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Etiology and Pathogenesis of Pneumonia in Children

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Abstract This review focuses on the etiology and pathogenesis of pneumonia in children. Over the last decade, there has been a significant expansion of the acute pneumonia pathogen spectrum. Apart from bacterial microflora, pneumonic viruses, mycoplasms, chlamydia, rickettsia, protozoa and fungi are becoming increasingly important in the development of pneumonia in children. The mechanism of pneumonia development has not been sufficiently studied. Most often, the pathogen from the nasopharynx penetrates and spreads aerobronchogenic way with the subsequent occurrence of the inflammatory process in acinuses. The abundance of lymphatic vessels in the lung tissue is important in pathogenesis, especially in young children.

Keywords Children, Lung, Etiology, Pathogenesis, Pneumonia, Viruses, Bacteria

Literature data from recent years suggest that mixed viral-bacterial infection plays a leading role in the etiological structure of acute pneumonia. In the first days of the disease various respiratory viral diseases are detected in 70-80% of cases: influenza virus - in 10 - 12%, parainfluenza - 12 - 15, adenovirus - 17 - 25, PC-virus - 7 - 10%, much less common enterovirus ECHO and Koksaki. The etiological significance of associations of viral, viral-virus-bacterial, viral-mycoplasma, viral-mycoplasma-bacterial, etc. should also be taken into account. Pneumonia caused by cytomegalovirus, ornithosis virus, etc. is described.

During the last decade, a significant expansion of the spectrum of acute pneumonia pathogens has been noted [46,82,95,114,123,159,176,191,208]. The era of the particular division of microorganisms into pathogenic and non-pathogenic has passed irrevocably. The circle of potential pathogenic microorganisms - yesterday's s saprophytes - is continuously expanding, and it is increasingly difficult to predict which of them, tomorrow, will add to the rapidly growing list of legalized pathogens [74]. In scientific publications, there is more and more information about a significant increase in the frequency of diseases caused by conditionally pathogenic microflora [9,68, 146,150,167,210].

Besides to bacterial microflora, pneumotropic viruses, mycoplasms, chlamydia, rickettsia, protozoa, and fungi are becoming increasingly important in the development of pneumonia in children [12,25,57,95,117,136,154,176,191, 203,206].

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It is well known that during several tens of years pneumococcus and staphylococcus remained dominant in the emergence and development of pneumonia in children [24,40,96,122,126,161,181,183]. In recent years, a distinct decrease in the etiological significance of these pathogens has been observed. Pneumococcus accounts not for 80% of all respiratory pathology as before, but from 15 to 45% [115,181].

It has been established that in infants, pneumococci play a smaller role - 8% of all bacterial pathogens in the first 6 months of life and 48% - in the second half of the year. This is due to the persistence of antipneumococcal antibodies obtained transplacental and breast milk at this age. From the second half of the year, antibody levels are rapidly declining, and the highest incidence of pneumococcal pneumonia is observed at the age of 2-3 years [112]. Thus, in children over 1 year old with OP complicated by pleuritis, pneumococcus was determined in 90% of cases in the study of pleural exudate [96].

Non-capsular hemophilic bacillus was in second place in frequency (38%) and much less often staphylococcus aureus (10%). According to Samsygina G. A. (1998), hemophilic bacillus accounts for 5-11% of all cases. Foreign authors noted healthy carriage of hemophilic bacillus in children from 2 to 13% of cases. The most frequent cause of pneumonia was in children aged 2 years and older (180).

Staphylococcus poses a great threat in contrast to pneumococcus and hemophilic stick In children of the first months of life [99]. In Tashkent, the etiology of complicated forms of OP was studied by T.A. Kuznetsova (1995). In comparison with the regions of moderate climate, she determined a high specific weight of hemophilic bacillus (21%), staphylococcus aureus was isolated in 15,3% of patients and as a pathogen was important in children of the first year of life. According to her data, all pneumonia in

children of the first months of life had staphylococcal aetiology. According to other authors [115], at the age up to 6 months, about 50% of pneumonia is of hospital-acquired origin. At this age, staphylococcus, Escherichia coli, and other representatives of the intestinal flora [klebsiella, proteus] are usually the pathogens.

Many authors claim the possibility of primary viral pneumonia. However, no convincing evidence has been found of the different nature of respiratory infection depending on the type of virus [23,65,94,108,117].

According to A. V. Zinseling's data, general pathomorphological signs of respiratory organ affection in case of viral infections are as follows: maximum involvement in pathological process of respiratory tract with typical changes of mucous membrane and less expressed inflammation in their lower parts; almost all the dead have blood circulation disorders and functional changes in the form of atelectasis and emphysema foci; possibility of development of severe internal organs affections.

According to some authors, the etiology of pneumonia is dominated by respiratory viruses, others by respiratory viral infection and others by the addition of bacterial infection. The dominant role of pathogenic staphylococcus in severe forms of acute focal and segmental pneumonia has been revealed.

Respiratory viruses are essential in the mechanism of acute pneumonia development. It is expressed in the fact that virusemia in the initial period of acute respiratory viral infection is able to cause circulatory disorders in pulmonary tissue, emphysematous changes, the formation of atelectases and favor the introduction of bacterial flora, especially staphylococcus. In recent years, synergistic effects of some viruses and bacteria have been established, such as adenoviral infection and staphylococcus (V. I. Seredina, 1971), influenza virus and staphylococcus (V. M. Stakhanova et al., 1975).

Acute viral-bacterial pneumonia occurs mainly within the first 3-5 days from the beginning of the respiratory viral disease. The etiological role of mycoplasma pneumonia in children ranges from 5 to 16% of cases. There are epidemiological outbreaks of mycoplasma pneumonia in children's groups.

Of the microbial pathogens in the bacteriological examination of sputum or tracheal contents of pneumonia patients, the pathogenic staphylococcus is sown in 25-35% of cases, hemolytic and green streptococcus - 17 - 20, pneumococcus - 6 - 12, Escherichia coli - 4 - 5, Proteus - 3 - 4, synagogue coli - 2 - 4, Frieddlender's coli - 2 - 4.5 and Pfeiffer's coli - in 3 - 5% of cases. Sometimes germs of the genus klebsiella are detected. One or a combination of these germs is sown.

When interpreting the value of the selected microbe in the etiology of pneumonia, it should be taken into account that its detection in the material from the respiratory tract, and especially from the pharynx, is not reliable evidence that this microbe is a causative agent of pneumonia. In addition, it is known that the results of bacteriological studies are affected by the use of penicillin and semi-synthetic penicillins starting from the first hours of hospitalization of a child with pneumonia.

The persistent sensitivity of pneumococcus, as well as green streptococcus to penicillin and semi-synthetic penicillins, dramatically reduces their sowing capacity on the second day after the use of these antibiotics. Staphylococcus aureus, which has pathogenic properties and resistance to penicillin and other antibiotics, is sown most often. Due to the prevalence of the pathogenic staphylococcus aureus in both adults and children (according to WHO - 30 - 50%) its importance in the etiology of pneumonia has increased. For recognition of pathogenic staphylococcus as an etiologic factor of pneumonia, it is indisputable that in addition to its detection in the material from the respiratory tract and yawning, the increase of anti-a-toxin titers in the blood serum, taking into account the dynamics of the disease, sowing of the microbe from the blood or pleural exudate.

Pathogenic staphylococcus, green and hemolytic streptococcus and pneumococcus are currently dominant in the etiology of pneumonia. The etiological role of Gram-negative flora (Escherichia coli, Proteus, synagogue coli, microbes of the genus klebsiella) is increasing, especially in children during the first 5 months of life.

In case of pneumonia, fungi of the genus Candidaalbicans are also found, parasites of which the most etiological role is played by Carini pneumocysts, causing interstitial pneumonia.

The mechanism of pneumonia development has not been sufficiently studied. Most often the pathogen from the nasopharynx penetrates and spreads aerobronchogenic way with subsequent occurrence of an inflammatory process in acinuses. Further progress of the inflammatory process can be made by increasing the existing foci or by the appearance of new foci in the more distant areas of the lungs, arising mainly lymphatically, which can be explained by the abundance of lymphatic vessels and their insufficient barrier function, especially in young children.

New pockets of inflammation in the lungs also occur bronchogenically when infected perspiration from pockets of inflammation enters bronchi and bronchioles during coughing and sneezing. Lymphogematogenic and hematogenic pathways of focal pneumonia are also possible. Especially has the property of penetrating into the bloodstream from primary foci of infection pathogenic staphylococcus. Hematogenic or lymphogematogenic development of focal pneumonia is observed in children mainly at an early age, and especially in the first months of life, if they have foci of staphylococcus infection activated by the layering of acute respiratory infection.

In case of lymphogematogenic spread of infection, intrathoracic lymph nodes with subsequent affection of peri-bronchial lymphatic vessels and alveolar passages are involved in the pathological process at the earliest stages of the disease. The lesion of the intradoracic lymph nodes with the expressed phenomena of lymphostasis and the subsequent development of pneumonia is reproduced

experimentally on rabbits by repeated rubbing of the staphylococcal emulsion into the region of the throat ring. The similar mechanism of affection of intrathoracic lymph nodes and staphylococcal pneumonia occurrence is observed in children of early age with the pathological process in amygdala caused by pathogenic staphylococcus.

The lymphogenic pathway of focal pneumonia cannot be ruled out, especially in infants, who have an insufficiently expressed barrier function of lymphatic tissue.

In the pathogenesis of acute pneumonia, it is essential to take into account the fact that when the pathogen enters the respiratory system, the child does not always develop inflammatory processes. The occurrence of pneumonia is possible only under favorable conditions for the development and reproduction of the causative agent. One of the important conditions conducive to the development and reproduction of microbes entering the lungs is a violation of lymph and blood circulation, as well as the development of primary atelectases, emphysema. The most frequent disorders of hemo- and lymphodynamics in the lungs, violation of vascular and tissue permeability, changes in respiratory function, its depth, rhythm, as well as the formation of atelectases and emphysema is observed in acute respiratory viral infections. Changes in pulmonary tissue in the form of circulatory disorders, desquamation and necrosis of the alveolar epithelium, caused by the influence of the virus or its toxins, predispose to the introduction and reproduction of secondary bacterial flora (pathogenic staphylococcus, streptococcus, pneumococcus and Gram-negative microbes - E. coli, synergic coli, proteins, etc.). Atelectases can be formed when the lungs are filled with blood by increasing the permeability of the capillary wall. Of course, the occurrence of primary atelectasis (complete and partial lung fall or part of it) does not lead to pneumonia without the participation of the exciter microbe. In acute pneumonia accompanied by endobronchitis, small secondary atelectases may occur as a result of bronchial occlusion with infected mucus.

In recent years, most researchers believe that the development of atelectasis is due to an increase in surface tension in the alveols due to the absence or significant decrease in surfactant activity. The latter is a surface-active extracellular lining of alveoli and begins to be synthesized from granular pneumocytes during the intrauterine fetal life period between the 21st and 24th weeks of pregnancy.

Chemically, surfactant is a complex lipid consisting predominantly of lecithin and sphingomyelin. Upon completion of the synthesis, the surfactant enters the amniotic liquid, reaching a concentration of up to 0.01 mg/l. The study of the quantitative ratio of lecithin to sphingomyelin in amniotic fluid during pregnancy allows to determine biochemical maturity of fetal lungs and predict the possibility of respiratory disorders during its intrauterine life.

Surfactant counteracts the force of surface tension in alveols at the boundary of air and liquid, affects the elasticity of pulmonary tissue, provides stability of alveoli form and respiratory function of lungs.

It is believed that the surfactant plays a major role in establishing normal breathing after the birth of the child, preventing the collapse of the exposed alveoli by reducing the surface tension therein. The decrease in the content of surfactant in the lungs is determined by the combination of atelectasis, edema, as well as by the formation of hyaline membranes (I. K. Esipov, 1976).

Despite the bactericidal properties of the surfactant, microbes, especially Gram-negative microbes, are capable of destroying it. Therefore, the decrease in surfactant activity due to microbial flora may contribute to atelectasis and pneumonia. In the inflammation zone in case of pneumonia, the amount of surfactant is reduced.

It is also significant that in children, especially infants, due to the relatively narrow lumen of bronchi and bronchiol, and tacjaslabo pronounced coughing, it is relatively easy to clog terminal bronchioles and bronchi with the subsequent development of small atelectases. Conditions contributing to lung stagnation as well as the formation of atelectases, are also important. Excessively tight diaper of the child, especially the first months of life, insufficient stay in the open air contribute to stagnation in the lungs, disturbance of depth and rhythm of breathing.

In understanding pathogenesis of pneumonia it is important to take into account research of A. I. Strukov and I. M. Kodolova (1959) on age morphology of bronchial tree and pulmonary segments in children. The lung segments of the child are externally similar to the lung segments of the adult, but they are characterized by smaller airway sizes - segmental and subsegmental bronchi, which are the backbone of the segment.

The development of structural elements of segmental and subsegmental bronchi is imperfect. Lung segments in children of early age are anatomically separated, clearly limited by narrow furrows with loose connective tissue layers. The limited segments are due to the wealth of loose connective tissue in the lungs. From anatomical features of bronchi - the angle of withdrawal. Direction, the width of lumen - aeration of segments depends, evacuation of secret from bronchi, the possibility of infection and spread of inflammatory process in bronchopuluous tissue.

In the downward path of infection, mono or polysegmental pneumonia occurs. Inflammation within the segment - from the acinus to the slice and from slice to slice - can spread contactly and lymphogenically, causing intracegmental changes characteristic of focal pneumonia. Polysegmental or monosegmental pneumonia may be of the cataral or interstitial type. It has been found that in children of early age, when localizing the inflammatory process in the upper lobes of the lungs, the 2nd posterior segment and very rarely the 2nd anterior segment are more likely to be affected. In the lower lobes of the lungs, 6, 9 and 10th segments are predominantly affected.

In the left lung, in addition to said segments, the inflammatory process localizes in the 4th and 5th segments. Chronic processes and bronchoectases are most frequently developed in the upper 6 segment.

In the pathogenesis of pneumonia, the functional state of the central and peripheral nervous system is of great importance. Experimental studies on dogs have found that irritation of upper cervical sympathetic nodes leads to increased excretion of the pituitary hormone vasopressin, which increases blood pressure in pulmonary arteries. This leads to the development of pulmonary edema and changes resembling those in large-scale pneumonia, and microscopic examination determines signs of lobular pneumonia of a desquamative-hemorrhagic nature. When animals are damaged by wandering nerves of the lung, vagus pneumonia (N. F. Filatov) occurs.

Lung fullness, which contributes to the easier onset of the inflammatory process, occurs as a result of the disruption of the function of the vasomotor center.

The state of nervous mechanisms of pulmonary tissue matters. I. V. Davydovsky (1958) believes that any increase or decrease in bronchial musculature tone is a factor predisposing to changes in lung function.

It is also necessary to take into account that children, especially infants, have imperfect immunobiological reactions of the organism. Cellular immunity indices for T- and B-lymphocyte activity, determined by the rosego formation method, are lower in children of the first year of life in comparison with adults. Content of serum immunoglobulins in children of early age is reduced in comparison with older children.

IgG carriers of antibodies to bacterial and viral antigens in children's serum are found in high concentrations, while IgM and IgA are found in minor concentrations. In contrast to IgM and IgA, IgG has been found to penetrate through the placenta from mother to fetus, i.e. IgG in newborn infants of maternal origin. Further on, by the end of the newborn period, IgG content significantly decreases with subsequent increase to the level of adults only by 9 years of life. IgM and IgA content increases from the newborn period onwards and reaches the adult level by the age of 12. However, children in the first six months of life have limited synthesis of IgM, IgA and especially IgG.

The peculiarity of general and specific immunobiological reactivity (weak barrier function of lymph nodes and connective tissue, mild vulnerability and increased permeability of mucous membranes, insufficient ability to produce antibodies, etc.) in infants and young children explains the presence of a pronounced sensitivity of the body, and especially lung tissue, to various microbes and viruses.

The state of immunobiological reactivity in children is the main factor in the pathogenesis of acute pneumonia.

Pneumonia most often develops and is more severe in children who are mixed or artificially fed, suffering from hypotrophy, exudative diathesis, rickets and others. In these children, the barrier function of bronchi is impaired and the content of nonspecific and specific protection factors (lysozyme, perdin, complement, interferon, immunoglobulins, etc.) is reduced. In children with rickets and hypotrophy, even before pneumonia occurs, there are pronounced disorders of basic vital functions (respiration, blood circulation, thermoregulation) and metabolic processes. Disturbance of immunological reactivity of children's organism may be caused by microbial, especially staphylococcal, or viral sensitization and may be the main factor in the mechanism of pneumonia development.

The basic in the mechanism of pneumonia development is oxygen insufficiency arising not only as a result of external breathing disturbance and decrease in the level of atmospheric oxygen entering the blood but also as a result of decrease in oxidative processes in 1 drop with decrease in oxygen utilization and the increased content of carbonic acid in the blood.

In the development of hypoxemia, disturbance of pulmonary respiration caused by damage to the alveolar epithelium is important. Essential is blood filling of the lungs, bronchospasm, presence of emphysema and atelectatic areas, at which diffusion of gases is complicated.

Significantly exacerbates oxygen insufficiency in pneumonia involvement in the pathological process of the circulatory system, expressed in toxic or dystrophic damage to the heart muscle, disturbance of capillary wall permeability, their expansion and often increase of venous pressure. These changes lead to a slowdown in blood flow and the development of circulatory (hemodynamic) hypoxemia. In infants, especially in the first half of the year, hypoxemia occurs relatively quickly due to early-onset circulatory disorders in the small circle (lnfostasis, stagnant hyperemia, edema of the alveolar epithelium). Also, in children of early, especially breast, age due to imperfections of nervous regulation, instability of exchange processes, oxygen deficiency is more pronounced than in older children. This is confirmed by the fact that oxygen absorption in 1 min in infants is 40 - 70 ml, in older children - 166 - 210 ml. Usually, in the severe course of pneumonia in children of an early age, hypoxemia is of a mixed nature, as it is due to oxygen deficiency and impaired hemodynamic processes.

According to 10. F. Dombrovskaya (1961), cyanosis in pneumonia is due not only to the change in the gas composition of the blood but also to a large extent depends on vasomotor disorders (paresis or narrowing of capillaries) resulting from the failure of the vasomotor center function. Changes in capillaries are responsible for early-onset cyanosis in children in the first months of life when there are no other manifestations of pneumonia. J. F. Dombrovskaya considers early, or primary, cyanosis to be the manifestation of a nerve-reflex reaction, depending on both on the strength of the irritant (the agent and its toxicity) and the immaturity of the nervous system. Secondary cyanosis is due to a change in the gas composition of the blood. In primary cyanosis, the blood gas composition may remain within normal limits. The use of oxygen in this phase of the disease is ineffective as oxygen therapy causes an irritating effect.

In case of a severe course of pneumonia, secondary cyanosis can coincide with the primary one.

It should also be taken into account that pneumonia violates the regulatory mechanisms of breathing due to involvement in the pathological process of the central

nervous system, which is particularly sensitive to oxygen deficiency.

The development of hypoxemia and hypoxia should also take into account disorders of liver, kidney, endocrine system, motor and secretory-enzymatic functions of stomach and intestine, etc. In children of early age, adrenal function is increased at the height of acute pneumonia, accompanied by an increase in the content of glycocorticoids, mineralocorticoids and catecholamines in the blood. However, in children of early age in whom pneumonia occurs against the background of thymomegaly or is complicated by an asthmatic component, a less pronounced increase in the level of glycocorticoids in the blood is revealed (P. A. Tabolin et al., 1976). It seems that the reserve capacity of adrenal glands in such children is reduced.

In the pathogenesis of hypoxia in acute pneumonia, the disorder of hemorrhage is important (S. S. Shamsiyev and N. P. Shabalov, 1978). Pneumonia with toxicosis and metabolic disorders is accompanied by erythropoiesis inhibition and erythrocyte hemolysis. The latter is known to provide transport of oxygen to tissues and carbon dioxide from tissues to lungs.

Reduction of quantitative content of vitamins - ascorbic acid, ergocalciferol, tocopherol, thiamine, riboflavin, pyridoxine is also significant.

In the case of acute pneumonia, metabolic processes are disrupted. The severe course of the disease is accompanied by hypoproteinemia caused by a decrease in the protein-forming function of the liver. In case of hypoproteinemia and dysproteinemia, production of antibodies is reduced, functions of enzymatic systems are impaired, processes of repamination and deamination of amino acids are perverted. As a result of the disruption of the oxylus and myrefluid processes in the blood, the content of ammonia, urea increases, the content of most free amino acids in the blood serum increases, and glutamine and aspartic (take part and neutralize ammonia accumulating in tissues during metabolism) - decreases. In blood serum of children suffering from pneumonia, the level of sulfhydryl and disulfide groups is reduced.

The activity of enzymatic systems (dehydration, cytochrome oxidase, coal anhydrase, catalase, etc.) affecting the processes of oxidation and reduction, cleavage and synthesis of protein, oxygen absorption by tissues, as well as the functional state of organs and systems is also important.

Increased activity of transaminases (amino-traisferases) of major importance in the transport of amino groups has also been established. As a result of toxic damage to various organs and systems, an increased amount of transaminases enters the blood serum. Transaminase activity is particularly increased in the severe course of pneumonia.

There is a disorder of lyiidoma, and also carbohydrate metabolism, which is confirmed by the presence of pathological glycemic curves and inclination to hypoglycemia. Due to the increase of glycolysis processes in blood serum, lactic acid content increases, which is one of the causes of metabolic acidosis. Blood serum increases the concentration of pyruvic acid [1,3,5,78,92].

Exchange of macro-ergic compounds is disturbed. The concentration of adenosine triphosphoric acid (ATP) in the blood decreases, which can be explained by the disruption of glycolysis processes and the effect of intoxication. The activity of alkaline phosphatase in the blood serum increases, which may be an indirect sign of the dominant influence of bacterial flora in pneumonia.

Changes in the water-electrolyte exchange are manifested by a delay in the body fluid, chlorides, hematocrit index fluctuations within the range of 0.25 - 0.6 l/l. The content of potassium in the blood serum and red blood cells is reduced, which may be due to its excessive excretion in the urine and violation of mineralocorticoid function of the adrenal cortex, the concentration of sodium - slightly increased. In case of severe pneumonia, a moderate increase in calcium levels, especially ionized, is determined in serum. The serum and lung tissue have a reduced trace element content.

The stated above testifies to the fact that the development of pathophysiological processes in pneumonia in children is based on complex and diverse mechanisms, the essence of which is reduced to respiratory insufficiency caused by changes in the function of external respiration and disturbance of tissue oxidation processes.

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