pathogenicity factors were studied, the taxonomic position of the pathogen was determined, peculiarities of clinical manifestations, variants of course, as well as principles of therapy were determined, so that each of these infections began to acquire its own classical features and a definite clinical picture [25, 51, 55, 58].

Chlamydia and mycoplasmosis remain one of the most common infectious diseases in the world today [72, 110, 109, 111, 117].

The analysis of foreign and domestic literature on the role of viral and atypical bacterial pathogens in the development of bronchial OAB in preschool children has shown that the most common of them are chlamydia, mycoplasma, respiratory syncytial virus infections. Mixt infections are an important feature and account for 20 to 70 per cent of the disease, the layering of which may be accompanied by a severe course of the disease [106, 109, 120].

Chl. pneumoniae and Mus. pneumoniae are intracellular pathogens, occupying the second and third place in a number of pathogens of AOB (74%) and often develop into chronic form (74%) and severe course of the disease [21], due to prolonged persistence and tendency to recurrence of the inflammatory process in the bronchi [65, 66].

Chl. pneumoniae and Myc. pneumoniae in respiratory tract lesions, often leading to a prolonged course, block and paralyse the mechanisms of mucociliary clearance, contributing to increased bronchial reactivity and impaired immunoregulation [80, 82, 89, 90].

In women of fertile age and in pregnant women, the high prevalence of diseases of the urogenital tract with chlamydial and mycoplasma infection may have a high infection rate with these microorganisms in young children, which predisposes to the creation of predisposing conditions for the development of diseases in newborns and in early childhood [94, 97, 104, 106].

Despite the research received on respiratory diseases of mycoplasma etiology, remains relevant to paediatrics. Achievements of long-term studies of Myc. Pneumoniae have made it possible to explain many features of mycoplasma infection. M. Pneumoniae have specificity in that the antigenic structure of the agent is not always recognised by the human body. At present, there are convincing data on the formation of AOB in respiratory mycoplasmosis [75, 86, 87, 95, 96, 110, 117, 119, 120].

The entrance gates for M. Pneumoniae are the mucous membranes of the upper respiratory tract, at the same time, in respiratory mycoplasmosis there is a decrease in a significant degree of cleansing function of the respiratory tract from mucus and other foreign microflora for a period of 1 to 3 years after the disease, as well as a decrease in the functional system of the respiratory tract and mucociliary activity of the bronchial epithelium, which increases the degree of invasiveness of the agent, leads to reinfection and penetration of pathogenic microflora, mixtinfection [13, 24, 78].

Romanovskaya O. F. et al. provide data in their works that M. Pneumoniae are prokaryotes and conditionally pathogenic microorganisms, having

small size, small genome, do not have a rigid cell wall, this ability makes them more protected from the impact of immune both humoral and cellular defence mechanisms of the organism. The lack of a rigid cell wall of this pathogen determines not only their cell polymorphism but also their resistance to penicillin antibiotics [57, 74, 75].

G. A. Samsygina (2019) indicate that coinfections of M. Pneumoniae and PC-virus lead to more pronounced histological changes with destruction of the tracheal epithelium. Chlamydia-mycoplasma association, in turn, is characterised by a more severe course, in which the mechanisms of such mutual influence remain undisclosed [80].

Mus. Pneumoniae differ from Chl. Pneumoniae in that they parasitise the membrane of eukaryotes, which determines the pathogenesis of the disease. Currently, more than 100 species of Myc. Pneumoniae, of which 14 species affect the human organism. However, of particular interest is Mus. Pneumoniae, which has the greatest pathogenicity, is the causative agent of respiratory mycoplasmosis, accounting for up to 16% of acute respiratory diseases in children [78, 79, 98].

Mycoplasma infection predominates in preschool and school-aged children and is reported in 9.8% of children under 1 year of age, in 21.1% of children –1–2 years of age, in 44.4% of children –3–6 years of age and in 61.6% of children over 7 years of age. The disease occurs all year round, with a low incidence in summer. The source of infection is patients in the acute phase of the disease or asymptomatic people. The route of transmission is airborne and the incubation period averages 3–11 days (sometimes up to 3 weeks). A baby can be infected by an infected mother during childbirth, passing through an 'infected' birth canal. The course of mycoplasma infection is different in children and adults, e.g. in children the bronchopulmonary tree is most often affected and inflammation of the pharynx, nose, bronchi and lungs develops. The frequency of morbidity and severity of course depends primarily on the state of the child's immune system, so children with 'low immunity' infected with Myc. Pneumoniae become ill more often and the course is more severe. Children can usually contract mycoplasma infection in pre-schools, schools or in crowded places through airborne transmission [12, 42, 63, 75].

After infection with mycoplasma infection, specific humoral and cellular immune reactions are formed in the body, which are aimed at elimination of the pathogen. However, the established immunity is short-lived, as a result of which re-infection cannot be ruled out [13, 21].

In recent decades, studies have shown significant changes in the microbial spectrum of respiratory tract infections, as well as an increased role of Chl. Pneumoniae in the development of AOB [8, 9].

Infection with Chl. pneumoniae usually occurs at preschool and school age, and reinfection can occur at any period of subsequent life. In children, Chl. pneumoniae is the etiological agent of AOB in 21–35% of cases at the age of 5–14 years, and in adolescents and persons at the age of 19–23 years – in 16–20% of cases [21, 26, 37, 76].

There are works in which it is indicated that Chl. pneumoniae due to high tropism to the epithelium of the respiratory tract, violating protective functions, contribute to the risk of bronchial infection by pathogenic microorganisms, penetration of allergens and toxic substances through the bronchial mucosa. The main feature is that the cell wall structure of Chl. pneumoniae has a kind of similarity with Gram-negative bacteria. As it was mentioned above, Chl. pneumoniae have tropism to villous epithelium of bronchi and completely immobilise villi within 48 h after infection. At the same time in the clinical picture the manifestation of AOB is possible [41, 46, 48].

In recent years, the importance of Chl.pneumoniae in the structure of respiratory infection in children has increased. The pathogen is low toxic, therefore, during the development of the disease, the symptoms of toxicosis are not pronounced. Characteristic signs are a prolonged cough (up to several weeks), possible attack-like character. Auscultatory examination reveals different calibre moist rales. Radiological findings include increased pulmonary pattern and infiltrative darkening. Infection of children more often occurs from mothers suffering from urogenital chlamydia, which can be a source of infection of children, which may be a differential diagnostic criterion for the disease [57, 58, 59].

After mycoplasma or chlamydia infection, children have recurrent respiratory illnesses, often with SBO and a prolonged, recurrent course This fact is probably associated with altered immunological reactivity and decreased resistance to pathogens arising from the disease, creating a favourable environment for persistence of microorganisms, contributing to chronicity and formation of complicated course of the disease. Antibacterial therapy of the disease in most patients with temporary suppression of the activity and growth of pathogens, does not contribute to the correction of the resulting immunological changes, increasing the likelihood of recurrent course of the disease. Most authors prove that AOB caused by chlamydial and mycoplasma infection is characterised by a severe course of the disease,

but at the same time the mechanisms leading to a severe course remain completely unexplored, and problems related to diagnosis and treatment persist [51, 63, 71, 72, 78, 86, 90].

It is of interest to further study of risk factors and clinical and immunological features of AOB with atypical microflora in children, requiring further research with the use of modern diagnostic criteria allowing to use them for the justification of examination [81, 100, 116].

Thus, further study of the impact of atypical microflora (Myc. Pneumoniae, Chl. pneumoniae) on the clinical and immunological picture of AOB in childhood is beyond doubt.

1.2 Clinical course of acute obstructive bronchitis in children depending on etiological factors

It is well known that the inflammatory process in the bronchi in children at an early age is mainly manifested by acute obstructive bronchitis and acute bronchiolitis [6].

Acute obstructive bronchitis is characterised by inflammation of the bronchial mucosa and the development of mucosal hyperplasia, airway obstruction, mucus hypersecretion or bronchial spasm due to deeper edema and mucosal hyperplasia. In preschool children, obstruction is mainly due to hypersecretion of viscous and thick mucus, as well as mucosal hyperplasia. Bronchial spasm is more pronounced in children over 4 years of age [5, 6, 7, 108].

It should be emphasised that most researchers assess bronchobstructive syndrome as a pathophysiological concept characterising bronchial conduction disturbance against the background of acute and chronic respiratory diseases [2, 15]. In English-language literature, bronchial obstruction is referred to as "wheezing" – wheezing syndrome [40, 103].

The development of obstructive syndrome on day 1–3 with catarrhal manifestations is characteristic for AOB. Excruciating spastic cough lasting about 10–14 days, dyspnoea of expiratory nature, noisy, wheezing breath, oral rales are the main clinical symptoms of the disease. In infants, clinical picture of AOB is characterised by bronchial patency syndrome with the presence of non-productive cough, pronounced catarrhal manifestations, dyspnoea of mixed or expiratory character, percussion is marked by a boxy sound, and at auscultation the phenomenon of prolonged exhalation, expiratory dry wheezes, sometimes differently scaled moist wheezes of diffuse

character. Localisation of auscultatory changes is more often detected on both sides, in 8–10% of subjects localisation of auscultatory changes in axillary and sublobar regions is possible. AOB lasts 4–10 days, with gradual disappearance, in parallel with the elimination of physical changes of the lungs [2, 3, 5, 19, 24, 50].

Acute obstructive bronchitis is clinically characterised by symptoms of respiratory failure: expiratory dyspnoea, distant wheezing, cyanosis of the nasolabial triangle, intercostal retraction, involvement of the accessory muscles of the lungs. Most often the disease begins gradually against the background of a satisfactory general condition of the child with a rare dry cough. Temperature increase, catarrhal phenomena intensification and respiratory failure development are registered on the 2–3 day from the beginning of the disease. A constant symptom in this category of patients is the abundance of moist and crepitating rales on inhalation and dry wheezing rales on exhalation throughout the lung fields. Perioral or generalised cyanosis, distant wheezes are one of the important signs of obstructive bronchitis. The severity of respiratory failure determines the severity of the course of the disease. The course of respiratory infection determines the degree of intensity of intoxication syndrome and temperature curve [67, 69, 70, 79, 80, 85, 93].

Regardless of the etiological factor, the main clinical manifestations of AOB are painful cough with scanty sputum, dyspnoea of expiratory character with audible wheezing, symptom complex of respiratory insufficiency, the appearance of dry wheezing and moist multicalibre rales in the lungs [18, 40, 44, 59].

In children of the first months of life, AOB is severe, often with the development of acute respiratory failure of II–III degree, with a high probability of death, which is up to 1% in respiratory syncytial infection, and up to 4–7% of hospitalised patients in parainfluenza and adenovirus infections. In children 5–7 years old, recurrent cases of AOB are up to 50% [43, 101].

Despite all the studies on the formation of AOB in children, the question of the causes of its recurrence remains open. The study of risk factors for the occurrence, age and clinical features of the course of BSE depending on the etiology of atypical infection remains poorly understood [64]. The significance of clinical and immunological features of the course of mixed viral-bacterial infections involving the main agents in the etiological structure of recurrent obstructive bronchitis in children has not been determined [7, 47, 55].

Thus, the results of scientific research in the field of AOB of atypical aetiology are diverse and contradictory. There are few studies on regional patterns of respiratory infections, including those associated with AOB, in the available literature. When confirming the diagnosis by prioritising laboratory methods for the diagnosis of atypical infection, we are often faced with ambiguous results of the clinical course of the disease, which are the target of further investigations.

1.3 Immunological aspects of acute obstructive bronchitis in children

Modern aspects of the etiology and pathogenesis of AOB take into account the development of pathological inflammatory process in the bronchi as a result of external and internal environmental factors, mainly infectious, immunoregulatory mechanisms of the body are of great importance [69, 73].

Currently, the study of cytokine regulation in various pathological conditions, including respiratory diseases, remains topical [61, 62].

Cytokine profile indicators are fundamentally important for clarification of pathogenetic critical links of acute obstructive bronchitis in children, necessary to improve diagnostic and prognostic criteria of the disease, which is necessary for optimal immunocorrective therapy.

The regulatory function of cytokines consists in the regulation of embryogenesis, including the immune system, regulation of basic physiological functions of the organism; regulation of defence reactions of the organism and regulation of tissue regeneration processes. Cytokines, interacting with other parts of the immune system, improve metabolic processes of the organism, which reflects the state of the immune response. Blood cytokines bind to specific receptors damaging the cytoplasmic membrane of cells, causing a cascade of pathological reactions, lead to enhancement or suppression of the activity of regulated genes [1, 17, 25].

In infectious and inflammatory processes in respiratory pathology, cytokines influence the formation of the pathological process. Cytokines formed in the cells of the immune system perform mediator function, intercellular co-operation, thus participating and regulating the inflammatory and immune response [25].

There are several types of cytokines:

1. Interleukins performing humoral communication between white blood cells;

2. Interferons – they protect the body from viruses;
3. Colony-stimulating factors they are necessary for the production of blood cells;
4. Tumour necrosis factors have anti-inflammatory, immunostimulatory and haematopoietic functions;
5. Cell growth transforming factors that have anti-inflammatory properties, inhibit antibody formation and cytotoxic cell differentiation;
6. Growth factors, these include fibroblast, epidermal and platelet-derived growth factors, regenerate damaged tissues.

Depending on their function, cytokines are divided into 2 groups: anti-inflammatory (IL-4, IL-10, IL-2, IFN-γ) and pro-inflammatory (IL-6, IL-8, TNF-a), and pathogens and allergens affect cytokine status. Thus, cytokine status indicators reflect the state of immune response and defence response of the organism [28, 34, 36].

The basis of the pathogenesis of the impact of atypical infections is the triggering of the cytokine cascade, in the form of pro-inflammatory and anti-inflammatory cytokines, the balance of which determines the peculiarities of the course and prognosis of the diseases [13, 20.] To date, immunoregulatory functions of the main cytokines in a variety of infectious diseases have been studied in sufficient detail [110].

In obstructive bronchitis, which are characterised by the development of bronchial obstruction, pathogens in interaction with macrophages, affect the balance of cytokines [1].

At present, the role of cytokine profile in AOB of atypical aetiology in children has not been practically studied. However, the study of cytokine parameters has a significant role in determining various links of pathogenesis and improves diagnostic capabilities in paediatric AOB. Determination of immune changes in AOB can be quite significant criteria for optimal immunocorrective therapy. The study of these issues makes it possible to determine the risk groups of recurrent course in children with first-onset AOB, which would determine the approach to the optimal methods of antiretroviral treatment in children [10, 23, 60].

The most important role in the pathogenesis of the disease belongs to the activation of inflammatory mediators, including interleukins, which stimulate the activation of mast cells, basophils, eosinophils and B-cells [11, 69].

In recent years, the study of the significance of interleukins in the development of relapsing-remitting OB has been continued. In children, high levels of IL-8, IFN-β are determined in acute obstructive bronchitis, indicating the

predominance of the cellular phase of the immune response over the humoral phase. The above data indicate that immunological markers of acute obstructive bronchitis can be high values of IL-6, IL-8, which confirms the importance of cytokines in the pathogenesis of bronchial obstruction [15].

The study of proinflammatory cytokines showed that IL-8, IL-1β and IL-4 levels increased in children with a decrease in α-INF, indicating a suppression of cellular mechanisms of immune status [34, 36].

IL-6 promotes proliferation of thymocytes, B-lymphocytes, activating the formation of inflammation phase proteins [1, 119].

During virosemia, IFNα differentiates antigen-activated T-helper cells into Th 1-type cells responsible for the cellular immune response, thus creating an antiviral defence. Another type of interferon IFN-γ leads to activation of macrophages, increases the production of anti-inflammatory cytokines and is an antagonist of IL-4, which promotes IgE synthesis. Interferonogenesis is thought to be altered in respiratory viral infections [22, 31].

INFα, being one of the factors of innate immune response of the organism, reacts to virus introduction, fulfilling a regulatory function in maintaining homeostasis in the human body. Due to its direct antiviral effect, IFNα suppresses the growth and development of intracellular microorganisms, further exerting immunoregulatory effect, preventing apoptosis, which leads to differentiation of antigen-activated T-helper cells, promoting the maturation of functionally active antigen-presenting dendritic cells [35, 39].

Undoubtedly, it is necessary to take into account the fact that chlamydiae themselves can change the reactivity of the host organism to pathogens and thus can influence the course of the infectious process and the outcome of the disease [21].

Many foreign authors cite the results of laboratory data of patients with chlamydial infection. In the general blood analysis, a relative decrease in the number of neutrophils and lymphocytes, as well as a decrease in the monocyte-lymphocyte ratio is noted [26, 41].

It is proved that in respiratory chlamydia local production of secretory IgA, activation of cytotoxic T-lymphocytes and formation of antibodies of IgM, IgA, IgG classes to chlamydial antigen develops [35, 39].

When determining the nature of immunological disorders (IgA, IgG, IgM) in children with acute obstructive bronchitis and evaluating immunocorrection with the drug Ismigen, the violation of immunological reactivity of the organism was revealed and the effectiveness of therapy in relation to the state of the immune system in children was shown [35, 39].

When treating bronchopulmonary pathology in children, it is necessary to take into account the pathogenetic orientation, in this regard, it is necessary to take into account the main indicators of the immune status of the organism [36].

Interferons are produced and are found in all nucleus-containing cells of blood and mucous membranes, are permanent natural factors of human anti-infection defence, including immunostimulatory and antiviral mechanisms [68, 83].

In the analysis of interferon status in respiratory viral infections it was proved that recombinant interferon alpha 2b with antioxidants allows normalising the level of IFNα production, with an increase in IFN-γ synthesis [84, 91].

Thus, the studies of the role of cytokine status in acute obstructive bronchitis in children, depending on the etiological factor indicate the inconsistency of the results obtained and the need for further study of the issue.

1.4 Laboratory and instrumental diagnostics of paediatric AOB

To diagnose bronchial obstruction syndrome, conventional laboratory and instrumental methods are performed. To determine and clarify the degree of severity of bronchoobstruction is carried out assessment of the functional state of the lungs. To functional methods for differential diagnostics of bronchial obstruction spirography methods are carried out. However, spirography is limited in paediatric practice, especially in young children, as it is necessary to actively participate in the study of the child [111, 114, 119].

The method of pycfloumetry is easy to perform, can be used in outpatient settings, by determining the volumetric air velocity during forced expiratory flow, and allows predicting BOS before clinical manifestations, which can be used in monitoring the disease [56, 113]. As well as the method of spirography, the use of pycfloumetry is limited to the age range of children (not earlier than 6 years) [65, 81].

Bronchophonography method, which is based on the analysis of amplitude-frequency characteristics of the spectrum of respiratory noises by fixing the curve of acoustic noise occurring during breathing, with subsequent mathematical processing. The method allows to expand the functional assessment of the lungs, obtained by routine methods of examination, to objectively assess the severity of the course of bronchial obstruction syndrome in children [18, 19].

The results of the study in children have shown high informativeness of bronchophonography in children primarily with obstructive disorders in the respiratory system. The peculiarities and regularities of distribution of bronchophonography parameters depending on sex, age and nosological form of the disease have been established [45].

The radiological picture of the lungs in BOS is not specific, changes characteristic of the underlying disease (bronchitis, bronchiolitis, bronchial asthma) are determined [5, 12, 81].

In the study of sputum in bronchitis in children aged 3–6 years, the growth of Staphylococcus aureus was determined, at the age of 7–12 years – Streptococcus pneumonia, at the age of 13–18 years – Staphylococcus aureus. The obtained data can be used to choose the tactics of treatment of this pathology. In the acute period of BOS, microscopy of sputum may reveal eosinophils, neutrophils [89].

Thus, the diagnosis of acute obstructive bronchitis with atypical microflora in children should be comprehensive, currently available enough highly specific and highly sensitive, which allow to verify the etiology of the disease and determine the possibility of early initiation of etiotropic treatment to improve the prognosis of the disease.

1.5 Principles of therapy for chlamydial and mycoplasma infections

At present, despite the ongoing research and improvement of therapy for bronchitis treatment, practitioners are often faced with their insufficient effectiveness in clinical practice. The resistance of pathogenic microorganisms is constantly increasing, which is associated with irrational antibacterial therapy and indicates the need for further research to improve the tactics of etiotropic and pathogenetic therapy [14, 19, 21, 22].

Identification of the aetiological factor of AOB is crucial for adequate aetiotropic therapy in the early stages of the disease [11].

The development, course and outcome of diseases caused by Chl. pneumoniae and Myc. pneumoniae are largely determined by the state of the paediatric organism, peculiarities of its homeostasis, immunological reactivity, the presence of concomitant diseases, biological properties of the pathogen, including its ability to prolonged persistence and many other factors [16, 32, 33].

Considering modern ideas about the role of pathogens, diagnosis and issues of differential diagnosis depending on the etiological factor, algorithm

of starting antibacterial therapy, the author noted that in recent years, there is still irrational use of macrolides and oral cephalosporins in the starting therapy of respiratory tract diseases. Thus, in out-of-hospital pneumonia, the use of β-lactam antibiotics for atypical pneumonia, carried out in 81% of patients was ineffective [29, 30, 88].

The efficacy of etiotropic therapy in AOB can be assessed by the elimination of clinical symptoms, normalisation of haemostasis and elimination of the pathogen [77].

The problem of rational use of antibiotic therapy remains due to the verification of the diagnosis of AOB, taking into account the identification of new and variability of existing aetiological agents, including atypical flora [4, 29].

It is necessary to develop rational approaches to the prescription of antibacterial drugs, in the absence of which or the use of outdated data, there is a risk of poor prognosis of the disease and the emergence of resistant strains of microorganisms, especially in atypical etiology.

Treatment of children with chlamydial and mycoplasma infection is carried out taking into account regional sensitivity, age, toxicity, tolerability for a particular child, previous and concomitant pathology and nosological form of the disease [78].

Myc. Pneumoniae and Chl. Pneumoniaea have several properties in common: they cannot be detected by conventional microbiological methods, they are obligate or facultative intracellular parasites and cause extrapulmonary symptoms, and because they lack the cell wall peptidoglycan, they do not respond to β-lactam antibiotics. However, they do respond to protein synthesis inhibiting drugs such as macrolides and tetracyclines, or to DNA synthesis inhibitors such as fluoroquinolones [13, 115].

Macrolides have the ability to accumulate in tissues and foci of lesions, it is necessary to take into account that this process is most intense in tonsils, lymph nodes, lung tissue, which determines their choice for the treatment of chlamydia.

The role of macrolides in the treatment of respiratory diseases has significantly increased. The peculiarity of pharmacodynamics of macrolides is their prolonged postantibiotic effect. The most widely used are 3 groups of macrolides: group 1–14-membered (erythromycin, oleandomycin, clarithromycin, roxithromycin); group 2–15-membered (azithromycin); group 3–16-membered (jozamycin, spiramycin, midekamycin). Macrolides (azithromycin, jozamycin, roxithromycin, clarithromycin,

midekamycin, spiramycin), have bacteriostatic at medium and bactericidal action at high doses of the drug, at the same time are effective against most Gram-positive bacteria, anaerobes, spirochetes, chlamydia and mycoplasmas [27, 82].

Macrolide antibiotics are still the most effective and frequently used drugs against mycoplasma and chlamydia infections.Myc. Pneumoniae andChl. Pneumoniaea *parasites* outside the cell and has no cell wall, the main purpose of which is to suppress and disrupt the protein synthesis of the microorganism. The first-generation macrolide drug erythromycin was first used to treat Myc. Pneumoniae and Chl. Pneumoniaea in children, due to its good antibacterial properties, at the same time can cause more obvious adverse reactions in the digestive tract, even cause phlebitis and local pain, long-term treatment can cause liver and kidney damage [107, 115].

Macrolides, with their long elimination period, retain their antibacterial activity for 4–5 days after antibiotic therapy. Since chlamydia and mycoplasmas are obligate intracellular parasites, prone to long-term persistence in the body of a child with transient immunological deficiency. In this regard, single courses of macrolides do not always lead to eradication of chlamydial and mycoplasma infections. Therefore, the use of immunomodulatory drugs is indicated in the treatment of almost all forms of chlamydial infection in children [105, 120].

However, with the emergence of Myc. Pneumoniae and Chl. pneumoniae strains resistant to macrolides gradually increased, and the total duration of febrile days, course and time of hospitalisation of children increased. At the same time, more inflammatory reactions and complications occurred [46, 105, 117]. Currently, macrolides in general and clarithromycin in particular are included in the recommendations for the treatment of respiratory tract infections caused by 'atypical' pathogens due to, on the one hand, the high antimicrobial activity of macrolides against chlamydia and mycoplasmas and the absence of significant resistance problems of the above pathogens, and on the other hand, the favourable safety profile of macrolides and the possibility of use in children from a very young age [27, 97, 102].

In recent years, there are studies indicating immune status disorders in bronchopulmonary diseases and, in some cases, the presence of primary and development of secondary immunodeficiency states, which indicates the need for immunocorrective therapy in AOB in children [39, 54].

Among the new-generation immunomodulators, the domestic drug Galavit deserves special attention [49, 70].

According to the literature, Galavit has immunomodulatory and anti-inflammatory properties, which is associated with the regulation of functional and metabolic activity of cells of innate and acquired immunity. The action of the drug restores phagocytic activity of monocytes and macrophages, increases bactericidal activity of neutrophils and cytotoxic activity of NK-cells. The use of Galavit increases the body's resistance to infectious diseases of both bacterial and viral genesis, accelerates the elimination of pathogenic agents from the body, reducing the frequency and duration of the disease. There is an increase and improvement of the functional activity of antibodies, improves the production of interferons (INF-α, INF-γ). In inflammatory diseases Galavit on average for 6–8 hours inhibits the pathological synthesis of tumour necrosis factor-α, interleukin-1, interleukin-6 and other pro-inflammatory cytokines, their cyclicity, as well as reducing intoxication syndrome in patients [52, 54, 92].

However, no data on the use of Galavit in combination with Clarithromycin in children with obstructive bronchitis and its effect on the state of cellular and humoral immunity were found in the available literature. In this regard, the aim of our study was to evaluate the efficacy of Galavit on clinical and immunological parameters in children with acute obstructive bronchitis.

Untimely undiagnosed and untreated atypical flora in children with AOB leads to repeated episodes and prolonged course of the disease, repeated hospitalisation, which requires additional economic costs and can lead to adverse outcomes with the possibility of developing chronic diseases.

At present, the relevance of research in children with atypical microflora is to define and improve diagnostic and prognostic clinical and laboratory methods of research, to improve therapeutic measures in order to form a personalised approach of patient management [53, 58].

Summarising the review of literature sources, we conclude that the interest in APS with atypical microflora in childhood is very relevant. Despite the introduction of modern diagnostic methods, the study of patterns of clinical and immunological changes, they remain insufficiently studied, which determines the need for research to optimise the diagnosis and therapy of the disease. The search for methods of early diagnosis and improvement of treatment efficiency can be accepted as a priority direction of the state policy in public health care.

Chapter 2. SCOPE AND METHODS OF RESEARCH

2.1 Scope of the research

The work was carried out in the Multidisciplinary Specialised Paediatric Surgical Clinic of Samarkand State Medical University and in the Paediatrics Department of the Samarkand branch of the Republican Scientific Centre for Emergency Medical Care. We examined 365 children with acute obstructive bronchitis aged from 5 months to 6 years among whom 90 patients with positive immunoenzyme analysis for chlamydia and mycoplasmas (group 1) were selected, and also retrospectively studied the case histories of 90 children with acute obstructive bronchitis without atypical microflora (group 2) with moderately severe and severe course of the disease. These children were hospitalised in the Multidisciplinary Specialised Children's Surgical Clinic of SamSMU, SFRNCEMP, and were under our observation for the period 2020–2022. All patients underwent general clinical examination methods, chest radiography, immunological methods of investigation.

Verification of the diagnosis of AOB was performed according to WHO requirements and classified according to the ICD-10 international classification of disease.

Anamnestic, clinical, laboratory, and instrumental examination data were taken into account in the diagnosis of the disease. Immunological methods were used to assess the immune status of children with acute obstructive bronchitis.

All patients underwent clinical and immunological, laboratory and functional (ECG, radiography) investigations. Infection with pathogens of persistent intracellular infections (Chlamidia pneumoniae, Mycoplasma pneumoniae) was judged according to the results of enzyme-linked immunosorbent assay (ELISA) using a standard commercial reagent kit "HEMA set of reagents for medical diagnostics" (Russia).

Group 2 children were divided into 4 groups depending on the therapy given.

The **first group (I)** of children received standard therapy.

The **second group (II)** of children received standard therapy and Clarithromycin was used as antibiotic therapy. Clarithromycin was administered 2 times a day orally at the rate of 15 mg/kg for children, treatment course 7 days.

The third group (**III)** received standard therapy and immunomodulator 'Galavit' in the form of suppositories and tablets depending on the age of patients. Galavit was applied sublingually in a dose of 1–2 tablets daily from 2 to 4 times a day with duration of 5 days to children from 3 to 6 years old. And also it was applied in the form of suppositories once a day for 5 days.

The **fourth group (IV)** received standard therapy with Clarithromycin (administered 2 times a day orally at the rate of children 15 mg/kg treatment course 7 days) and immunomodulator Galavit (used sublingually in a dose of 1–2 tablets daily from 2 to 4 times a day with a duration of 5 days in children from 3 to 6 years, in the form of suppositories once a day for 5 days, then every other day 5 more suppositories).

When the condition improved, all children received physiotherapy: electrophoresis on the chest, vibromassage.

Observation of 90 children with AOB was carried out in hospital and consultative dispensary office during the first year (6 months after discharge from hospital). The effectiveness of therapy was assessed by the dynamics and rate of regression of clinical symptoms, normalisation of laboratory and immunological parameters.

2.2. Research methods

Immunological research methods

We conducted immunological studies of humoral immunity indices, cytokines and antibodies to Chl. pneumoniae and Myc. pneumoniae antigens. pneumoniae. Immunological blood studies were performed in the laboratory of the Multidisciplinary Specialised Clinic of Children's Surgery of SamSMU (chief physician Dr. M. Sc., Professor J. A. Shamsiev). The following indicators of humoral immunity (IgA, IgM, IgG, IgE) and cytokine status (INF-γ, IL-6, IL-8, IL-1ß) were studied. Immunological studies were performed twice by enzyme-linked immunosorbent assay on admission of children to the hospital and 6 months after discharge from the hospital.

Determination of cytokines (interleukins) IL-1ß, IL-6, IL-8, TNF-α, ḡ-INF

Vector-Best (Russia) test kits were used for cytokine determination. The method is based on a three-stage 'sandwich' variant of solid-phase enzyme immunoassay using horseradish peroxidase as an indicator enzyme.

After completing the basic steps, 100 μl of tetramethylbenzidine plus solution is added to all wells. Incubate in a light-protected place for 25 minutes at room temperature. Stop the reaction by adding 100 μl of stop reagent solution. Measure the value of optical density of solutions in wells of strips on a vertical scanning spectrophotometer in two-wave mode: at the main wavelength of 450 nm and the reference wavelength in the range of 620–655 nm. Quantitative evaluation of the results is carried out by constructing a calibration curve manually or with the use of commercial software, reflecting the dependence of optical density on concentration for the standard antigen and allowing comparison of the tested samples with it.

Determination of IL-1ß, IL-6, IL-8, TNF-α, ḡ-INF levels

The first monoclonal antibodies (MCABs) are pre-immobilised on the inner surfaces of the cells of solid ELISA plates. In the first two vertical rows of cells, the plates are filled with 100 μl of standards each: A – 0 pg/ml of the cytokine under investigation, B – 50 pg/ml, C – 250 pg/ml, D – – 500 pg/ml, E – 1000 pg/ml, F – 2000 pg/ml of the cytokine. The remaining cells are filled with 100 mcl of samples each. The samples and standards are added in the recommended buffers. The plate is incubated for 2 hours in a thermoshaker at 37 C and 700 r/min. After incubation, the solution is removed from the cells using a pipette. The cells are then washed 5 times by adding 350 mcl of wash solution to each cell. At the end of washing, remove any residual liquid from the wells by tapping the plate upside down on filter paper. Then 100 mcl of conjugate #1 is added to each well. Incubate for 60 min in a thermoshaker at 37 C and 700 r/min. After incubation, the solution is removed from the cells using a pipette. The cells are then washed 5 times by adding 350 mcl of wash solution to each cell. At the end of washing, remove any residual liquid from the wells by tapping the plate upside down on filter paper. Then 100 mcl of conjugate #2 is added. This is followed by washing and staining steps. Enzyme immunoassay methods are highly specific, rapid (immunoassay setup time is less than 5 h) and relatively easy to perform. The sensitivity threshold for these test systems is up to 0.5 pg/ml.

Determination of class immunoglobulins IgA, IgM, IgG, IgE

To determine immunoglobulins of classes IgA, IgM, IgG, and IgE, test kits from "OOO HEMA" (Russia) were used. The determination of total immunoglobulin classes A, M, G, and E is based on the use of the "sandwich" version of the solid-phase enzyme-linked immunosorbent assay (ELISA). Murine monoclonal antibodies against human total IgA, IgM, IgG, and IgE are immobilized on the inner surface of the wells of the plate. In the wells of the plate, upon adding the test sample, the total IgA, IgM, IgG, and IgE in the sample bind to the antibodies on the solid phase. The resulting complex is detected using a conjugate of rabbit polyclonal antibodies against human IgA, IgM, IgG, and IgE with horseradish peroxidase. As a result, a "sandwich" bound to the plastic is formed, containing peroxidase. During incubation of substrate solution with a tetramethylbenzidine (TMB), the solutions in the wells become colored. The intensity of the coloration is directly proportional to the concentration of total immunoglobulins IgA, IgM, IgG, and IgE in the samples being tested. The concentration of these total immunoglobulins in the samples is determined using a calibration curve that plots optical density against the content of IgA, IgM, IgG, and IgE in the calibration samples.

Determination of IgM and IgG antibodies to Chlamydia pneumoniae and Mycoplasma pneumoniae

To determine IgM and IgG to the antigens of Chlamydia pneumoniae and Mycoplasma pneumoniae, test kits "HEMA" (Russia) were used. The determination of IgM and IgG antibodies to the antigens of Chlamydia pneumoniae and Mycoplasma pneumoniae is based on the use of an indirect variant of the solid-phase enzyme immunoassay. On the inner surface of the wells, the antigens – Mycoplasma and Chlamydia – are immobilized. Antibodies from the sample bind to the antigens on the surface of the wells. The resulting complex is detected using a conjugate of murine monoclonal antibodies against human IgM and IgG with horseradish peroxidase. As a result, a "sandwich" bound to the plastic is formed, containing peroxidase. During incubation with the tetramethylbenzidine (TMB) substrate solution, the solutions in the wells become colored. The intensity of the coloration is directly proportional to the concentration of specific IgM and IgG antibodies against the antigens Chlamydia pneumoniae and Mycoplasma pneumoniae. The concentration of IgM and IgG antibodies against the antigens Chlamydia pneumoniae and Mycoplasma pneumoniae in the test samples is calculated using the formula:

Cut off = ODMID + 0.2 PI = OD of sample / Cut Off

The coefficient of variation for the determination of IgM and IgG antibody levels against the antigens *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* in the same serum (plasma) sample, using the kits "Mycoplasma IgM-ELISA, " "Mycoplasma IgG-ELISA", "Chlamydia IgM-ELISA", and "Chlamydia IgG-ELISA", does not exceed 8.0%. The presented research methods will allow for the early detection of infectious agents causing atypical microbial flora in AOB, contribute to the provision of adequate treatment, and largely determine its effectiveness.

Virological Research Methods

The fragment to be determined is a specific section of nucleic acids of pathogens of human acute respiratory viral infections: RNA of respiratory syncytial virus (human Respiratory Syncytial virus, hRSv), parainfluenza viruses of types 1, 2, 3 and 4 (human Parainfluenza virus 1–4, hPiv), rhinoviruses (human Rhinovirus, hRv), DNA of adenoviruses of groups B, C and E (human Adenovirus B, C, E, hAdv).

Reverse transcription and PCR reactions were performed using commercial "Reverta" and "Amplisens-200" kits manufactured in Russia.

Statistical processing of the study results was carried out step-by-step:

1.1. Preparation of material for statistical analysis

2.2. Statistical analysis proper.

Analysis of the obtained data included calculation of the arithmetic mean of the variation series (M) and its standard error (m). The reliability of differences obtained in the compared groups was assessed by Student's t-criterion. To find out the degree of interrelation between the studied indicators, the paired correlation coefficients (r) were calculated.

Pearson's correlation coefficient was calculated by the formula:

$$r_{xy} = \frac{E(x_i - x)(y_i - y)}{\sigma_X \sigma_Y}$$

x_i – value taken in the sample X, y_i – sample values Y; x – average value for X, y – average value for Y. E is the expectation; σ_X – *i*s the standard deviation of X; σ_Y – is the standard deviation of Y.

Assessment of reliability of the differences between the indicators of the compared groups (differences were considered statistically significant at the level of $p < 0.05$):

– on qualitative binary traits – XI-squared test with Yates correction.

Chapter 3. CLINICAL AND LABORATORY CHARACTERISTICS OF EXAMINED CHILDREN WITH ACUTE OBSTRUCTIVE BRONCHITIS

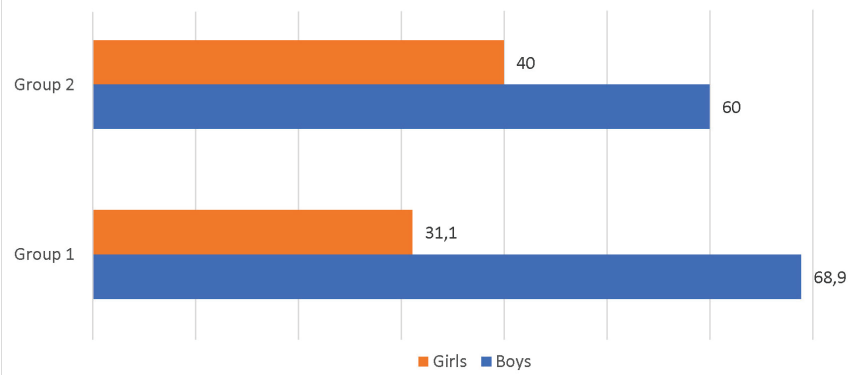
3.1 Comparative general characterization of examined children with acute obstructive bronchitis with and without atypical microflora

Active identification of etiologic factors of respiratory infections and development of criteria for timely diagnosis and treatment is, from the position of clinical bronchology, a promising scientific direction.

Based on the objectives we studied the clinical features of the course of acute obstructive bronchitis and the sick children were divided into 2 groups: Group 1 children with AOB without atypical microflora, Group 2 children with AOB with atypical microflora.

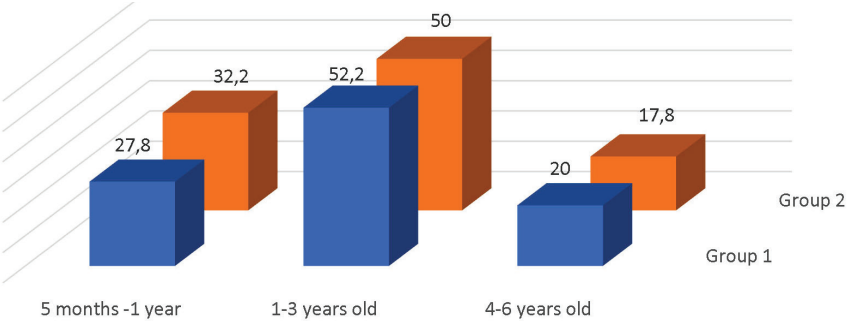
Among the examined boys were slightly more than girls in both groups 62 (68.9%) and 54 (60.0%) respectively, 28 (31.1%) and 36 (40.0%) respectively. As in some other types of pediatric pathology, the predominance of morbidity among boys seems to be related to the peculiarities of the physiology of the sexes (Fig. 3.1.1).

Figure 3.1.1 Distribution of patients by sex of the first and second groups



We analyzed the distribution of patients by age. The data are presented in Fig. 3.1.2. Children aged 1 to 3 years of life prevailed among the observed patients in both groups 47 (52.2%) and 45 (50%), respectively.

Figure 3.1.2 Distribution of patients by age in both groups



Note: 1 group of patients with AOB without atypical microflora, 2 group of patients with AOB with atypical microflora

Of those examined in group 1, there were 25 (27.8%) children aged 5 months to 1 year, 47 (52.2%) children aged 1 to 3 years, and 18 (20.0%) children aged 4 to 6 years. In the second group, there were 29 (32.2%) children aged 5 months to 1 year, 45 (50.0%) children aged 1 to 3 years, and 16 (17.8%) children aged 4 to 6 years.

Thus, of the examined 180 children with acute obstructive bronchitis, regardless of the atypical microflora, children aged 1 to 3 years prevailed (52.2% and 50.0% respectively). Children aged 1 to 3 years were more frequent and boys predominated (68.8% and 54% respectively). In both groups, anemia in mothers during pregnancy was significantly more frequent and ranged from 64.4% to 76.2% of cases. At the same time, it was the most frequent in mothers of the second group 76.2%. Pyelonephritis was also significantly more common in group 2 mothers in 6.7% of cases compared to 1.1%. In group 2, almost every second mother was significantly ($p < 0.05$) more likely ($p < < 0.05$) to have acute respiratory diseases during pregnancy in 17.05% of cases. Definite chlamydia and mycoplasma infection in mothers, threat of abortion was the highest in group 2 and was 22.2% against 3.33% in group 1. Vomiting of pregnant women was reported in both groups but the highest percentage was in group 2 (14.4% and 50.7% cases, respectively) Single case was with COVID and nephropathy of pregnant women in group 2 (таб. 3.1.1).

Table 3.1.1 Anamnestic data of mothers of children with AOB in groups 1 and 2

	1 group (n=90)		2 group (n=90)		Total	p
	n	%	n	%	n=180	
Anemia	58	64.4	60	76. 2%	70.3%	p < 0.05
Pyelonephritis	1	1.1	6	6.7	3.9%	p < 0.01
Frequent ARD	7	7.78	16	17.05	12.4%	p < 0.05
Chlamydia and mycoplasma infection, threatened abortion	3	3.33	21	22.2	12.7%	p < 0.05
Pregnancy vomiting	13	14. 4	46	50.7	32.5%	p < 0.05
Nephropathy	–	–	3	3.32	1.66	p < 0.01
COVID	–	–	1	0.9	0.45	p < 0.01
Smoking fathers	12	13. 3	32	34.8	24.05%	p < 0.05

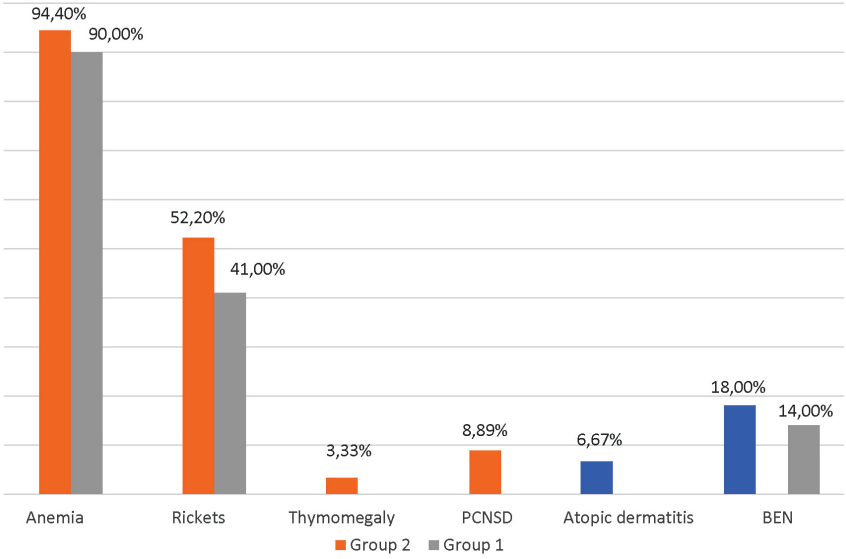
Note: p – reliability of differences between group 1 and group 2

In group 1, 98% of children were born prematurely, only 2% of children were born prematurely. The majority of children in Group 2 were also born prematurely by gestational age 95.5%, 4 (4.5%) were born prematurely. Among the examined children under 1 year of age, 59 (65.5%) children in Group 1 were naturally fed, 19 (21.1%) were artificially fed, and 12 (13.4%) were mixed-fed. In group 2.56 (62.3%) children were naturally fed, 23 (25.5%) children were artificially fed, and 11 (12.2%) children were mixed-fed. On average, 32.2% of children in both groups were diagnosed with DPN.

Anemia in group 1 children was found in 90.0% of cases, it should be noted that in 70% of cases anemia was of the first degree. The causes of anemia of mixed genesis from anamnestic data were such factors as prematurity, early artificial feeding, mismatch of nutrition and age, as well as acute respiratory infections, especially before 1 year of age, and worm infestations in children from 3 to 6 years of age. Vitamin D-deficient rickets was diagnosed in 41.0% of children, anemia was found in group 2 in 94.4%, in contrast to group 1, children with II and III degrees of severity prevailed, rickets in 52.2%, and thymomegaly of the first degree was registered in

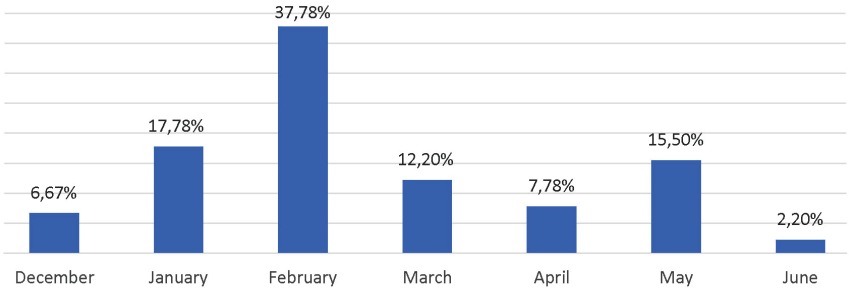
3.33% of the examined patients. Only children in group 2 were registered with a diagnosis of PCNSD by a neurologist in the first year of life (8.89%), as well as with atopic dermatitis (6.67%). Figure 3.1.3 summarizes the frequency of comorbidity in obstructive bronchitis in the examined children.

Figure 3.1.3 Frequency of comorbidity in children with AOB in the study groups



Among the 180 sick children we examined, the incidence was most frequent during the winter-spring months (January-May) (fig. 3.1.4).

Figure 3.1.4 Overall seasonality of AOB prevalence in both groups



Thus, anemia, toxemia of pregnancy, toxemia of pregnancy, and acute respiratory infections were significantly more frequent in mothers during pregnancy in the examined children of both groups. Also, fathers' smoking was noted in the groups in the range from 29.2% to 38.5% of cases. It should be noted that in group 2, the above-mentioned pregnancy pathology was more frequent than in group 1. In addition, chlamydia and mycoplasma infection, threatened abortion, and tobacco abuse by fathers were more frequent in group 2 than in group 1.

Thus, from the anamnestic data of mothers of children with AOB in both groups, anemia, frequent ARD and vomiting of pregnancy were noted. In addition, in the first group, besides these pathologies, chlamydia and mycoplasma infection and pregnancy termination, pyelonephritis were also found. Preterm infants prevailed in both groups. There were no special differences in the type of feeding. An unfavorable premorbid background and concomitant pathology had a significant impact on the severity of the course of the disease in the patients we examined. In both groups the majority of children suffered from anemia, but in group 2 the II and III degree of severity was diagnosed more often, in contrast to group 1 it was more often of the I degree. Anamnesis was aggravated in children with acute bronchitis in group 2 also by the presence of PCNSD, atopic dermatitis and thymomegaly. In children with obstructive bronchitis on the background of atypical microflora the presence of the above mentioned diseases, unlike children of group 1, influenced the duration of the disease (it lasted longer in children of group 2) and the clinical symptoms were joined by the symptoms of these diseases.

3.2 Clinical peculiarities of AOB in the examined children

In group 1 children examined by us, a moderately severe course of AOB was diagnosed in 74.4% of cases and a severe course in 25.6% of cases. In Group 2, the disease was moderately severe in 61.1% of cases and severe in 38.9% of cases.

The severity of the condition in children with AOB on admission to hospital was determined by symptoms of general intoxication and respiratory failure. Intoxication syndrome was more pronounced in group 1 of patients, lethargy was observed in 39% of patients in group 1 and in 17.8% of patients in group 2. Decreased appetite with restlessness in 63 (70%) patients versus 52 (58%) in group 2. Duration of intoxication syndrome was longer in group I mainly in infants.

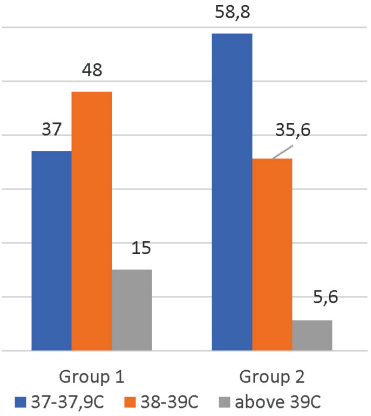
Table 3.2.1 Respiratory failure in children with AOB depending on groups

RF	1 group (n = 90)	2 group (n = 90)	p < 0.05	Total group of AOB (n = 180)
I degree	67 (74.4%)	55 (61.1%)	p 1–2	122
II degree	23 (25.6%)	34 (37.8%)	p 1–2	57
III degree	–	1 (2.2%)	p 1–2	1

Note: p < 0.05 – reliability of differences between age groups

Respiratory failure was observed in both groups. In group 1, RF of the I degree was diagnosed in 67 (74.4%) children, in group 2 in 55 (61.1%) children. RF II degree was diagnosed in 25.6% of cases and in group 2 in 37.8% of cases. III degree RF was diagnosed only in group 2 children, which amounted to 2.2%. Clinical signs appeared 4–5 days after the onset of the disease in children with AOB without atypical microflora. And in children with atypical microflora 2–3 days after the onset of the disease. Intoxication syndrome was also manifested by increased body temperature.

Figure 3.2.1 Temperature curve data depending on the presence of atypical microflora



In all observed patients at admission there was an increase in body temperature. In children with AOB without atypical flora, the temperature on admission was within 37 °C – 37.9 °C in 37.0%, over 38 °C in 48% of chil-

dren, over 39 °C in 15% of children. In 58, 8% of children of group 2 the temperature was within 37 °C–37.9 °C, body temperature over 38 °C was noted in 35.6% of patients, over 39 °C was observed in 5, 6% of patients (fig. 3.2.1, $p < 0.05$).

All examined patients with AOB in both groups had runny nose, sneezing, hyperemia of the mucous membrane of the pharynx, difficult breathing, these symptoms of respiratory syndrome lasted from 5 to 7 days. Cough was observed in 100% of cases in both groups, in children with AOB with atypical microflora it appeared in the first 2 days of the disease and lasted in the second group on average 12.38 ± 0.39 days, and in the first group on average 10.38 ± ± 0.49 days. In the first 5 days from the onset of the disease, especially at the age of 1 to 3 years, the cough was frequent and dry and strongly bothered children of both groups. The use of mucolytics in the majority of patients, along with reduction of cough, resulted in increased sputum excretion. In particular, in 3 young children, the use of ambroxol and ACC resulted in abundant sputum production and increased obstruction, and parents had to seek medical help.

The peculiarity of cough in group 2 was a longer persistence of rare cough in 81.1% of children without etiotropic treatment after discharge from the hospital. In group 2 in 73.1% of cases there were symptoms of general intoxication, sleep disturbance, especially in children under 1 year of life. The same decrease in appetite in patients observed by us for more than 5 days was detected more often in children from 1 to 3 years of age in both groups.

Expiratory dyspnea was registered in 51% of the examined children, especially those aged 2 to 4 years and children of group 2.

At auscultation in the lungs of all children at admission to the hospital hard breathing was heard. In all patients different kinds of wheezes were also heard at auscultation, so in 35 (38.8%) children of the first group symmetrical diffuse dry wheezes and in 40 patients of the second group asymmetrical diffuse dry wheezes were heard against the background of rigid breathing, that was 44.4% (group 2) more than in group 1. The combination of dry and moist wheezes amounted to (27.0% and 34.4% respectively), abundance of moist multicaliber wheezes was heard in (12.0% and 15.6% respectively) children.

The duration of the disease duration of AOB in children averaged 7 to 14 days. We analyzed laboratory studies. Laboratory study of the general blood analysis in the children examined by us in all groups revealed a decrease in hemoglobin and the number of erythrocytes, in connection with which the patients were given a concomitant diagnosis of anemia of mixed genesis.

Calcium content in the blood of children up to 1 year of life was also investigated, so in 35 patients of the first group and in 30 (33.3%) children in the second group there was a decrease in the indicators, in connection with which the correction with calcium preparations was carried out.

In the general analysis of urine pathology in both groups no changes were found except for one child in group 2 who had proteinuria up to 0.066 g/l, repeated urine analysis was normal after treatment in this patient after 10 days.

Radiologic changes of the chest were observed in both groups in the form of the following changes: diffuse strengthening of the pulmonary pattern on both sides, small linear and looping shadows, which were detected in 70% (126) of children. In 12.2% (22) of the examined children, signs of pulmonary tissue ballooning were registered. Radiologic signs of thymus enlargement of the 1st degree were found in 3.33% of patients. ECG studies were performed in 166 (92.2%) patients. Analysis of ECG findings revealed the following changes sinus tachycardia in 18 (21.7%), left ventricular hypertrophy in 12 (14.5%) children ($p < 0.05$). Thus, no special differences were noted on ECG in both groups.

Ultrasound of the abdominal cavity and kidneys was also performed in 54 (30%) patients, in particular, in 54 (30%) patients, among whom 1 (3.7%) patient was found to have mirror position of internal organs, including the heart. No other changes in the abdominal cavity and kidneys were detected.

Bronchologic examination in the form of bronchoscopy was performed in 3 (3.33%) patients of group 2 in the form of diagnostic bronchoscopy to exclude a foreign body of the lower respiratory tract, catarrhal endobronchitis was diagnosed, the foreign body was excluded.

Thus, more often APS developed in males in group 1 in 68.9% of children and in group 2 in 60% of children, respectively. The obtained data on age correlate with the data of many authors [3], which indicate the predominant development of AOB in children of the first 3 years of life. The burden of passive smoking was 13.3% and 34.8%, respectively. The above risk factors are also widely described in the literature [3, 100]. Adverse course of pregnancy in mothers of sick children was noted in the form of anemia in 70.3%, in addition, vomiting of pregnancy. In the children we examined, the course of the disease was more often moderate in group 1 in 74.4%, severe course was observed in 25.6% of cases, in group 2 moderate course was observed in 61.1%, and severe in 38.9% of cases. Dyspnea in all patients was predominantly of expiratory nature and was accompanied by respiratory failure of various degrees of severity.

Chapter 4. OWN RESEARCH RESULTS

4.1 Etiologic structure of examined children with AOB with atypical microflora

Virological examination was performed in 67 patients with AOB by polymerase chain reaction (PCR). Compared to other pathogens, PC virus was detected significantly more often. Thus, in the control group MS-virus was detected in 50.0% of cases, in the second group 46.7%, in the third group 44.5%, in the fourth group 50.0%. Adenovirus infection was significantly more frequently detected in group III and group IV. Rhinovirus infection was detected in equal amounts in groups I, II, III. (таб. 4.1.1).

Table 4.1.1 Etiologic structure of examined children with AOB with atypical microflora

Indicators	I group (control) (n = 18)		II group (n = 15)		III group (n = 18)		IV group (n = 16)	
	N	%	N	%	N	%	N	%
PC-virus	9	50.0	7	46.7	8	44.5	8	50.0
Adenovirus	4	22.2	3	20.0	6	33.3	5	31.25
Parainfluenza virus	3	16.7	3	20.0	2	11.1	2	12.5
Rhinovirus	2	11.1	2	13.3	2	11.1	1	6.25
Total	18		15		18		16	

According to researchers, one of the main causes of AOB in preschool children are associated infections of viral and bacterial origin, in particular chlamydia and mycoplasmas [48].

In the examined patients, along with viral infection, atypical microflora was also detected, as it was said above, which is presented in (Fig. 4.1.1).

To diagnose the etiologic structure of AOB with atypical microflora, PCR diagnostics was performed, which revealed the most frequent combination of atypical microflora with PC viral infection, which amounted to 37.4%.

Adenovirus-chlamydia 16.5% and parainfluenza-chlamydia infection were combined in almost equal amounts. B 15.0%. 1.5–4.5% of cases, the following viral associations with atypical microflora occurred: adenovirus-chlamydia-mycoplasma infection, rhinovirus-chlamydia-mycoplasma infection, rhinovirus-mycoplasma infection, rhinovirus-chlamydia infection, parainfluenza-mycoplasma infection (4.1.1).

Figure 4.1.1 Etiologic structure of examined patients with AOB in preschool children

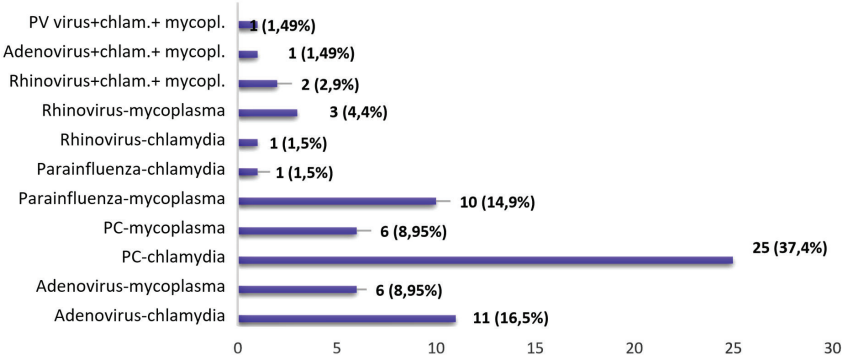
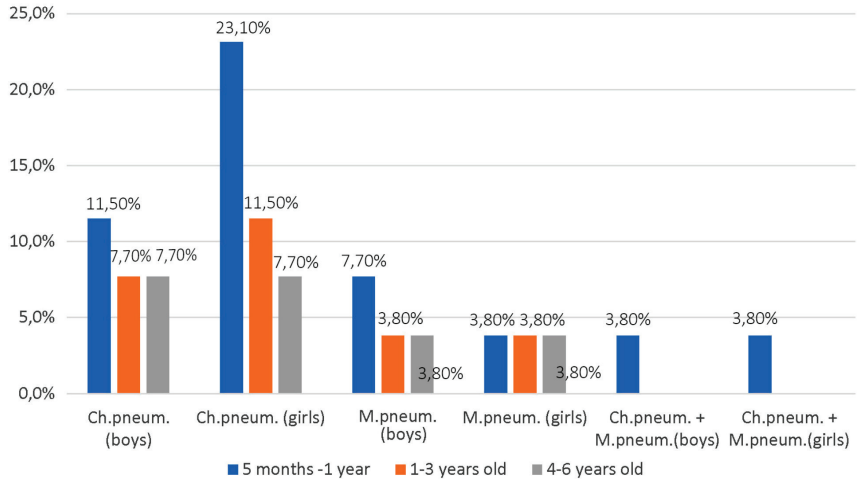


Figure 4.1.2 Frequency of occurrence of atypical microflora in children with AOB depending on sex and age in group I

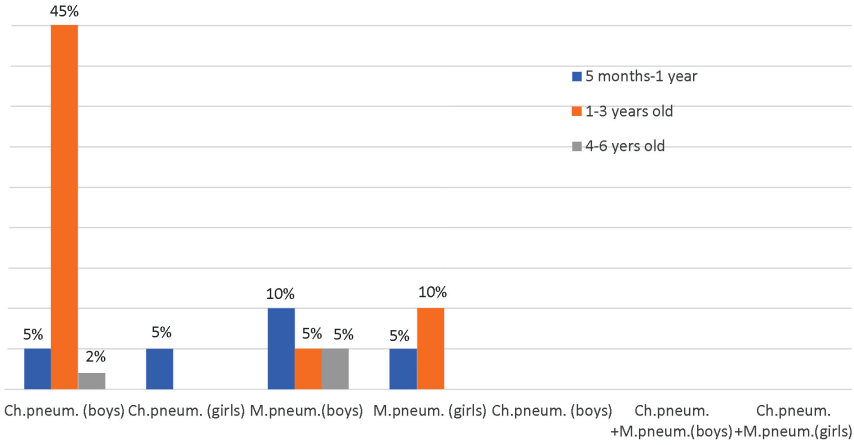


A total of 365 children aged from 5 months to 6 years with the diagnosis of acute respiratory tract infections (outpatient and inpatient) were examined by the method of continuous sampling. 90 children (24.7%) had IgM, IgG antibodies in different titers to Ch.pneumoniae, M.Pneumoniae.

The distribution of patients by frequency of atypical microflora in children with AOB by sex and age in Group I is presented in (Figure 4.1.2).

As presented in Figure 4.1.2, in group I, Ch. pneumoniae was found in 3 (11.5%) boys and 6 (23.1%) girls in the age group from 5 months to 1 year, in 2 (7.7%) boys and 3 (11.5%) girls in the age group from 1 to 3 years and in the age group from 4 to 6 years in 2 (7.7%) boys and girls. Antibodies to M. pneumoniae were detected in 2 (7.7%) boys and 1 (3.8%) girl in the age group from 5 months to 1 year. In the age group from 1 to 3 years in 1 (3.8%) boy. The pathogen was not detected in girls in this age group. In the age group, M. pneumoniae was detected in 1 (3.8%) boy and in a girl (Figure 4.1.2). The association of Ch. pneumoniae and M. pneumoniae in the age group from 5 months to 1 year was equal in both boys and girls and amounted to 1 (3.8%). In other age groups the association of Ch. pneumoniae and M. pneumoniae was not detected.

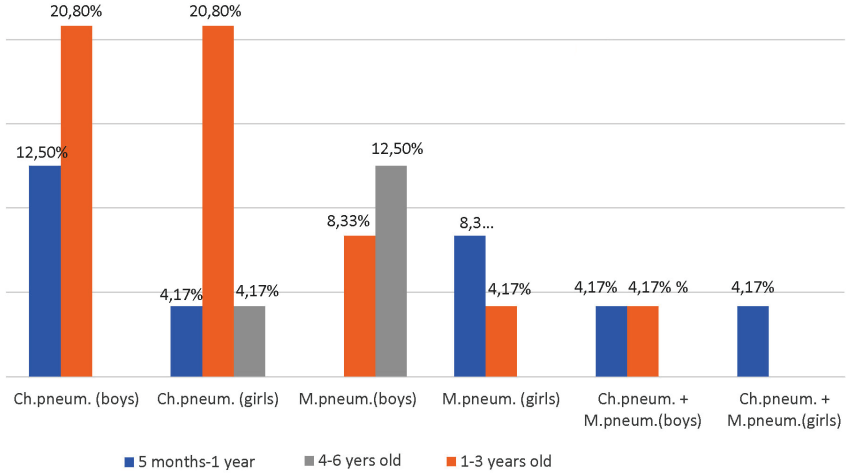
Figure 4.1.3 Frequency of occurrence of atypical microflora in children with AOB by sex and age in group II



In group II in patients in the age category from 5 months to 1 year Ch. Pneumoniae was detected in equal numbers in both sexes 1 (5%). Antibodies to this pathogen were detected in 9 (45%) boys in the age category from

1 to 3 years. No antibodies to Ch. Pneumoniae were detected in girls in this age category. In boys aged 4 to 6 years, antibodies to Ch. Pneumoniae were detected in 2 (10%). In this age category, antibodies to Ch. Pneumoniae were not detected in girls. Antibodies to M. pneumoniae in boys in the age group from 5 months to 1 year were detected in 2 (%), and in 1 (5%) girls. In the age group from 1 to 3 years, antibodies to M. pneumoniae were detected in 1 (5%) boy and 2 (10%) girls. Antibodies to M. pneumoniae were detected in 1 (5%) boy in the age group from 4 to 6 years. No antibodies to M. pneumoniae were detected in girls in this age group. Association of Ch. pneumoniae and M. pneumoniae was not detected in this group (Figure 4.1.3).

Figure 4.1.4 Frequency of occurrence of atypical microflora in children with AOB by sex and age in group III

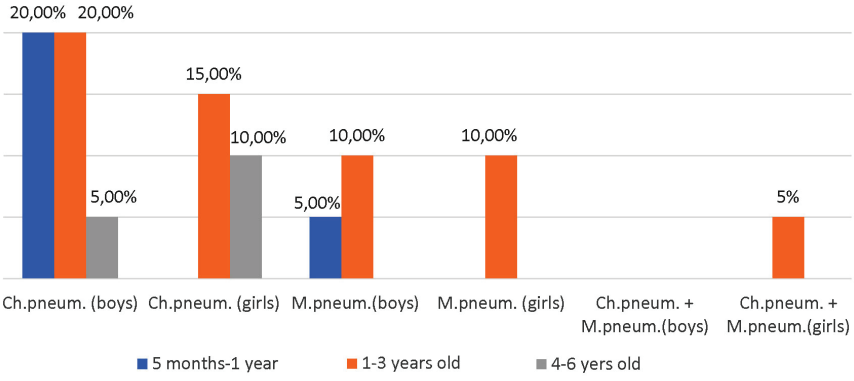


In group III, antibodies to Ch. Pneumoniae in the age group from 5 months to 1 year were detected in 3 (12.5%) boys and 1 (4.17%) girl. Antibodies to Ch. Pneumoniae were detected in equal amounts in 5 (20.8%) boys and girls in the age group from 1 to 3 years. In the age group from 4 to 6 years, antibodies to Ch. Pneumoniae were detected in 1 (4.17%) girl, and no antibodies to Ch. Pneumoniae were detected in boys of this age group. Antibodies to M. pneumoniae in the age category from 5 months to 1 year were not detected in boys, 1 (4.17%) girl was detected. Antibodies to M. pneumoniae was determined in 2 (8.33%) boys and 1 (4.17%) girl

in the age category from 1 year to 3 years. In the age category, antibodies to M. pneumoniae were detected in 3 (12.5%) patients. No antibody to M. pneumoniae was detected in this age group in girls. Association of Ch. pneumoniae and M. pneumoniae were detected in this group in 1 (4.17%) boy in the age group from 1 to 3 years, and in 1 (4.17%) girl in the age group from 4 to 6 years (Figure 4.1.4).

In group IV, antibodies to Ch. Pneumoniae were detected in 4 (20%) boys in the age category from 5 months to 1 year, and no antibodies to Ch. Pneumoniae were detected in girls in this age category. Antibodies to Ch. Pneumoniae were detected in 4 (20%) boys and 3 (15%) girls in the age category from 1 to 3 years. In the age category of children from 3 to 6 years, antibodies to Ch. pneumoniae were detected in 5% (1) of boys and 10% (2) of girls. Antibodies to M. pneumoniae were detected in 5% (1) of cases in boys in the age category from 5 months to 1 year. No antibodies to M. pneumoniae were detected in girls in this age category. In 10% (2) cases antibodies to M. pneumoniae were detected in both sexes. And 1 (5%) girl had antibodies detected in association with Ch. pneumoniae and M. pneumoniae (Figure 4.1.5).

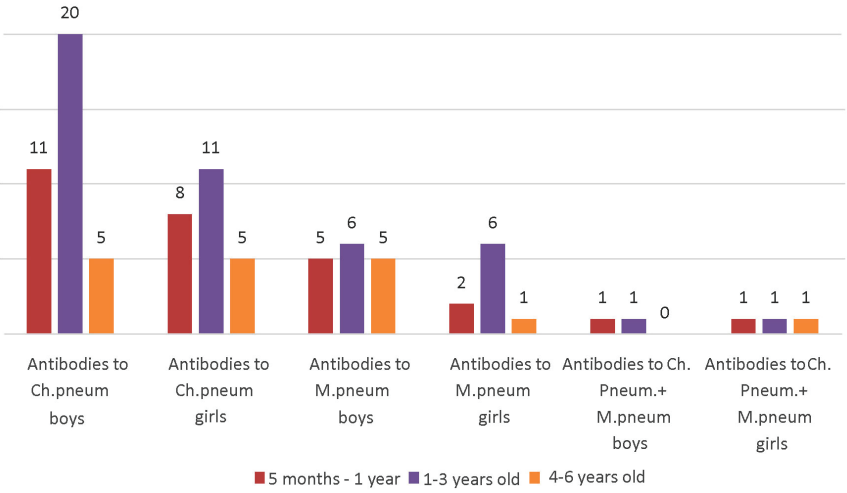
Figure 4.1.5 Frequency of occurrence of atypical microflora in children with AOB by sex and age in group IV



When analyzing the prevalence of Ch. rneumoniae by sex, seropositive boys 36 (40.0%) patients and girls 24 (26.6%) children were recorded, and M. Rneumoniae was found to be seropositive in 16 boys, which amounted to 17.8% of children, and 2 times less frequently in 9 (10.0%) girls with AOB. Of the examined children who had co-infection with Ch. pneumoniae and

M. Pneumoniae, girls prevailed in 3.33% of cases than boys in 2.22% ($p < < 0.05$). (Figure 4.1.6).

Figure 4.1.6 Frequency of atypical microflora in children with AOB by gender and age



Thus, based on the data obtained, the predominant etiologic factor in our examined children is PC virus infection, and according to anamnestic data, children were most often admitted in winter and spring months. Along with PC virus, adenovirus infection and parainfluenza virus were detected. In the children we examined, the most frequent etiologic factor was PC virus and adenovirus infection. Rhinovirus infection was the least common. Our data are comparable with the data of M. V. Lim [56] for Samarkand region, in children with AOB examined by them, the greatest amount of PC-virus was observed in young children. Thus, among the examined patients in the etiologic structure in all groups PC-virus infection prevailed in all groups, which amounted to 50.0% in group I, 46.7% in group II, 44.5% in group III, and 50.0% in group IV. Adenovirus infection was in the second place and it was reliably more frequently detected in groups III and IV. Parainfluenza infection was also frequently detected in groups I and II, 16.7% and 20.0%, respectively. Among those examined, morbidity was observed more often in winter-spring months, with a peak in January through May months.

Thus, unfavorable premorbid background and concomitant pathology had a significant influence on the severity of the course of the disease in

the patients we examined. In children with obstructive bronchitis against the background of the above-mentioned diseases in contrast to children who did not have aggravating factors, the disease course was longer and the clinical symptoms were accompanied by symptoms of these diseases. Thus, in children on the background of PCNSD, such symptoms as monotonous cry, convulsive readiness, restlessness and chin tremor were added to the clinical picture of AOB with atypical microflora.

Of 365 patients, 90 had a combination of viral infection with atypical bacterial flora with the development of mixed viral-chlamydia and viral-mycoplasma infections.

4.2 Clinical features of the course of AOB with atypical microflora depending on the type of differentiated therapy

This subchapter summarizes clinical features of the course of AOB with atypical microflora depending on the type of differentiated therapy. In the moderate course of the disease in 65.5% of cases only Ch. rneumoniae was detected in comparison with the severe course of AOB. Ch. rneumoniae infection in children with severe course of the disease was detected 2 times less frequently ($p < 0.05$). In children in whom only M. rneumoniae was detected, the disease course was moderately severe (68.4%). Severe course of the AOB in children with M. rneumoniae infections was detected in 23.7% of children. Rneumoniae was detected in 23.7% of children, i.e. 3 times less often than in patients with Ch. rneumoniae infection only. It should be noted that the majority of those who became sick with AOB M. rneumoniae were boys among those who had only Ch. rneumoniae infection (tab. 4.2.1, $p < 0.05$).

Table 4.2.1 Distribution of children infected with Ch. rneumoniae and M. rneumoniae. Pneumoniae depending on the severity of AOB

Seropositive children	Disease severity					
	Total (n = 90)		Moderate severity (n = 52)		Severe (n = 38)	
	Abs.	%	Abs.	%	Abs.	%
to Ch. Pneumoniae	60	66.7	34	37.8	26	28.9
to M. Pneumoniae	25	27.8	16	17.8	9	10.0

Seropositive children	Disease severity					
	Total (n = 90)		Moderate severity (n = 52)		Severe (n = 38)	
	Abs.	%	Abs.	%	Abs.	%
to Ch. pneumoniae and M. Pneumoniae	5	5.5	2	2.2	3	3.33
Total	90	100%	52	57.8%	38	42.2%

Thus, in the etiologic structure of the examined patients in all groups PC-virus infection prevailed in all groups, which amounted to 50.0% in group I, 46.7% in group II, 44.5% in group III, and 50.0% in group IV. Adenovirus infection ranked second and was significantly more frequently detected in groups III and IV. Parainfluenza infection was also frequently detected in groups I and II, 16.7% and 20.0%, respectively. Among those examined, morbidity was observed more frequently in the winter-spring months, with a peak from January to May. Of 365 patients, 90 had a combination of viral infection and atypical bacterial flora with the development of mixed viral-chlamydia and viral-mycoplasma infections. RF I degree of severity was registered in 55 (%) children, more often at early age from 5 months to 3 years (68.91%) ($p < 0.05$). RF II degree was observed in 34 (37, 8%) and was significantly more frequent at the age of 1 to 3 years and was 40% ($p < 0.05$) (tab. 4.2.2).

Table 4.2.2 Degrees of respiratory insufficiency in examined children depending on age

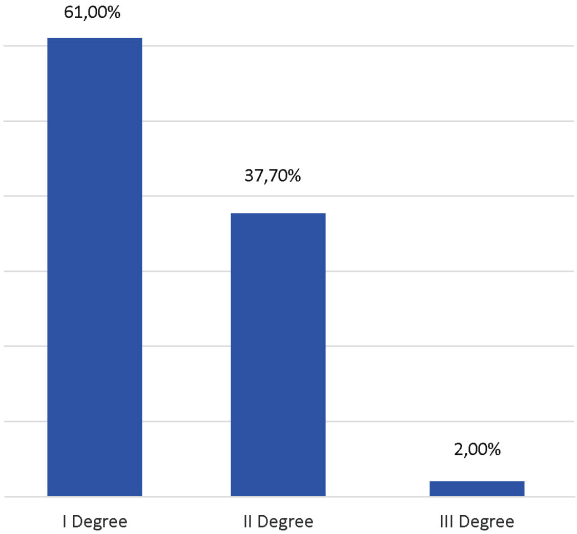
RF degrees	5 month.-1 year (n=29)	1–3 years old (n=45)	4–6 years old (n= 16)	p < 0.05	Total AOB (n=90)
I degree	25 (86%)	26 (57.8%)	4 (25%)	p 1–2. p 1–3	55
II degree	4 (14%)	18 (40%)	12 (75%)	p 1–2	34
III degree	–	1 (2.2%)	–	p 1–2	1

Note: $p < 0.05$ – reliability of differences between age groups

Grade III of RF was recorded in 1 (1.11%) patient aged 1 to 3 years (2.2%) (Table 4.2.2). This patient was diagnosed with PCNSD in the form of infantile

cerebral palsy and required treatment in the intensive care unit. The clinical manifestations of RF III degree in this patient were adynamia, periodically replaced by agitation, periods of apnoea, total pallor of the skin and tachycardia. Dyspnoea increased with feeding, and there was also a retraction of the pliable areas of the chest during breathing. The severity of respiratory insufficiency in children with AOB is presented in the (Figure 4.2.1).

Figure 4.2.1 The severity of respiratory depression in children with AOB



Distribution of patients and medicines taken by patients in groups is presented in the table below (таб. 4.2.3).

Table 4.2.3. Distribution of patients by groups

Groups	Treatment
I group	received standard therapy
II group	Standard therapy and Clarithromycin. Clarithromycin in a dose of 2 times a day orally at the rate of children 15 mg/kg course of treatment was 7 days.
III group	Standard therapy and immunomodulator 'Galavit'. Galavit sublingually in a dose of 1–2 tablets daily from 2 to 4 times a day, a course of 5 days in children from 3 to 6 years, or in

Groups	Treatment
	the form of suppositories once a day, a course of 5 days from 5 months to 3 years.
IV group	Standard therapy, Clarithromycin and Galavit according to the scheme depending on age. Clarithromycin in a dose of 2 times a day orally at the rate of children 15 mg/kg course of treatment 7 days. Galavit was used sublingually in a dose of 1–2 tablets daily from 2 to 4 times a day with duration of 5 days for children from 3 to 6 years old. And also it was used in the form of suppositories once a day for 5 days, then after a day 5 more suppositories for children aged from 5 months to 3 years.

The data of analysis of clinical effectiveness of differentiated treatment of patients showed that after the treatment the general condition of patients improved in all groups, but in group II, in which children received clarithromycin and in group IV, which also received clarithromycin and additionally Galavit, improvement of general condition was noted 2 days earlier than in groups I and III.

Restlessness of children in the form of crankiness, poor sleep, decreased appetite at 1.5 days less was also noted in group II (2.55 ± 0.18) and group IV (2.45 ± 0.15) ($p < 0.001$). Decrease in body temperature in children was noted in group II (1.95 ± 0.17) and IV (1.80 ± 0.15) at the end of 2 days after the start of treatment, and in the traditional group (I) on 4 days (4.0 ± 0.20) and in group III (2.92 ± 0.15) on 3 days from the start of treatment ($p < 0.001$).

In group I which received traditional treatment the cough was stopped on the 12th day from the beginning of the disease (12, 38 ± 0, 39), in group III which received Galavit along with standard treatment the cough was stopped on the 10th day (10.38 ± 0.49), the cough was stopped on the 6^{th}–7^{th} day in children of groups II and IV which additionally received Clarithromycin, group IV also received Galavit ($p < 0.001$).

Thus, in these groups, the cough was relieved in a shorter time ($p < 0.001$). Rare cough (1–3 times a day) in group I was noted for 4–5 days after its relief. Cyanosis of the nasolabial triangle in group I on 1.5 days was longer in contrast to the other 3 groups. Expiratory dyspnoea in groups II and IV disappeared significantly ($p < 0.05$) faster than in groups I and III ($p < 0.01$) (Tab 4.2.4).

Table 4.2.4 Dynamics of elimination of the main clinical symptoms

Indicators (days)	I group (n=26)		II group (n=20)		III group (n=24)		group (n=20)	
	M	m	M	M	M	m	M	M
General condition	4.44	0.32	2.85*	0.17	3.50	0.21	2.80*	0.19
Restlessness	3.95	0.34	2.55*	0.18	3.29***	0.15	2.45*	0.15
Temperature	4.0	0.20	1.95*	0.17	2.92*	0.15	1.80*	0.15
Cyanosis of the nasolabial triangle	3.27	0.23	2.78	0.32	2.47**	0.21	2.43**	0.16
Expiratory dyspnoea	3.75	0.37	2.67*****	0.33	3.25	0.22*****	2.89	0.24
Cough	12.38	0.39	7.35*	0.37	10.38*	0.49	6.75*	0.24
wheezes (wheezing and wet wheezing)	5.04	0.17	3.75*****	0.20	4.63****	0.20*****	3.20	0.24

*Note: P_1, P_2, P_3 – reliability of differences between control group and groups 2, 3, 4 respectively *P < 0.001;** P < 0.01; ***P > 0.1; ****P > 0.5; *****P < 0.05*

The wheezes, especially whistling wheezes, were longer in groups I and III (5.04 ± 0.17; 4.63 ± 0.20), respectively. Percussion box sound was noted in 57 (63.3%) children, and tympanic sound in 11 (12.2%) children, the rest of the patients had percussion lung sound.

Our data showed that after the treatment in the group of children who received Clarithromycin and Galavit the improvement of general condition was noted 2 days earlier, temperature decreased on the 2 nd day after the beginning of treatment, cough reduction was noted on the 6 th–7 th day, cyanosis of the nasolabial triangle disappeared 1.5 days earlier. Dyspnoea significantly more often disappeared faster also in this group, and auscultatory data also were eliminated wheezing in earlier terms in comparison with the control group.

Thus, differential therapy for AOB with atypical microflora has a good clinical effect.

4.3 Indicators of humoral immunity in children with SARS depending on the type of differentiated therapy

The results of the study of humoral immunity parameters after treatment are presented in (Table 4.3.1).

As shown in the table, after treatment antibody to Ch. Pneumoniae IgM was (1.10 ± 0.14), in group 2 (0.95 ± 0.18), in group 3 (1.06 ± 0.12), whereas in group IV it was (0.59 ± 0.04) which was significantly lower when compared with other groups ($p < 0.001$).

The results of the studies showed that there were no differences between the groups in the content of antibodies to Ch. Pneumoniae Ig G. Antibodies to M.pneumoniae IgM in all investigated groups were at the same level 0.91 ± 0.21; 0.93 ± 0.22; 0.94 ± 0.18 respectively for I, II, III, groups, except for group IV which was 0.59 ± 0.06, i.e. it was lower in contrast to other groups.

Table 4.3.1 Comparative ELISA analysis of chlamydial and mycoplasma infection in patients of the compared groups after treatment

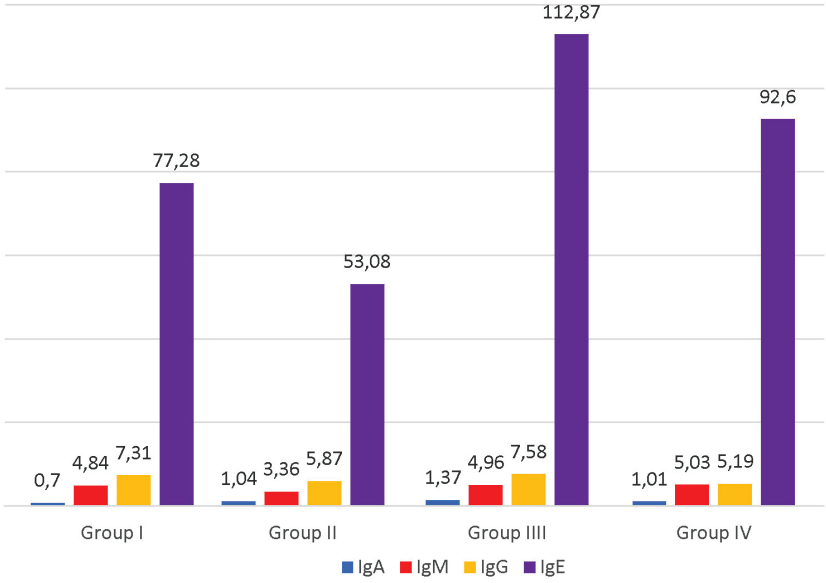
Indicators	I group (n=26)		II group (n=20)		III group (n=24)		IV group (n=20)		P_1	P_2	P_3
	M	m	M	M	M	m	M	m			
Ch. pneum. IgM (PI < 1.1)	1.10	0.14	0.95	0.18	1.06	0.12	0.59	0.04	>0.5	>0.5	<0.001
Ch. pneum. IgG (PI < 1.1)	2.80	0.12	2.72	0.16	2.58	0.22	2.79	0.12	>0.5	>0.5	>0.5
M. pneum. IgM (PI < 1.1)	0.91	0.21	0.93	0.22	0.94	0.18	0.59	0.06	>0.5	>0.5	>0.1
M. pneum. IgG (PI < 1.1)	2.79	0.22	2.87	0.15	2.72	0.15	2.83	0.12	>0.5	>0.5	>0.5

Note: P_1, P_2, P_3 – reliability of differences between control group and groups 2, 3, 4, respectively

The study of antibodies to M.pneumoniae IgG did not reveal any differences between the groups (Table 4.3.1).

To determine the differential differences of immunological indicators of humoral immunity in children with mycoplasma and chlamydia infections, we evaluated the indicators in the age aspect before and after treatment. Thus, in group I, which received standard therapy in children aged 5 months to 1 year IgA content was within the norm 0.70 ± 0.08 g/l (Figure 4.3.1), while in children from 3 to 6 years old the indicators were in the lower limit of the norm, and these data were statistically not significant (P > 0.05) and amounted to 0.93 ± 0.16 g/l in children aged 1–3 years old, 0.96 ± 0.14 g/l in children from 3–6 years old. In this group, IgA content in children aged 5 months to 6 years almost did not change after treatment.

Figure 4.3.1 Dynamics of IgA, IgM, IgG, IgE content in I, II, III, IV groups at the age of 5 months to 1 year (before treatment)



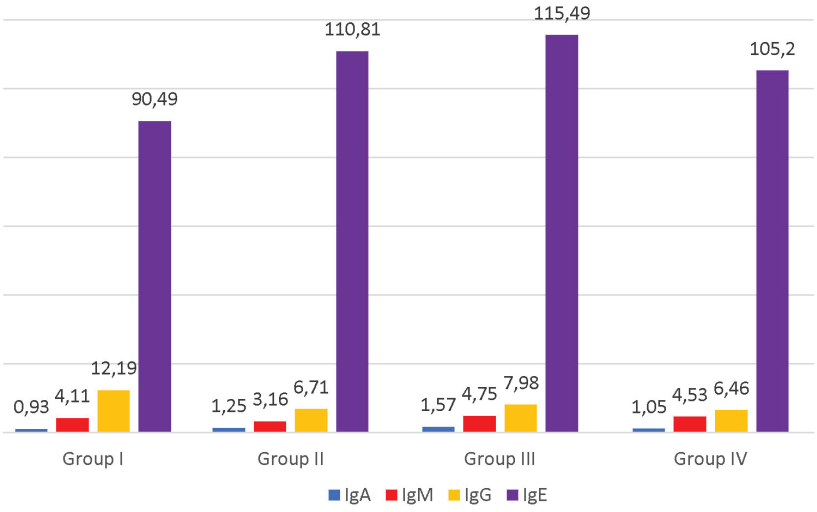
The following results were obtained for the IgA content in group II, which received clarithromycin along with standard treatment: before treatment, no differences were found in the age groups and the indices were within normal limits and not statistically significantly significant (Figure 4.3.1; 4.3.2; 4.3.3) (p > 0.05). After treatment in this group there was a non-significant increase in IgA content, which did not exceed the age norms

($p > 0.05$). In group III, which received Galavit in addition to standard treatment, after treatment there was an increase in IgA content to the upper limits of the norm, but the values were not statistically significant (Figure 4.3.4; 4.3.5; 4.3.6) ($p > 0.05$). In group IV, which received both clarithromycin and Galavit in addition to standard treatment, IgA levels were statistically significantly elevated in the group of children aged 1 to 6 years, and in children aged 1 to 3 years before treatment IgA content was 1.05 ± 0.006, while after treatment it was 1.51 ± 0.008 ($p < 0.05$) (Figure4.3.2). In patients aged 3 to 6 years, 0.091 ± 0.14; 1.42 ± 0.15 ($p < 0.05$) respectively was also increased after treatment.

The content of IgM in children of group 1 from 5 months to 6 years, i.e. in all age groups there was an average 2-fold increase in its content in blood and the indicators were significantly significant (Figure 4.3.1; 4.3.2; 4.3.3). After treatment, all age groups showed normalisation of IgM values and the values were also significantly significant ($p < 0.05$) (Figure 4.3.4; 4.3.5; 4.3.6).

In patients of group II the content of total IgM at the age of 5 months to 1 year was found to be increased 2.5 times, and in the group from 1 to 3 years and from 4 to 6 years 1.5 times before treatment (Figure 4.3.1; 4.3.2; 4.3.3). After treatment, the IgM content normalised in all age groups and was $0.60 \pm \pm 0.21$; 1.34 ± 0.20; 1.39 ± 0.36 g/l, respectively (Figure 4.3.4; 4.3.5; 4.3.6).

Figure 4.3.2 Dynamics of IgA, IgM, IgG, IgE content in I, II, III, IV group at the age of 1 year to 3 years (after treatment)



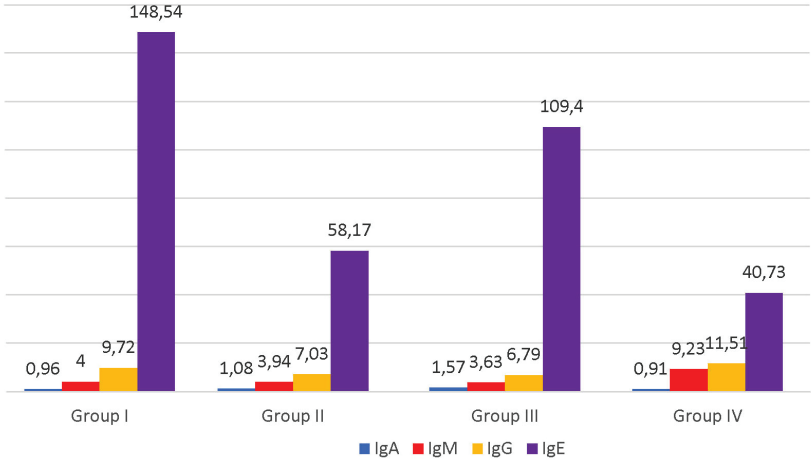
In group III, as well as in the previous groups, there was an increase in IgM content from 1.5 to 4 times (4.96 ± 0.47; 4.75 ± 0.47; 3.63 ± 0.43, respectively) and the indices were significantly significant (P < 0.05) (Figure 4.3.1; 4.3.2; 4.3.3). Also IgM values normalised after treatment (Figure 4.3.4; 4.3.5; 4.3.6).

When comparing IgM levels in group IV, which received both clarithromycin and Galavit, no differences with the previous groups were found.

We also determined serum IgG content in all groups. There were no differences between the groups before treatment and the values in all groups were within the age-related normal range and significantly significant (p < 0.05) (Figure 4.3.1; 4.3.2; 4.3.3). After the treatment in group I in the age category from 5 months to 1 year there was not significant increase of indices and made 19.20 ± 1.59 g/l, also in the group from 4 to 6 years old the data were slightly higher than the age norm (21.14 ± 1.86 g/l) (Figure 4.3.4; 4.3.6).

There was also a slight increase from normal in all age groups in Group II and in Group III after treatment in all age groups and averaged 21.42 ± ± 1.19 g/L in Group II, 21.17 ± 1.34 g/L in Group III) (p < 0.05) (Figure 4.3.1; 4.3.2; 4.3.3).

Figure 4.3.3 Dynamics of IgA, IgM, IgG, IgE content in group I, II, III, IV at the age of 4 to 6 years (before treatment)



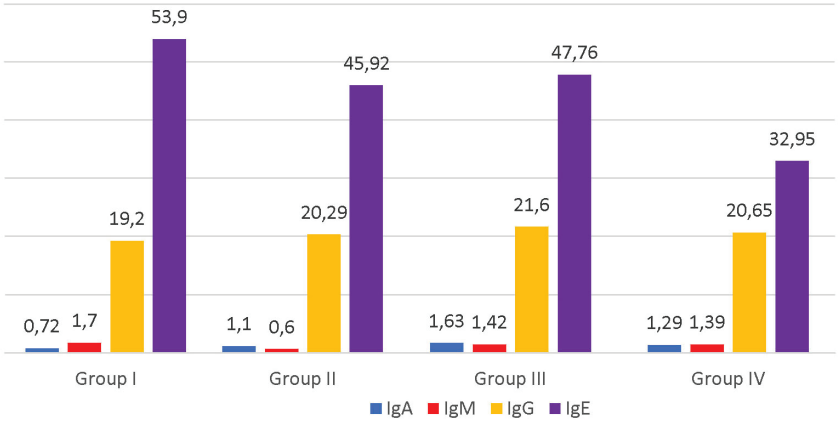
The content of IgG in group IV after treatment was as follows: at the age of 5 months to 1 year there was a slight increase from the norm and was 20.65 ± ± 3.23 g/l (Figure 4.3.4), at the age of 1 to 3 years 21.82 ± 0.99 g/l (Figure 4.3.5), at the age of 4 to 6 years 24.87 ± 1.35 g/l (Figure 4.3.6), that is, in this group

there was such a tendency, the higher the age of the child, the indicators were higher than the norm.

IgE content in all age groups regardless of the method of treatment was elevated, especially in the age group from 1 to 3 years old, and these indicators were increased 2–3 times, and the highest IgE content figures were up to 115.49 ± 20.21 IU/l in the age group from 1 to 3 years old (Figure 4.3.2), compared to the norm from 1 to 3 years old 45 IU/ml. In patients from 5 months to 1 year old there was also an increase in the amount of IgE and it was 77.28 ± 16.46 IU/l; 53.08 ± 9.70 IU/l; 112.87 ± 19.68 IU/l; 92.6 ± 37.99 IU/l, respectively (Figure 4.3.1). In the age category from 4 to 6 years old the indices fluctuated within the norm in group II and IV (58.17 ± 10.84 IU/l; 40.73 ± 24.20 IU/l, respectively), the indices in group I and III were elevated 148.54 ± 44.76 IU/l; 109.40 ± 18.2 IU/l, respectively (Figure 4.3.2).

After treatment at 5 months to 1 year of age, there was a one fold decrease in the elevated values compared to before treatment and was 53.90 + + 10.54 IU/L (Figure 4.3.4).

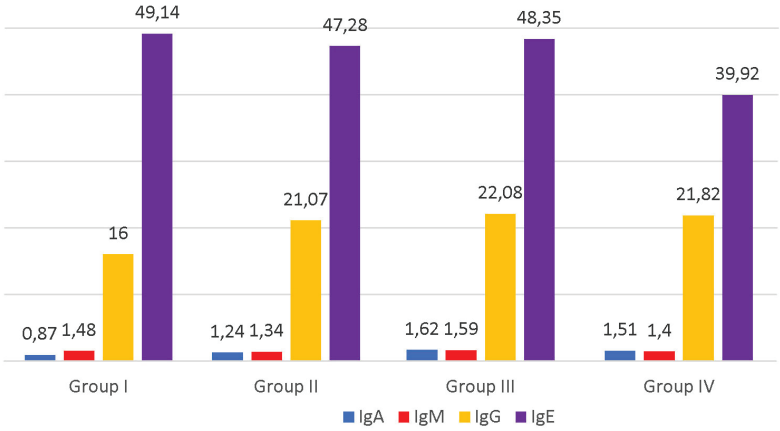
Figure 4.3.4 Dynamics of IgA, IgM, IgG, IgE content in group I, II, III, IV at the age of 5 months to 1 year (after treatment)



In the age group from 1 to 3 years of age, the values normalised after treatment (Figure 4.3.5) despite the fact that these values were 2.5 times higher than the pre-treatment norm (Figure 4.3.2). Children from 4 to 6 years of age had the highest pre-treatment and post-treatment values, unlike

other age categories, and after treatment these values also remained elevated 2.5 times the pre-treatment norms (Figure 4.3.3; 4.3.6). In group II at the age of 5 months to 1 year after treatment the IgE content decreased but did not normalise and was 45.92 + 6.48 IU/l with a norm of 30 IU/l (Figure 4.3.4). At the age of 1 to 3 years IgE content before treatment was 2 times the norm, after treatment it normalised and was 47.28 + 2.44 IU/l (Figure 4.3.5).

Figure 4.3.5 Dynamics of IgA, IgM, IgG, IgE content in group I, II, III, IV at the age of 1 to 3 years (after treatment)

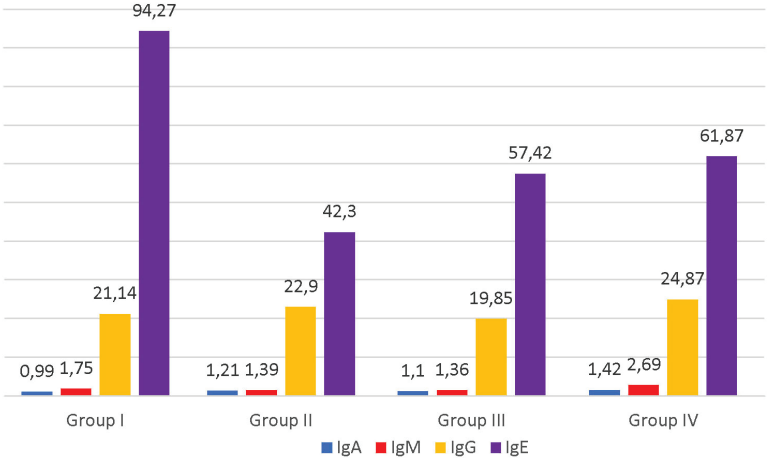


In the age group from 4–6 years, the IgE content before and after treatment was within the normal range (Figure 4.3.3; 4.3.6).

In group III the IgE content at the age of 5 to 1 year was almost normalised and amounted to 47.76 +5.36 IU/l as in the previous groups was elevated. In the age group from 1 to 3 years with 2-fold increase before treatment there was normalisation of this indicator after treatment. In children with AOB with atypical microflora at the age from 4 to 6 years old it was 1.5 times increased before treatment (Figure 4.3.3) and normalised after treatment and amounted to 57.42 + 14.0 IU/l (Figure 4.3.6). In group IV in children aged from 5 months to 1 year IgE content was increased 3 times, despite this it normalised and was 32.95 + 0.64 IU/l (Figure 4.3.1). The content of IgE at the age from 1 year to 3 years before treatment was 105.20 + 18.64 IU/l (4.3.2), after treatment it was 39.92 + 4.02 IU/l, which corresponds to the norm (Figure 4.3.5).

Between 4 and 6 years of age, IgE content is within normal limits after treatment (Figure 4.3.6).

Figure 4.3.6 Dynamics of IgA, IgM, IgG, IgE content in group I, II, III, IV aged 4 to 6 years (after treatment)



Thus, in a comparative analysis of post-treatment indicators of antibodies to Ch.pneumoniae IgM in children who received clarithromycin and Galavit normalised, in the other two groups they remained at the level of the highest limits of the norm. This indicates incomplete sanation of atypical microflora and the transferred infection. In children with AOB associated with atypical microflora, the indicators of humoral immunity revealed changes in the form of statistically significant increase in the level of IgA only in group IV, which received clarithromycin and Galavit, which proves the effectiveness of treatment. When examining the level of IgM, which remained within the normal range before and after treatment in all groups, indicating the acuteness of the inflammatory process in the bronchi. As the child recovered, the content of IgG slightly increased, but remained within the normal range.

The content of IgE before treatment in all groups was repeatedly elevated compared to the age norm. The highest values were observed in group I at the age of 1 to 3 years. After treatment, positive dynamics in the form of IgE level reduction was observed in all groups. However, these indicators, although decreased, did not reach the norm. Only in group IV the values reached the upper limits of the norm. It should be noted that in group I at the age of 1 to 3 years, who had the highest values compared to the norm, there was also normalisation of IgE levels after treatment. These changes indicate the importance of the role of allergy in the development of AOB in children.

Expressed immune disorders in children with AOB of chlamydia-mycoplasma association contributes to long-term persistence of infection in the respiratory tract and may contribute to the development of chronic inflammation and bronchial hyperreactivity, which leads to recurrences of AOB when a child falls ill with ARI of any etiology.

4.4 Cytokine status of children with AOB after treatment

The results of immunological examination of children showed that the characteristic signs after treatment in all groups were a decrease in IL-1ß, IL-6 IL-8, as well as normalisation of elevated IFN-γ in all groups.

As a result of the study the increase of IL1ß level in group I after treatment was 13.10 ± 0.62 pg/ml in group II 9.27 ± 0.64 pg/ml, in group III 10.78 ± 0.66 pg/ml in group IV 7.34 ± 0.35 pg/ml. As can be seen from the indices the best indices were significantly more frequent in groups II, IV, which received complex therapy with clarithromycin and Galavit. IL-6 also normalised also in group II and IV, whereas in group I and in group III remained above normal (14.15 ± 0.78 pg/ml and 11.26 ± 0.92 pg/ml respectively ($p < 0.001$) (Table 4.4.1).

The characteristic increase of IL-8 was noted in the control group and was 12.77 ± 0.77, and in the other groups the indices normalised. Moreover, in group IV the IL-8 content in blood was the lowest compared to other groups (Table 4.4.1).

Table 4.4.1 Comparative analysis of cytokine status in patients of the compared groups after treatment

Indicators after treatment	1 group control (n=26)		2 group (n=20)		3 group (n=24)		4 group (n=20)		P_1	P_2	P_3
	M	M	M	m	M	M	M	M			
IL-1ß	13.10	0.62	9.27	0.64	10.78	0.66	7.34	0.35	<0.001	<0.01	<0.001
IL-6	14.15	0.78	8.49	0.86	11.26	0.92	6.76	0.66	<0.001	<0.02	<0.001
IL-8	12.77	0.77	9.64	0.71	10.63	0.66	6.73	0.30	<0.01	<0.05	<0.001
INF-γ	12.85	0.54	12.63	0.91	13.24	0.47	12.57	0.42	>0.5	>0.5	>0.5

Note: P_1, P_2, P_3 – reliability of differences between control group and groups 2, 3, 4, respectively

Thus, the data obtained suggest that the changes in the concentrations of the cytokines studied show the continuation of active synthesis of pro-inflammatory cytokines as IL-1ß, IL-6 and IL-8.

INF-γ remained within the normal range regardless of our treatment, indicating low antiviral immunity.

4.5 Immunological parameters in children with Atypical microflora AOB depending on the type of treatment

When analysing the literature sources devoted to immunological parameters of children with AOB with atypical microflora there were obtained different data, but most literature sources refer to the fact that the mechanism of insufficiency of some parts of immunity on the background of which there is a constant antigenic stimulation of the immune system occurs most often as a result of frequent repeated respiratory diseases, and they eventually lead to the development of secondary immunodeficiency states [120, 121]. An understanding of the immunopathological mechanisms that underlie the development of AOB in children with atypical microflora is necessary to prescribe pathogenetically based therapy and develop effective preventive measures [5, 31].

In the course of our work we analysed the indicators of the humoral link of immunity, in particular IgA, IgM, IgG, IgE and interleukins INF-γ, IL6, IL-8, IL-1*γ*.

Immunological studies were performed on all patients by enzyme-linked immunosorbent assay.

Taking into account the age periodisation, the examined children with AOB were divided into 3 groups:

1) from 5 months to 1 year;
2) from 1 to 3 years;
3) from 4 to 6 years;

The indicators of these children were compared with the data norms given in the instructions (HEMA LLC, manufactured in Russia).

Serological blood tests for antibodies to chlamydia and mycoplasma out of 365 children were positive in 90 children. In the acute period antibodies to Ch.pneumoniae IgM were high and averaged 2.07 ± 0.20; 1.69 ± 0.20; 1.84 ± 0.22; 2.10 ± 0.23 respectively by groups. Antibodies to Mycoplasma pneumoniae IgM were 1.08 ± 0.20; 1.11 ± 0.23; 1.14 ± 0.23; 0.98 ± 0.21 respectively by groups.

Thus, in the acute period there was a significant increase in antibodies to Ch.pneumoniae IgM and antibodies to M.pneumoniae IgM in all groups regardless of age.

Antibodies to Ch. pneumoniae IgG remained not elevated 0.44 ± 0.06; 0.42 ± 0.06; 0.37 ± 0.05; 0.76 ± 0.15, respectively, by group; antibodies to Mycoplasma pneumoniae IgG 0.44 ± 0.09; 0.30 ± 0.08; 0.35 ± 0.06; 0.23 ± ± 0.04, respectively, by group;

Thus, in the acute period in children with acute acute infection with both chlamydia and mycoplasma infection the indices of antibodies to Ch.pneumoniae IgG and antibodies to Mycoplasma pneumoniae IgG significantly remained within the normal range (Table 4.5.1).

The results of cytokine status of examined children with AOB revealed a significant increase in the level of IL-1ß, IL-6, IL-8, INF-γ in the blood of children with AOB with atypical microflora.

Table 4.5.1. Comparative analysis of ELISA of chlamydial and mycoplasma infections in patients of the compared groups

Indicators	**1 control group (n=26)**		**2 group (n=20)**		**3 group (n=24)**		**4 group (n=20)**	
	M	**m**	**M**	**m**	**M**	**m**	**M**	**M**
Ch.pneum. Ig M (PI)	2.07	0.20	1.69 $p_1>0.2$	0.20	1.84 $p_2>0.5$	0.22	2.10 $p_3>0.5$	0.23
Ch.pneum. Ig G (PI)	0.44	0.06	0.42 $p_1>0.5$	0.06	0.37 $p_2>0.5$	0.05	0.76 $p_3<0.05$	0.15
M. pneum. Ig M (PI)	1.08	0.20	1.11 $p_1>0.5$	0.23	1.14 $p_2>0.5$	0.23	0.98 $p_3>0.5$	0.21
M. pneum. Ig G (PI)	0.44	0.09	0.30 $p_1>0.2$	0.08	0.35 $p_2>0.5$	0.06	0.23 $p_3<0.05$	0.04

Note: p_1, p_2, p_3 – reliability of differences between the control group and groups 2, 3, 4, respectively

During the early inducible response, macrophages produce IL-1b, IL-6, IL-8, INF- γ, which are pro-inflammatory cytokines. IL-6 is also secreted, which is an anti-inflammatory cytokine. Determination of elevated levels of IL-6, the action of which determines the development of the inflammatory process after the introduction of the microbe into the body [3].

As a result of researches the increase of IL-1ß level up to 19.42 ± 0.79 pg/ml; 23.60 ± 0.62 pg/ml; 21.21 ± 0.59 pg/ml was established in comparison with the control group the reliability of difference was ($p < 0.05$) (Table 4.5.2).

Table 3.5.2. Comparative analysis of cytokine status in the examined patients

Indicators (normal)	Groups								P		
	1 control (n=26)		2 (n=20)		3 (n=24)		4 (n=22)		P_1	P_2	P_3
	M	m	M	m	M	M	M	m			
IL-1b 0–11 pg/мl	21.63	0.79	19.42	0.79	23.6 0	0.62	21.21	0.59	<0.05	<0.05	>0.5
IL-6 0–10 pg/мl	22.00	1.00	17.78	1.11	21.75	0.80	23.01	0.94	<0.01	>0.5	>0.5
IL-8 0–10 pg/мl	21.15	0.70	18.34	0.82	21.15	0.58	20.58	0.80	<0.01	>0.5	>0.5
INF-γ 0–15 pg/мl	20.58	0.82	17.73	1.15	21.27	0.64	20.08	0.80	<0.05	>0.5	>0.5

Note: P_1, P_2, P_3 – reliability of differences between control group and groups 2, 3, 4, respectively

The mechanism of anti-infective defence between the host organism and the microorganism is based on complex interactions. The main mechanisms of defence factors are its polymorphism [31].

In our studies, there was a 2.1-fold increase in IL-6 concentration at admission with acute obstructive bronchitis in children in relation to the control group 22.0 ± 1.0pg/ml, and there was also a characteristic 2-fold increase in IL-8 in children at admission during the acute period with AOB with atypical microflora. There was also a 1.4-fold increase in INF-γ (20.58 ± ± 0.82 pg/ml; 17.73 ± 1.15 pg/ml; 21.27 ± 0.64 pg/ml; 20.08 ± 0.80 pg/ml, re-

spectively) in all groups, which was proved to be significantly different ($p < 0.05$) between them.

Thus, based on the results obtained, the study found an increase in blood levels of IL-1ß 1.9-fold, IL-6 2.1-fold, IL-8 2-fold, and INF-γ 1.4-fold ($p > 0.5$).

To reveal the direct or indirect effect of antibodies to Ch.pneumoniae IgM, IgG and antibodies to M.pneumoniae IgM, IgG on the content of interleukins and immunoglobulins in blood, a correlation analysis between the studied immunity parameters was performed (Table 4.5.3).

Table 4.5.3 Correlation analysis between indices of humoral immunity and cytokines

	Chlam Ig M	Chlam.Ig G	Mycop Ig M	MycopIg G
IL-1ß	0.80	0.70	0.88	0.85
IL-6	0.84	0.72	0.86	0.81
IL-8	0.79	**0.65**	0.77	0.73
INF-γ	0.79	**0.66**	0.79	0.74
Ig A	0.82	**0.69**	0.85	0.86
IgM	0.83	0.73	**0.91**	**0.92**
IgG	0.83	0.74	**0.94**	**0.92**
IgE	0.78	0.72	**0.90**	0.89

Note:

significant positive correlations

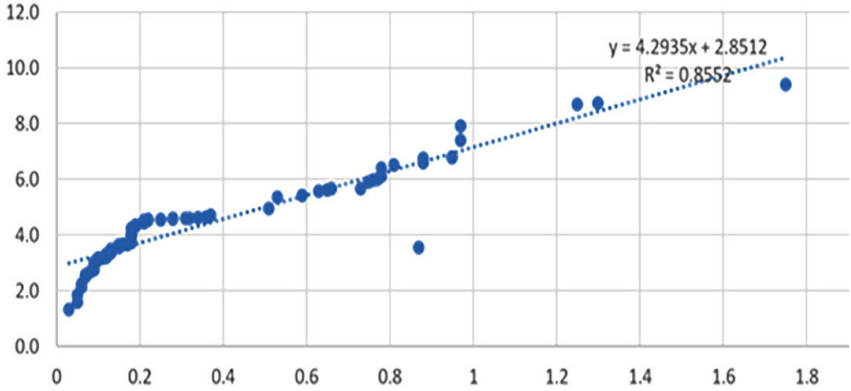
strongly positive correlations

weak correlations

The results of correlation analysis revealed 32 significant correlations: among them 5 strongly positive and 3 weak. Immunoglobulin M content was strongly positively correlated with antibodies to Mycoplasma pneumoniae IgM ($r = + 0.82$).

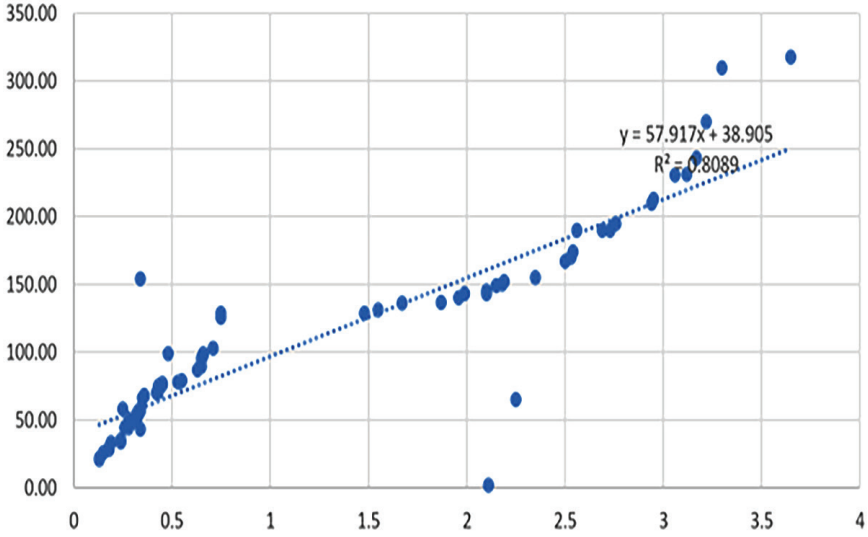
The content of total IgG was strongly positively correlated with antibodies to Mycoplasma pneumoniae IgM ($r = + 0.94$), also a strong positive correlation was found between the content of total IgM and antibodies to Mycoplasma pneumoniae IgG ($r = + 0.92$) (Figure 4.5.1).

Figure 4.5.1 Correlation of M.pneumoniae IgG to IgM antibodies



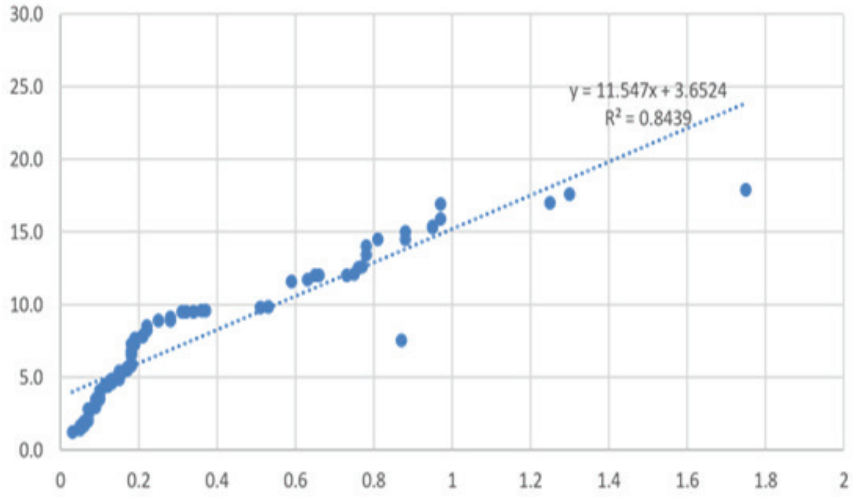
The content of total IgE was strongly correlated with M.pneumoniae IgM antibodies (r = + 0.90) (Figure 4.5.2).

Figure 4.5.2 Correlation of M.pneumoniae IgM to IgE antibodies



And there was also a strong positive correlation between total IgG with antibodies to M.pneumoniae IgG (r = + 0.94) (Figure 4.5.3).

Figure 4.5.3 Correlations of M.pneumoniaeIgM to IgE antibodies



IL-8 content had a low correlation with Ch.pneumoniae IgG antibodies (r = 0.65). There was a low correlation between INF-γ and with antibodies to Ch.pneumoniae IgG (r = 0.66), as well as IgA with antibodies to Ch.pneumoniae IgG (r = 0.69).

Positive correlation was observed between IgE and antibodies to M.pneumoniae IgG (r = 0.89). There was a positive correlation between IL-1ß and antibodies to antibodies to M.pneumoniae IgM (r = 0.88).IL-6 had a medium positive correlation with antibodies to Ch.pneumoniae IgM (r = 0.84). Positive correlation was noted between total IgM and antibodies to Ch.pneumoniae IgM antibodies (r = 0.83). There was a positive correlation between IgG and antibodies to Ch.pneumoniae IgM antibodies (r = 0.83). There was a mean positive correlation between IL-6 and Mycoplasma pneumoniae IgM antibodies (r = 0.86). There was a mean positive correlation between IgA and Ch.pneumoniae IgM (r = =0.82), and between IgA and antibodies to M.pneumoniae IgM antibodies (r = 0.85). There was a moderately positive relationship between IgA with Mycoplasma pneumoniae IgG antibodies (r = 0.86). IL-6 showed posi-

tive correlation with M.pneumoniae IgG antibodies (r = 0.81). There was a mean positive correlation between IL-1ß and antibodies to Mycoplasma pneumoniae IgG (r = 0.85).

Thus, correlations of humoral immunity and cytokine status with atypical microflora were revealed. The results of correlation analysis indicate a high degree of correlation of IgG, IgM, IgE concentration with antibodies to M.pneumoniae IgM and antibodies to M.pneumoniae IgG, which indicates the tension of compensatory and adaptive reserves.

The obtained data can be used as diagnostic criteria for the detection of atypical microflora, changes in immunological parameters imply the inclusion in pharmacotherapy of effective antibacterial and immunocorrective drugs, the use of which improve clinical and laboratory parameters.

4.6 Catamnestic observations of the study groups

The groups of children were followed up 6 months after discharge from hospital. In the catamnesis, recurrence of AUB was registered in the first group in 12 (33.%) out of 26 patients, in the second group in 2 (10%) out of 20 patients and in the third group also in 2 (8.3%) out of 24 patients, in the fourth group no recurrent episodes of AUB were detected. In children of group I and III, IgM antibodies to Ch. rneumoniae and M. Rneumoniae were detected in the case of recurrence of OPD, and these children were recommended outpatient treatment along with standard treatment – clarithromycin (15 mg/kg ^{2} times a day treatment course of 7 days) and Galavit in the age dosage. All children underwent general clinical examination, as well as control of immunological examination for atypical microflora 6 months after discharge from hospital.

In children of group IV who took clarithromycin and Galavit, no IgM antibodies to the causative agents Ch. pneumoniae and M. pneumoniae were detected during the catamnesis.

Table 4.6.1 presents a comparative analysis of ELISA of chlamydia and mycoplasma infections after 6 months in all patients, including children in groups I and III, who had a repeat episode of the AOB, who additionally received clarithromycin and Galavit along with standard treatment.

As can be seen from the indicators of IgM antibodies to C.pneumoniae in all groups ranged from 0.27 ± 0.03 to 0.40 ± 0.06, IgG antibodies to C.pneumoniae ranged from 0.69 ± 0.04 to 0.98 ± 0.04, which indicates the normalization of antibodies after chlamydia infection.

Thus, antibodies to C.pneumoniae IgM and C.pneumoniae IgG via 6 months have returned to normal.

Table 4.6.1 Comparative analysis of ELISA of chlamydia and mycoplasma infections in patients of the compared groups in the catamnesis

Indicators in the catamnesis	**1 control group (n=26)**	**2 group (n=20)**	**3 group (n=24)**	**4 group (n=20)**
	M ± m	**M ± m**	**M ± m**	**M ± m**
Ch.pneum. IgM (PI > 1.1)	0.40 ± 0.06	0.27 ± 0.03 p_1>0.05	0.28 ± 0.03 p_2>0.05	0.29 ± 0.04 p_3>0.05
Ch.pneum. IgG (PI > 1.1)	0.98 ± 0.04	0.77 ± 0.07 p_1>0.05	0.85 ± 0.05 p_2>0.05	0.69 ± 0.04 p_3>0.05
M.pneum. IgM (PI > 1.1)	0.43 ± 0.06	0.28 ± 0.06 p_1>0.05	0.31 ± 0.06 p_2>0.05	0.24 ± 0.04 p_3>0.05
M.pneum. IgM (PI > 1.1)	0.95 ± 0.08	0.95 ± 0.07 p_1>0.05	0.78 ± 0.08 p_2>0.05	0.81 ± 0.05 p_3>0.05

Note: P_1, P_2, P_3 – the reliability of the differences between the control group and groups 2, 3, 4, respectively

Antibodies to M.pneumoniae IgM also normalized in all groups and ranged from 0.24 ± 0.04 to 0.43 ± 0.06, that is, IgM antibodies to M.pneumoniae also normalized. The normal level of IgG antibodies to M.pneumoniae was observed in all groups and amounted to 0.95 ± 0.08; 0.95 ± 0.07; 0.78 ± 0.08; 0.81 ± 0.05 correspondingly. (P > 0.05) and indicates the normalization of antibodies after infection.

Thus, catamnestic follow-up of patients after 6 months revealed that in children with AOB in children with atypical microflora, there was no recurrence in group IV, whereas in the I control group, recurrence of the disease was noted in 33% of children who were prescribed clarithromycin at a dose of 15 mg / kg ^{2} times a day in addition to standard treatment. Our data prove the expediency of prescribing clarithromycin in the detection

of atypical microflora in children with OOB to prevent recurrence of the disease. As proof of the effectiveness of our treatment, we present a clinical example of a child with AOB associated with atypical microflora.

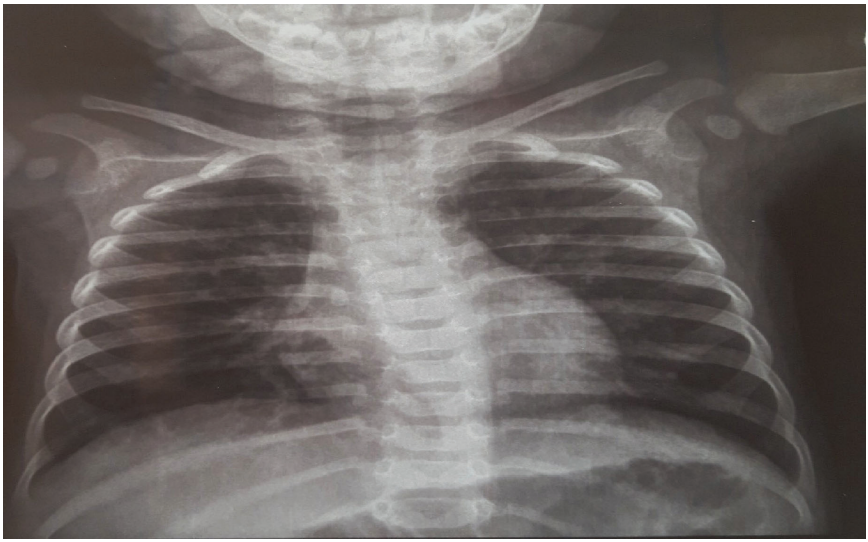
A clinical case of acute obstructive bronchitis in a child with atypical microflora.

Patient I. is 9 months old. He became acutely ill, with an increase in body temperature to 38.5 °C. On the 2 nd day of the disease, a severe cough joined. Therefore, they turned to the clinic. From the anamnestic data of the patient from the first pregnancy, which occurred against the background of anemia, vomiting of pregnant women, the threat of termination of pregnancy, urgent delivery, birth weight 3210 g. A child from 4 months on artificial feeding. This episode of acute obstructive bronchitis is repeated, the first at the age of 6 months. The condition is of moderate severity. The skin is pale. There is a slight cyanosis of the nasolabial triangle. The size of the large fontanel is 1.5 × 2.0 cm, pulsating on palpation. During the examination, the auxiliary muscles participate in the act of breathing. The respiratory rate per minute is 50. With percussion of the lungs, a box sound is determined, with auscultation: asymmetric, moist, multi-caliber wheezes on both sides against the background of hard breathing. The examination revealed a slightly pronounced intoxication syndrome and a moderately pronounced catarrhal syndrome. On the day of admission, the temperature is 38.5 °C. During auscultation, muffled heart tones. The pulse is 146 beats per minute. When examining the pharynx, there is moderate hyperemia of the palatine tonsils, the language is "geographical".

Survey results. Hemogram Hb-95 g/l, leukocytes- 12.3 × 109 /l, ESR – 17 mm/h. In the leukoformula: E-3%, P-6%, C-29%, L-53%, M-9%. The analysis of a smear from the nasopharyngeal mucosa for viruses by PCR revealed a respiratory syncytial virus. Antibodies to Ch.pneumoniae have been identified in the blood by ELISA.

Chest X-ray in children. On the chest X-ray there are signs of swelling of the lung tissue with an increase in the pulmonary pattern more due to the branching of small vessels of the lungs. On examination, the pulmonary fields are transparent, focal shadows and infiltrations are not detected. On the X-ray, the roots of the lungs are not structural and expanded. Diaphragm dome, median shadow, sinuses without pathology.

Figure 4.6.1 Chest X-ray of the patient; 9 months



Diagnosis. Acute obstructive bronchitis. RF of the I degree. Concomitant disease: Anemia of the first degree.

Treatment. Viferon rectally, vibration massage, Clarithromycin 75 mg 2 times a day per os.Galavit 1 candle 1 time a day for 5 days. Against the background of the therapy, after 3 days, there was a moderately positive dynamics in the form of relief of RF (without the participation of auxiliary muscles, the disappearance of cyanosis, normalization of respiratory rate), normalization of body temperature from day 3 of the disease, reduction of catarrhal phenomena from day 5.

This clinical example demonstrates the features of the course of acute obstructive bronchitis associated with Ch.rheimopiae in an early child: a history of repeated episode of obstructive bronchitis, the presence of high fever, symptoms of minor intoxication, severe cough from day 2 of the disease in the blood, leukocytosis with a slight increase in ESR and signs of grade 1 RF. It should be noted the unfavorable premorbid background in the patient in the form of anemia, pathology of pregnancy and childbirth in the mother. It should be noted the positive dynamics of the disease after taking etiotropic treatment in the form of Clarithromycin and Viferon, as well as Galavit, which is an immunomodulator. 6 months after discharge from the hospital, the child did not have a repeat episode of the disease.

4.7 Indicators of immunoglobulins A, M, G, E and cytokine status in children with AOB atypical microflora in the catamnesis of the examined patients

For a comparative assessment and state of humoral status indicators in the children treated by us, including after 6 months, as well as in children of the control group who were re-treated with clarithromycin and Galavit, studies of the content of immunoglobulins A, M, G, E in the age aspect were conducted. Normalization of immunoglobulins of all groups was noted in all groups except for group III, which received only the drug Galavit without Clarithromycin. The content of immunoglobulins A, M, G, E in the age aspect is presented in (Figure 4.7.1).

Figure 4.7.1 Indicators of humoral immunity in children of groups I, II, III, IV aged from 5 months to 1 year

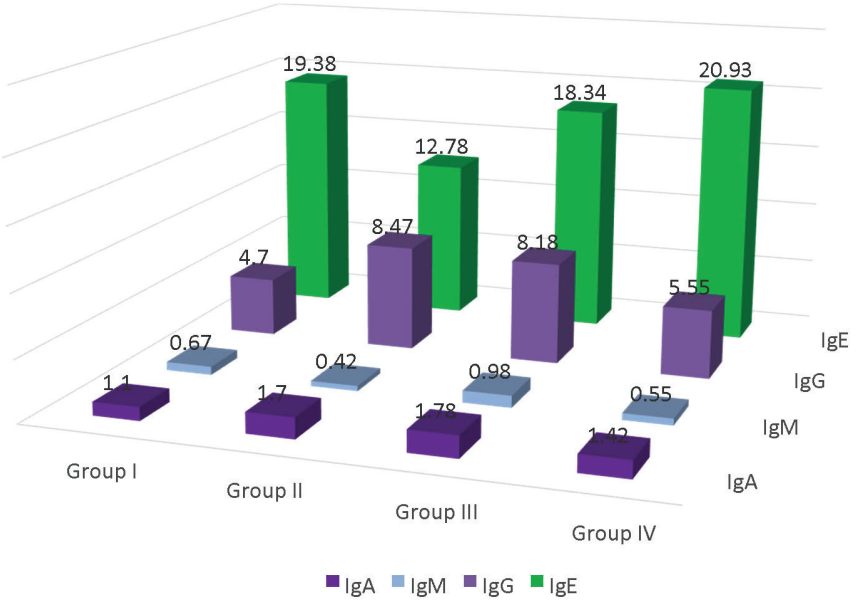


Figure 4.7.2 Indicators of humoral immunity in children of groups I, II, III, IV aged from 1 to 3 years

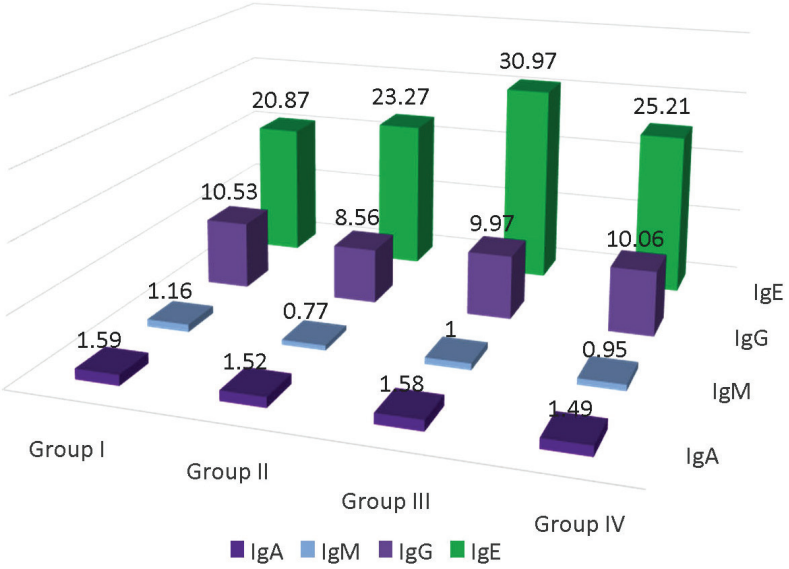
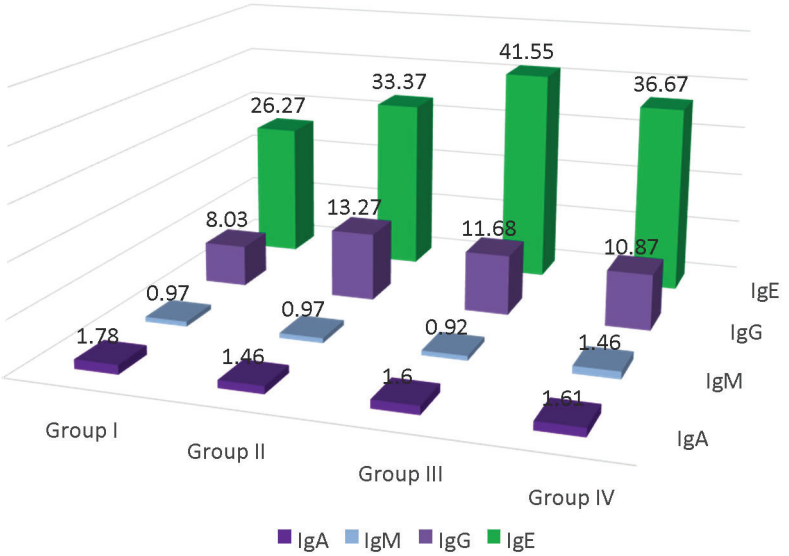
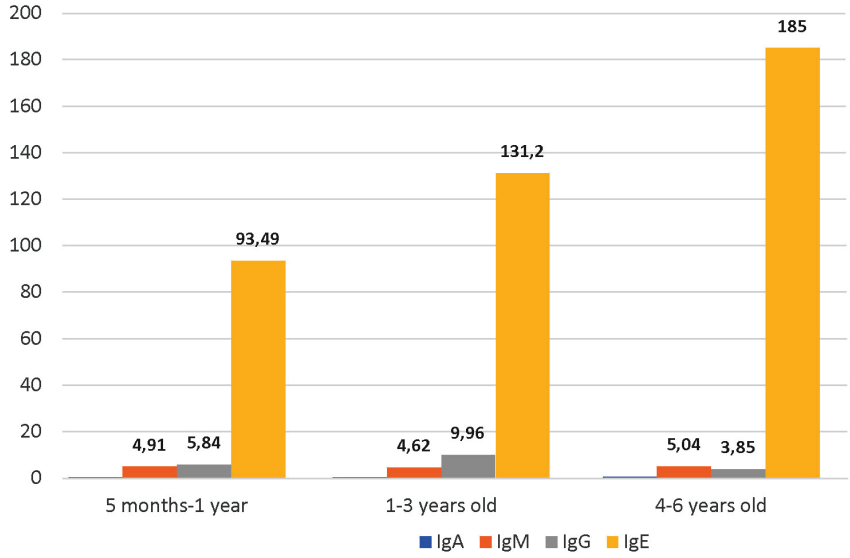


Figure 4.7.3 Indicators of humoral immunity in children of groups I, II, III, IV aged 4 to 6 years



In 16 patients, as indicated above in groups I, II, III, a repeated episode of AOB was noted. These patients were hospitalized and examined.In the study of humoral immunity indicators (see Figure 4.7.4), very low IgA values were revealed in these children: in the age group from 5 months to 1 year, it was 0.30 ± 0.05 g/l, at the age from 1 year to 3 years, 0.43 ± 0.08 g/l ($p<0.05$), at the age of from 4 to 6 years of age, 0.48 ± 0.06 g/l ($p < 0.05$), which apparently served as a background for recurrent disease. A low level of IgA indicates a decrease in local immunity of a temporary or permanent nature, increased breakdown of immunoglobulin, as well as the fact that it is in a state associated with immune complexes.

Figure 4.7.4 Comparative characteristics of humoral immunity indicators in children with AOB atypical microflora with a recurrent episode



The IgM content, respectively, by age category was 4.91 ± 0.64 g/l; 4.62 ± ± 1.12 g/l ($p<0.05$); 5.04 ± 0.17 g/l (Figure 4.7.4; $p<0.05$). Igg class antibodies, which are normally the first secreted during the humoral response of the immune system to the primary contact of the body with the antigen, an increase in this indicator indicates the presence of an acute infectious process in the body. The IgE content in these children showed an increase in its amount in the age category from 5 months to 1 year and amounted

to 93.49 ± 22.11 units /l, in the age category from 1 year to 3 years 131.2 ± ± 38.86 units/l ($p<0.05$), in the age category from 4 to 6 years 185.0 ± ± 19.69 units/l ($p<0.05$). These children underwent differentiated treatment methods with the inclusion of clarithromycin and Galavit.

Thus, the role of the immune system in the occurrence, course and outcome of infectious diseases of the respiratory system in children is of great importance.

Catamnestic observations after 6 months in all patients, including this group with a repeated episode of AOB, showed the effectiveness of our differentiated treatment of children with AOB with atypical microflora, which was confirmed by indicators of humoral immunity in the form of normalization of IgA, IgM, IgG, IgE values.

6 months after the onset of the disease, a comparative analysis of the cytokine status was performed in all patients (Table 4.7.1).

Table 4.7.1 Comparative analysis of cytokine status in patients of the compared groups in the catamnesis

Indicators in the catamnesis	**1 control group (n=26)**	**2 group (n=20)**	**3 group (n=24)**	**4 group (n=22)**	**P_1, P_2, P_3**
	M ± m	**M ± m**	**M ± m**	**M ± m**	
IL-1b	5.76 ± 0.35	5.75 ± 0.38	5.78 ± 0.35	5.90 ± 0.40	$p > 0.05$
IL-6	4.66 ± 0.39	4.34 ± 0.38	6.21 ± 0.31	6.24 ± 0.35	$p > 0.05$
IL-8	4.82 ± 0.36	5.36 ± 0.32	5.22 ± 0.33	5.89 ± 0.50	$p > 0.05$
INF-γ	9.14 ± 0.45	8.62 ± 0.60	9.88 ± 0.62	10.38 ± 0.75	$p > 0.05$

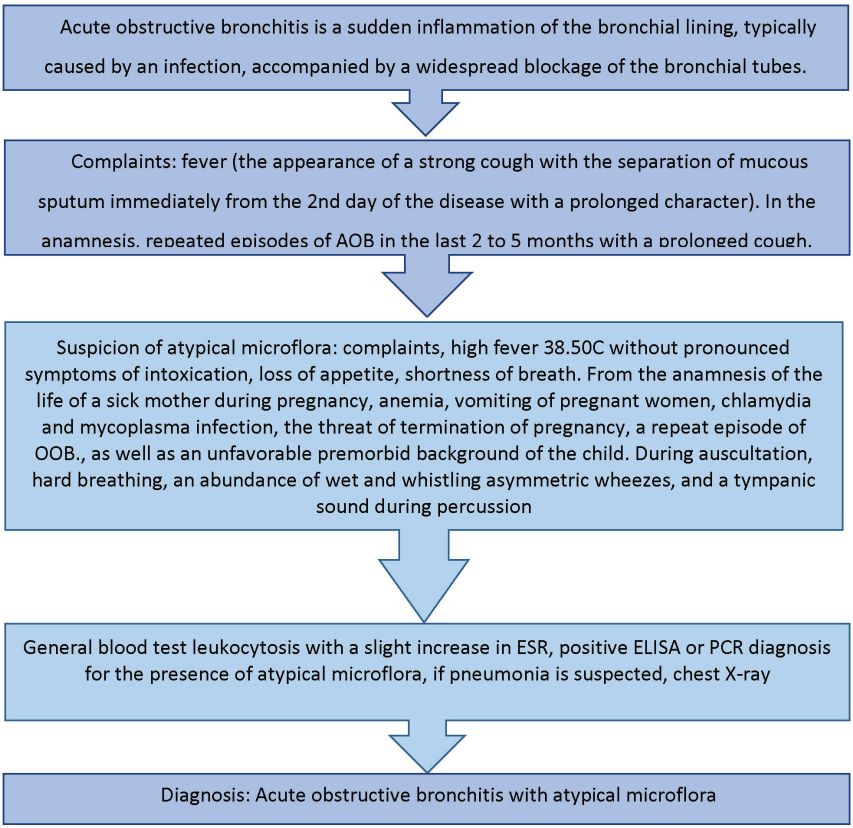
Note: P_1, P_2, P_3 – the significance of the differences between the control group and groups 2, 3, 4, respectively

The indicators of IL1ß, IL-6, IL-8, INF-γ in all groups in the catamnesis returned to normal after 6 months.

Thus, catamnestic observations showed the effectiveness of prescribing in addition to standard treatment in children with OB atypical microflora of clarithromycin and Galavit, which led to normalization of cytokine status and humoral immunity.

Based on our research, an algorithm for diagnosing AOB with atypical microflora has been developed (Figure 4.7.5).

Figure 4.7.5 Algorithm for the diagnosis of acute obstructive bronchitis with atypical microflora



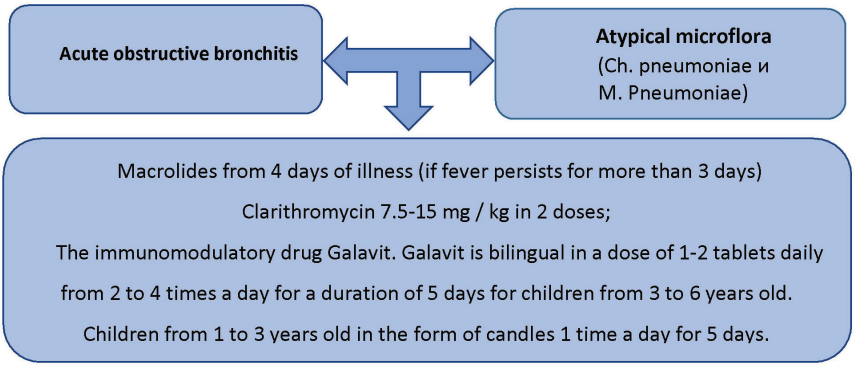
To make a diagnosis, it is necessary to take into account the patient's complaints and, unlike acute bronchitis in children with atypical microflora, a strong cough is noted immediately from the 2 nd day of the disease and it persists for a long time. In addition, an objective examination shows the onset of the disease without severe intoxication, despite the high temperature. In the lungs, an abundance of wet asymmetric wheezing is auscultatively listened to against the background of hard breathing, catarrhal phenomena persist for a long time and have a protracted character. We also revealed in a general blood test in patients with atypical AOB microflora, moderate leukocytosis with slightly increased ESR, a repeated episode of the disease. With these symptoms, this contingent of patients needs PCR

or serodiagnostics. With positive results, it is necessary to carry out treatment with macrolides, in particular clarithromycin at a dose of 15 mg / kg.

We have also created a scheme of antibacterial therapy for the detection of atypical microflora in children with AOB (Figure 4.7.6).

The scheme of antibacterial therapy depending on the etiology of bacterial bronchitis in children

Figure 4.7.6. The scheme of antibacterial therapy in children with atypical microflora



Based on our research, we recommend that if a child has AOB with suspected viral mycoplasma and viral chlamydia etiology of the disease with clinical and laboratory signs, which are presented in the algorithm from day 4 of the disease and a positive laboratory test for atypical microflora, prescribe macrolide clarithromycin at a dose of 15 mg / kg in 2 doses for 7 days.

Catamnestic studies after 6 months revealed a recurrence of AOB associated with viral chlamydia infection, which also had immune disorders, and therefore we recommended a unified approach to medical examination in children with atypical microflora, which includes an examination by an immunologist, if necessary, the use of immunomodulatory drugs and mandatory control of bacteriological sanitation.

Thus, a full-fledged medical examination of patients with AOB in children with viral mycoplasma association prevents the risk of adverse outcomes such as the risk of transition to BA, various immune disorders.

The main criterion for evaluating various treatment methods is the effectiveness and safety of therapy, while the expenditure of material, labor and financial resources spent on carrying out the appropriate method plays an

important role. Thus, along with medical efficiency, economic accessibility is also of great importance.

We have determined the material costs of using the timely therapy program developed by us based on the determination of antibodies to atypical microflora, in particular to chlamydia and mycoplasma in AOB in children., in contrast to the cost minimization analysis, the cost effectiveness analysis of the compared options is characterized by greater or lesser, but not equivalent effectiveness. Therefore, it is very important to assess the degree of need for analysis, depending on the level of reliability of the data.

Calculation of the economic efficiency of the introduction of timely therapy based on the determination of antibodies to atypical microflora, in particular to chlamydia and mycoplasma in children with AOB (incremental cost-effectiveness ratio/CERincr), recommended by WHO experts.

The costs of all analyses were calculated. This analysis is based on the calculation of the cost efficiency increment coefficient CERincr, which is performed using the following formula:

$$CER_{incr} = (C_1 - C_2) / (Ef_1 - Ef_2)$$

CER_{incr} – the coefficient of cost efficiency increment, which shows the amount of costs required to achieve an additional result when using a more efficient and more expensive technology, or in other words, the ratio of additional investments and additional effect;

C_1 и C_2 – the cost of treatment according to the standard of acute obstructive bronchitis with atypical microflora;

Ef_1 и Ef_2 – efficacy in macrolide and immunomodulator treatment.

A technical and economic analysis was carried out for one patient presented in (Tables 4.7.2 and 4.7.3).

Table 4.7.2 The cost of research and standard treatment

Type of activity		
Research and medicines	General blood test	16600.0
	General urine analysis	10700.0
	Chest X-ray	63200.0
	A bed of days	1440000.0
	Food	230000.0
	Ceftriaxone	63000.0
	Ambroxol	7200.0

Type of activity		
	Suprastin	20000.0
	Dexamethasone	4000.0
	Syringe	17500.0
	UHF therapy	43200.0
	Chest massage	81.200
Total cost per 1 patient		1.996.600.0

Note:[1]–№ 5245

Table 4.7.3 The costs of our proposed research and treatment

Type of activity		
Research and medicines	General blood test	16600.0
	General urine analysis	10700.0
	Chest X-ray	63200.0
	A bed of days	45000.0
	Food	1152000.0
	Ceftriaxone	115000
	Ambroxol	53000.0
	Suprastin	7200.0
	Dexamethasone	20000.0
	Syringe	96000
	UHF therapy	43200.0
	Chest massage	81.200
Total cost per 1 patient		1703100

The study took into account the cost of bed days, diagnosis, nutrition and ongoing therapy. The cost of standard treatment in children with AOB without determining atypical microflora amounted to 1996.600 soums, subject to the determination of atypical microflora in children with AOB, the total amount of treatment was 1.703.100 soums. With standard treatment, the cost per 1 patient for 10 days amounted to 1996.600 soums, and in the treatment of children with atypical microflora, bed days decreased by 2 days and at the same time the cost amounted to 1.703.100 soums.

Thus, if appropriate treatment is carried out depending on the etiological factor, in this case, when identifying atypical microflora and conducting appropriate therapy, the economic efficiency was 1.996.600––1.703.100 = 293.500. sum.

Summarizing the data obtained, it can be stated that the use of differentiated treatment regimens in AOB patients with atypical microflora 6 months after discharge from the hospital showed stabilization of immunological parameters of cytokine and immunological status by suppressing the reproduction of pathogens and preventing disease recurrence.

CONCLUSION

Diseases of the lower respiratory tract are characterized by various clinical and morphological manifestations, which are caused by anatomical and physiological features of the child's body, often leading to bronchial obstruction and the etiological agent of the disease. Bronchoobstructive syndrome is often the initial manifestation of various pathological conditions of the respiratory system, at the same time it determines both the severity of the course of the underlying disease and its prognosis [19, 68, 70, 102].

According to a number of researchers, the development of AOB is significantly influenced by a premorbid background: allergic, atopic diseases, perinatal pathology of the central nervous system, rickets, nutritional disorders, irrational feeding, frequent colds, hereditary pathology of the bronchopulmonary system [100, 108].

According to Achilova D. N. (2019) and other researchers, the development of AOB is influenced by an unfavorable environmental situation and secondhand smoke in the family. Thus, tobacco smoke leads to hypertrophy of the bronchial glands of the mucous membrane, as a result of which mucociliary clearance is disrupted, the progress of mucus through the bronchi slows down, and destruction of the bronchial epithelium develops [3, 121].

Currently, the unfavorable environmental situation of the environment is a fairly important etiological factor in the formation of AOB in children [81, 105].

The etiological role of atypical microflora in the development of AOB is to a certain extent due to the intracellular nature of the existence of these pathogens [11, 16, 20, 26, 32, 33, 41].

As a result of numerous studies, the structure and morphology of atypical pathogens were identified, pathogenicity factors were studied, the taxonomic position of the pathogen was determined, the features of clinical manifestations, course options, as well as the principles of therapy were determined, so each of these infections began to acquire its characteristic classical features and a certain clinical picture [25, 51, 55, 59].

Nowadays, chlamydia and mycoplasmosis remain one of the most common infectious diseases in the world [73, 111, 110, 112, 118].

An analysis of foreign and domestic literature on the role of viral and atypical bacterial pathogens in the development of bronchial AOB in pre-

school children has shown that the most common of them are chlamydia, mycoplasma, respiratory syntial viral infections. An important feature is a mix of infections and account for from 20 to 70% of the disease, the layering of which may be accompanied by a severe course of the disease [107, 110, 121].

Chl. pneumoniae and Mus. pneumoniae, when affected by the respiratory tract, often lead to a prolonged course, block and paralyze the mechanisms of mucociliary clearance, contributing to an increase in bronchial reactivity and disrupt immunoregulation [81, 83, 90, 91].

After infection with mycoplasma infection, specific humoral and cellular immune reactions are formed in the body, which are aimed at eliminating the pathogen. However, the established immunity is short-lived, as a result of which re-infection is not excluded [13, 21].

After mycoplasma or chlamydia infection, repeated respiratory diseases in children often occur with BOS and a prolonged, recurrent course. This fact is probably associated with altered immunological reactivity and reduced resistance to pathogens that have arisen during the disease, creating a favorable environment for the persistence of microorganisms that contribute to the chronization and formation of a complicated course of the disease. Antibacterial therapy of the disease in most patients with temporary suppression of the activity and growth of pathogens does not contribute to the correction of the immunological changes that have arisen, increasing the likelihood of a recurrent course of diseases. Most authors prove that AOB caused by chlamydia and mycoplasma infection is characterized by a severe course of the disease, but at the same time the mechanisms leading to a severe course remain completely unexplored, problems associated with diagnosis and treatment persist [51, 64, 72, 73, 79, 87, 91].

To date, the therapeutic effectiveness of immunotropic drugs in the treatment of respiratory mycoplasmosis has been proven, but there is no data on the possible use of this group of drugs for the prevention of infection. The need for specific chemoprophylaxis with macrolides in the detection of foci of respiratory mycoplasmosis is also discussed [74]. Summarizing the review of literary sources, we have concluded that the interest in AOB with atypical microflora in childhood is very relevant. Despite the introduction of modern diagnostic methods and the study of the patterns of clinical and immunological changes, they still remain insufficiently studied, which determines the need for research to optimize the diagnosis and therapy of the disease. The search for methods of early diagnosis and improvement of

the effectiveness of treatment can be accepted as a priority area of public health policy.

The aim of the study was to identify the clinical and immunological features of the course of obstructive bronchitis with atypical microflora at the present stage in order to improve diagnostic results with the subsequent development of differentiated treatment methods.

The objectives of the study were:

- To identify the frequency of occurrence, risk factors for the development and features of the clinical course of atypical microflora in children with AOB in modern conditions;
- To identify the features of the immune and cytokine status of atypical microflora in children with AOB in modern conditions, to determine their correlation;
- To identify the diagnostic value of the enzyme immunoassay in AOB in children with atypical microflora;
- To substantiate the effectiveness of modified therapy for children with AOB associated with atypical microflora and analyze the immediate outcomes of the disease.

The dissertation work presents the results of clinical observation and examination of 90 patients with obstructive bronchitis with atypical microflora identified from 365 children with obstructive bronchitis aged 5 months to 6 years. Among them, 90 patients with AOB with atypical microflora, whose age ranged from 5 months to 6 years, were hospitalized in the Specialized Clinic of Pediatric Surgery of SamSMU, SFRTSEMP for the period 2020–2022. The distribution of children with AOB with atypical microflora by place of residence revealed that the majority of children lived in rural areas 77.80%.

In our study, children from 5 months to 1 year of age accounted for 32.2%, from 1 to 3 years of age 50.0%, and from 4 to 6 years of age 17.8%. Boys predominated among the surveyed 60%.

When analyzing the prevalence by gender, out of 54 boys, seropositive tests for Ch.pneumoniae were found in 36 (40%), and in 37 girls in 24 (26.6%). M.rpeimopiae was established out of 54 boys in 16 (32.1%) and in 9 girls (24.3%) out of 36. 2 (3.8%) boys had combined seropositive tests for Ch.pneumoniae and M.rheimopiae. In 3 (8.1%) girls, both Ch.pneumoniae and M.rheimopiae were detected. Of the examined patients, co-infection was observed more in girls and amounted to 8.1% of cases, and in boys 3.8% ($p<0.05$).

An analysis of the maternal life history of the children we examined revealed anemia during pregnancy in 68.2%, pyelonephritis 10.0%, TORCH infection, threat of termination of pregnancy 42.3%, toxicosis of pregnant women 51.1%, nephropathy 3.3%, COVID 1.11%. The burden of second-hand smoke was 35.5%. 95.5% of children were born on time, 4 were born prematurely, which was (4.5%). There were 56 (62.3%) on natural feeding, 23 (25.5%) on artificial feeding. Among the 90 examined AOB patients with atypical microflora, rickets occurred in 52.2%, atopic dermatitis 6.67%, thymomegaly 3.33%, PCNDS in 8.89%, BEN 32.2%.

Of the 90 patients, a virological study was conducted in 67 patients by PCR and it was found that the most common pathogen of AOB was the MS virus in association with Ch.pneumoniae and it amounted to 37.4%. Next, adenovirus infection + Ch.pneumoniae 16.5%, parainfluenza + Ch.pneumoniae 14.9%, then MS + M. pneumoniae in an equal ratio. Adenovirus infection + M.pneumoniae in 8.95%, and in other cases a small amount in equal proportions association of parainfluenza + M. Pneumoniae, rhinovirus infection + Ch.pneumoniae, adenovirus +Ch.pneumoniae +M.

Pneumoniae, PC-virus infection + Ch.pneumoniae + M. Pneumoniae 1.49%.

The origin of OOB has a substantial impact on the age distribution, timing of onset, characteristics of the disease progression, and the presence of aggravating factors in the children's pre-existing conditions. AOB caused by atypical microorganisms typically exhibits a moderate severity, with the most common etiological agent being Ch.pneumoniae in combination with the MS virus. The clinical symptoms typically manifest on days 4–5, presenting as a low-grade fever, mild signs of toxicity, a persistent cough, and a combination of wheezing (whistling and wet) and shortness of breath during exhalation in the majority of cases.

Among the children we studied, the disease was moderately severe in 57.8% of cases and severe in 42.2% of cases. In children with Ch.pneumoniae infection, the disease was predominantly in an average severe form in 65.6% of cases, while in children with M. Pneumoniae infection alone, an average severe course was observed in 68.4% of cases. The severe form was three times more prevalent in children with M. Pneumoniae infection and was more common in boys than in girls. Clinical signs of AOB with atypical microflora appeared 4–5 days after the onset of the disease, in the form of an increase in body temperature in most patients 35.6% to 37 °C, and from above 38 °C in 58.9% and only 5.6% of patients over 39 °C. It should be noted that in patients with high body

temperature, intoxication syndrome (weakness, decreased appetite, lethargy) was poorly expressed.

Respiratory syndrome (hyperemia of the mucous membrane of the pharynx, runny nose, sneezing, shortness of breath) was observed in all patients. Cough in the first two days of the disease was noted in 70% of children, in the rest it appeared on the 5th day after the onset of the disease and more often in children aged 1 to 3 years. The rare cough persisted for a long time even after discharge from the hospital. Decreased appetite was detected for more than 5 days from 1 year to 3 years. Shortness of breath occurred in all patients and was predominantly expiratory in nature. The duration of shortness of breath is 3.14 ± 0.29 days.

RF of the first degree of severity was recorded in 55 (61.0%) children, more often at an early age from 5 months to 3 years (68.91%) ($p < 0.05$). Grade II RFwas observed in 34 (37.0%) and was significantly more common between the ages of 1 and 3 years and amounted to 40% ($p < 0.05$). Grade III RF was registered in 1 patient aged 1 to 3 years (2.0%).

Hypocalcemia in every third examined patient under the age of 1 year in 30 patients, 33.3% of 90 patients. On average, in all groups, leukocytosis reached up to 10.04 × 10 ± 0.47 and the amount of ESR averaged 14.30±0.35 mm/h. These indicators indicate that leukocytosis is noted with atypical microflora, but at the same time ESR increases slightly. Eosinophilia was typical from 4 to 6 years old, which is probably due to a helminthic invasion, which was detected in 89% of children of this age. A chest X-ray revealed diffuse enhancement of the pulmonary pattern on both sides, small linear and loopy shadows in 70% of children, signs of pulmonary tissue swelling in 12.2%, and grade I thymomegaly in 3.3%. ECG showed changes in the form of sinus tachycardia in 21.7%, hypertrophy of the left ventricle in 14.5% of children. Ultrasound of the abdominal cavity and kidneys revealed no pathology. In 3 children, diagnostic bronchoscopy excluded the diagnosis of a foreign body of the lower respiratory tract. The incidence was more frequent in winter (mainly January and February) and spring (mainly March and May) months.

The results of the immunological examination we obtained revealed a different nature of violations of the immune status of children with AOB with atypical microflora, which indicates that in this disease there are changes in both the cytokine status system and humoral immunity. Taking into account the age periodization, patients with AOB with atypical microflora were divided into 3 groups:

I. from 5 months to 1 year
II. From 1 year to 3 years
III. From 4 to 6 years old

Regardless of age, antibodies to Ch.pneumoniae IgM and M.Pneumoniae IgM were significantly elevated in all 90 patients in the acute period. Antibodies to Ch.pneumoniae IgG and M.Pneumoniae IgG in the acute period remained low also in all age groups.

The results of the cytokine status of the examined children are characterized by the fact that the levels of IL-1b, IL-6, IL-8, INF-γ were significantly increased in children with AOB atypical microflora. IL-1b, IL-6, IL-8, and INF-γ produced by macrophages during an early inducible response are proinflammatory cytokines. At the same time, IL-6 is an anti-inflammatory cytokine. Their action completely determines the development of the inflammatory process that develops when a microbe is introduced into a macroorganism [3].

All age groups of children with AOB with atypical microflora had significantly low IgA values. These rates were especially low in children aged 4 to 6 years old. After treatment, there was a slight increase in IgA content in all groups and the best indicators were in children who received clarithromycin and Galavit in addition to standard treatment. The IgM content, regardless of age, was increased by 2 times compared to the norm. After treatment, normalization of this indicator was observed in all age groups and the data were significantly significant. The IgG content, regardless of age, was within the age norm before treatment and the data were significantly significant; after treatment, children from 1 to 6 years old showed a slight increase from the norm and directly correlated with age. The older the child, the higher the numbers above the norm. The IgE content in all age groups was increased by 2 times before treatment, after treatment the IgE content decreased, but the indicators did not normalize, which indicates an allergic mood of humoral immunity in AOB children with atypical microflora.

The cost of standard treatment in children with AOB without determining atypical microflora was 2.303.500 soums, provided that atypical microflora was determined in children with AOB, the total amount of treatment was 1.703.100 soums. With standard treatment, the cost per 1 patient for 10 days amounted to 1996.600 soums, and in the treatment of children with atypical microflora, bed days were reduced by 2 days and at the same time the cost-effectiveness amounted to 1.703.100 soums.

Thus, if appropriate treatment is carried out depending on the etiological factor, in this case, when identifying atypical microflora and conducting

appropriate therapy, the economic efficiency was 1.996.000–1.703.100 = = 293.500 soums.

Our data showed that after treatment in the group of children who received Clarithromycin and Galavit, an improvement in the general condition was noted 2 days earlier, the temperature decreased 2 days after the start of treatment, a decrease in cough was noted on 6–7 days, cyanosis of the nasolabial triangle disappeared 1.5 days earlier. Dyspnea significantly disappeared faster more often in this group, and auscultative data were also eliminated, wheezing at an earlier time compared with the control group.

Thus, catamnestic observation of patients after 6 months revealed that in children with AOB in children with atypical microflora, there was no recurrence in group IV, whereas in the control group, recurrence of the disease was noted in 33% of children who were prescribed clarithromycin at a dose of 15 mg/kg^2 times a day in addition to standard treatment and Galavit in an age-appropriate dosage. Our data prove the expediency of prescribing clarithromycin in the detection of atypical microflora in children with AOB to prevent recurrence of the disease.

Taking into account the literature data, as well as our own observations of children with AOB associated with atypical microflora, having changes in immune status, data from catamnestic observations, allows us to conclude that diseases in this contingent of patients have a tendency to relapse. To prevent adverse outcomes in this cohort of patients, it is necessary to carry out specific chemoprophylaxis with macrolides, immunomodulators, as well as control of bacteriological sanitation.

Thus, differentiated therapy for AOB with atypical microflora in accordance with the proposed algorithms has a good clinical and economic effect.

PRACTICAL RECOMMENDATIONS

1. For the differential diagnosis of the etiology of AOB in children between typical and atypical microflora, an algorithm for diagnosing a combination of clinical and laboratory studies should be used.
2. In the presence of the following data, all children should undergo a blood test for ELISA and PCR for early diagnosis of the presence of atypical microflora:
   - Burdened medical history (TORCH infection of mothers, repeated episode of AOB for 3 to 6 months, prolonged cough after the first episode of obstructive cough);
   - Complaints (high fever 38.5 °C, loss of appetite, shortness of breath);
   - Objective data: the presence of RFI, II degrees, bronchoobstructive syndrome, hard breathing with an abundance of moist and whistling asymmetric wheezes, tympanic or pulmonary sound;
   - Laboratory data: in the general blood test, leukocytosis with a slight increase in ESR, increased Ig E.
3. In children with AOB who have antibodies to atypical microflora detected by ELISA, it is recommended in the complex therapy of acute obstructive bronchitis in children with atypical microflora to use the macrolide "Clarithromycin" twice a day at the rate of 15 mg / kg per os 2 times a day for 5 days and the immunomodulatory drug "Galavit" in the form of injections, candles and tablets depending on the age of the patients. Galavit was used sublingually in a dose of 1–2 tablets daily from 2 to 4 times a day with a duration of 5 days for children from 3 to 6 years old. It was also used in the form of candles 1 time a day for 5 days, then 5 more candles a day later for children from 5 months to 3 years old.
4. Children who have undergone AOB with atypical microflora are recommended to undergo catamnestic observations for 6 months with careful monitoring of ELISA and PCR for chlamydia and mycoplasma in order to prevent recurrence and chronization of infection.

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