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MECHANISM OF ACTION OF ANTIBACTERIAL DRUGS IN COMMUNITY-ACQUIRED PNEUMONIA IN YOUNG CHILDREN

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Abstract. *The prevalence of infectious diseases of the respiratory system and, first of all, pneumonia among the population, the presence of various etiological factors and conditions for the appearance of diseases, doctors of various specialties - therapists, surgeons, neuropathologists - predetermine the occurrence of this disease. Faced with this pathology. Few or atypical clinical signs characteristic of the modern course of pneumonia complicate the diagnosis and complicate the treatment of the patient. The presence of diseases accompanied by decompensation against the background of an infectious lung lesion worsens the prognosis and increases the risk of death. It is especially important to correctly diagnose infectious lung disease in time and to prescribe adequate antibacterial therapy.*

Key words: *drugs, antibiotics, pharmacokinetics, drug effects.*

МЕХАНИЗМ ДЕЙСТВИЯ АНТИБАКТЕРИАЛЬНЫХ ПРЕПАРАТОВ ПРИ ВНЕБОЛЬНИЧНОЙ ПНЕВМОНИИ У ДЕТЕЙ РАННЕГО ВОЗРАСТА

Аннотация. *Распространенность инфекционных заболеваний органов дыхания и, в первую очередь, пневмонии среди населения, наличие различных этиологических факторов и условий возникновения заболеваний, врачи различных специальностей — терапевты, хирурги, невропатологи — предопределяют возникновение этого заболевания.*

Столкнувшись с этой патологией. Малочисленные или нетипичные клинические признаки, характерные для современного течения пневмонии, затрудняют диагностику и осложняют лечение пациента. Наличие заболеваний, сопровождающихся декомпенсацией на фоне инфекционного поражения легких, ухудшает прогноз и увеличивает риск летального исхода. Особенно важно вовремя правильно диагностировать инфекционное заболевание легких и назначить адекватную антибактериальную терапию.

Ключевые слова: *лекарственные препараты, антибиотики, фармакокинетика, лекарственные эффекты.*

The prevalence of infectious diseases of the respiratory system and, first of all, pneumonia among the population, the presence of various etiological factors and conditions for the appearance of diseases, doctors of various specialties - therapists, surgeons, neuropathologists - predetermine the presence of this disease. Faced with this pathology. Few or atypical clinical signs characteristic of the modern course of pneumonia complicate the diagnosis and complicate the treatment of the patient. The presence of diseases accompanied by decompensation against the background of an infectious lung lesion worsens the prognosis and increases the risk of death.

It is especially important to correctly diagnose infectious lung disease in time and to prescribe adequate antibacterial therapy. Pneumonia is a group of acute infectious diseases of different etiology and pathogenesis, characterized by focal damage of the respiratory parts of the lungs and the presence of alveolar exudation (see picture).

Modern classification defines the following types of pneumonia: 1) community-acquired - CP (ambulatory) - acquired outside a medical institution; 2) nosocomial (hospital, in-hospital) - acquired in a medical institution; 3) aspiration; 4) pneumonia in people with severe immune deficiencies - pneumonia caused by congenital immunodeficiency, HIV infection, iatrogenic immunosuppression.

This division is based on the difference in the conditions in which the disease occurs and the approaches to the selection of antimicrobial therapy. Among registered pneumonias, the most common is CAP (ambulatory). They firmly occupy a leading position in the composition of acute infectious diseases of urban residents. Etiological factors of SAP Due to significant limitations, none of the microbiological methods can detect all potential triggers of bronchopulmonary infection, so the etiology of the infectious process cannot be determined in 30-50% of patients.

More than 100 microorganisms that can cause SAP have been described, almost all of which have been isolated at least once during lung tissue biopsy. However, in routine practice, they rely on microbiological studies of blood, sputum or pleural fluid and the results of serological studies to make an etiological diagnosis. Information on the etiology of SAP obtained in various studies depends on the following factors: the investigated patient population (age, the presence and severity of concomitant diseases - chronic obstructive pulmonary disease - COPD, immunodeficiency conditions; places of development of pneumonia - nursing homes, isolated groups); endemic characteristics and epidemiological situation of the region during the study; set of used diagnostic methods, their sensitivity and specificity, criteria for evaluating the obtained results. The etiology of CAP is directly related to the microflora, usually colonizing the upper respiratory tract. The most common causative agent of CAP is Streptococcus pneumoniae, which, according to various authors, causes the disease in 30-50% of cases in people of all ages.

Haemophilus influenzae is less common (10-20%). Up to 10% of CAP is caused by an association of two or more microorganisms, most commonly S. pneumoniae and H. influenzae.

However, in each case, it is not clear whether both microorganisms are equivalent etiological agents or whether one of them serves only as a predisposing factor for infection caused by another pathogen. Staphylococcus aureus, Moraxella, gram-negative bacteria (Klebsiella pneumoniae, Escherichia coli, Enterobacter spp., Pseudomonas spp., etc.), viruses (respiratory syncytial, influenza A and B viruses, parainfluenza) play a lesser role. . Although atypical microorganisms - Chlamydophila (Chlamydia) pneumonia, Mycoplasma pneumoniae and Legionella pneumophila - cause 8 to 30% of SAP cases, it is difficult to accurately assess the role of these pathogenic microorganisms in the etiological structure of SAP. adequate diagnostic methods. The role of oral microflora anaerobes (Peptostreptococcus spp., Bacteroides spp., Veilonella spp., etc.) in the genesis of CAP is small, but significantly increases with aspiration pneumonia, which occurs in 6-10%. conditions against the background of mental retardation, encephalopathy, trauma, cerebrovascular diseases.

Post-influenza pneumonia is most often caused by hemolytic streptococcus serogroup A (Streptococcus pyogenes), S. aureus, H. influenzae, or S. pneumoniae. The most common causative agent of CAP in smokers is nontypeable strains of H. influenzae. In patients with immunodeficiency, including neutropenia, in addition to pneumococci, staphylococci and gram-negative bacteria, pneumocystis carinii (Pneumocystis carinii), atypical mycobacteria, fungi and

cytomegalovirus are often found (the latter are symptoms of HIV infection). It should also be noted that a number of infectious diseases - pulmonary tuberculosis (Mycobacterium tuberculosis), Q fever (Coxiella burnetii), psittacosis (Chlamydophila psittaci), chlamydia infection in children (Chlamydia trachomatis), endemic mycoses (histoplasmosis, blastomycosis), gantavirus pulmonary syndrome (Hantaviruses), tularemia (Francisella tularensis), other highly dangerous infections (anthrax - Bacillus anthracis, cholera - Yersinia pestis) - is caused by damage to the lower respiratory tract.

The pathogenesis of CAP has four pathogenetic mechanisms of infection of the respiratory tract of the lungs leading to the development of pneumonia. The main mechanism is microaspiration of bacteria that make up the normal microflora of the oropharynx. In this case, it is important to increase their virulence against the background of the massiveness of the dose of microorganisms or damage to the protective mechanisms of clearing the tracheobronchial tree.

Such conditions can occur with a viral respiratory infection, associated with the dysfunction of the ciliated epithelium and a decrease in the phagocytic activity of alveolar macrophages. A less observed way of pneumonia is the inhalation of microbial aerosol, which is usually observed during infection with obligate pathogens (Legionella spp., etc.). In terms of the frequency of infection, microorganisms are hematogenously transmitted from an extrapulmonary focus of infection (endocarditis of the tricuspid valve, septic thrombophlebitis of the pelvic veins) and directly from a limited focus of infection (liver). spread is less important. abscess, mediastinal diseases, penetrating wounds of the chest cavity, etc.). Based on the pathogenesis of pneumonia, their etiological structure is often represented by the microflora of the upper respiratory tract, the composition of which may differ in different patients depending on the external environment surrounding the person, age, general health, and the presence of concomitant diseases. diseases and previous antibacterial therapy. Taking into account these features is important for predicting the etiology of CAP, planning the tactics of microbiological examination of the patient and choosing a rational empiric antimicrobial therapy. Microbiological diagnosis Despite the development of laboratory diagnostic methods, the etiological diagnosis of SAP cannot be determined in 30-50% of cases.

This is partly due to certain difficulties in obtaining the complete material from the site of inflammation in time and interpreting the research results. What makes the etiological diagnosis of SAP extremely difficult is the following: the absence of sputum (especially in the early stages of the disease) and the difficulty of obtaining it in children; it is impossible to obtain bronchial secretion by invasive methods due to the severity of the patient's condition, insufficient qualification of medical personnel or other reasons; contamination of the bronchial contents with microflora of the oropharynx; High rate of carriage of S. pneumoniae, H. influenzae and other conditional pathogens (from 5 to 60% in different age groups and populations); use of antibacterial drugs at the pre-hospital stage. It cannot be ruled out that some cases of SAP of unknown etiology are caused by pathogens that are still unknown to science or uncultivable forms of microorganisms (including L-forms of bacteria that require special growth factors).

Despite the limited diagnostic value of the examination of freely expectorated sputum in patients without mechanical ventilation, this type of material is essential in microbiology laboratories.

It is mandatory to evaluate the suitability of the sputum sample before performing the culture examination. Sputum is of satisfactory quality if more than 25 neutrophils and less than 10 epithelial cells are detected in the field of view of sputum under a Gram-stained smear microscope at a magnification of 100. The importance of examining sputum culture is also the diagnosis of nosocomial pneumonia (NP). also lies in the identification of resistant strains of possible pathogens.

It should be remembered that even if microorganisms are isolated from sputum, difficulties may arise in the correct interpretation of the test result.

The importance of isolated microorganisms to distinguish colonization from infection should be critically evaluated, since sputum samples are often contaminated with microflora colonizing the oropharynx and upper respiratory tract of patients. At the same time, it is necessary to try to determine the etiology of CAP, which will first of all allow choosing the most appropriate drug against a specific microorganism in a specific patient and reduce the risk of developing unwanted drug reactions and resistance of the pathogen to antibiotics. during treatment. Second, to obtain information about the occurrence of infections that require infection control measures (for example, legionellosis) or preventive measures in contact persons (M. tuberculosis); collecting information on resistant pathogens, avoiding unnecessary overuse of antibiotics in the population.

Third, improving the cost-effectiveness index by using a narrow-spectrum antibiotic that is cheaper to treat and less harmful to the patient. The effectiveness and reliability of microbiological diagnosis of CAP largely depends on the nature of the studied material, the methods used and their combinations, and the correct interpretation of the obtained results.

A reasonable balance should be maintained between the intensity and invasiveness of the diagnostic procedures performed on the patient and the prescription of empiric antibiotic therapy without establishing a clear etiological diagnosis. Bacteriological examination of sputum is indicated for patients with SAP treated in an outpatient setting. Epidemic (eg, legionellosis, mycoplasma infection) or special clinical or epidemiological reasons may require serological testing. The set of studies in hospitalized patients is determined by the severity of the disease, the presence of epidemiological risk factors, and the effectiveness of empiric therapy.

The microbiological diagnostic program includes the study of clinical material from the respiratory tract, blood and pleural fluid (see table). Serological tests have limited diagnostic value and, as a rule, are not used in the examination of patients with suspected NP. These tests, which are of epidemiological importance, may be useful in some cases, for example, in the retrospective diagnosis of Legionnaires' disease. Antimicrobial therapy Taking into account the expansion of the range of potential infectious agents, there is a clear trend to use broad-spectrum antibacterial agents as initial therapy. anaerobes in pneumonia), now H. influenzae, M. catarrhalis and the possible role in drug selection. gram-negative bacteria are taken into account, chlamydia, legionella, viruses and fungi in the etiology of CAP in adult patients.

For S.pneumoniae, the most common causative agent of S.pneumoniae in all age groups of patients, the increasing number of penicillin-resistant strains is a significant problem. In some countries, the resistance of pneumococci to penicillin can reach 60%. The drugs of choice for the treatment of pneumococcal pneumonia are β-lactam antibiotics - benzylpenicillin, aminopenicillins, including protected ones, second and third generation cephalosporins. Macrolide antibiotics are backup agents for β-lactam intolerance.

Early fluoroquinolones (ciprofloxacin, ofloxacin, pefloxacin, lomefloxacin) are characterized by low activity against pneumococci (risk of clinical and bacteriological treatment failure). New drugs, new fluoroquinolones (levofloxacin, moxifloxacin) are also highly effective.

At the same time, pneumococcal resistance to tetracyclines (34-43%) and co-trimoxazole (14-38%) continues to increase.

Later, drugs of this group (levofloxacin, moxifloxacin, gatifloxacin) are characterized by high antipneumococcal activity (B. Kronemyer, 2003), resistance was not detected when used in Russia. H. influenzae is the second most common cause of SAP, especially in smokers and patients with COPD. Aminopenicillins (amoxicillin, taken orally, is preferable to ampicillin because it is absorbed 2 times better from the gastrointestinal tract), 2-4 generation cephalosporins, carbapenems and fluoroquinolones have high natural activity against Haemophilus influenzae.

The main mechanism of resistance development in H. influenzae is the production of broad-spectrum β-lactamases (up to 10% of strains) capable of destroying natural and semi-synthetic penicillins and first-generation cephalosporins. The drugs of choice for the treatment of CAP caused by resistant strains of H. influenzae are protected aminopenicillins and second-generation cephalosporins (III-IV generation cephalosporins and carbapenems have no advantage).

Macrolides have clinically significant activity. M. catarrhalis ranks third among the causative agents of CAP, and 80-90% of strains produce β-lactamases that destroy benzylpenicillin, aminopenicillins, and first-generation cephalosporins. The activity of β-lactamases is completely suppressed by inhibitors, so amoxicillin/clavulanate, second-generation cephalosporins, fluoroquinolones, and to some extent macrolides remain active. S. aureus is not a typical causative agent of KAP, but its importance increases in elderly patients, alcohol abusers and drug addicts, as well as after influenza. 70-80% of strains produce β-lactamases, destroying natural and semi-synthetic penicillins except for oxacillin and methicillin.

However, they are completely suppressed by inhibitors and are not able to destroy cephalosporins and carbapenems. The drugs of choice for the treatment of staphylococcal CAP are oxacillin, amoxicillin/clavulanate, and I-II generation cephalosporins (III generation cephalosporins are less active in vitro, oral cefixime and ceftibuten have no antistaphylococcal activity). For allergies to β-lactams, macrolides are used (clarithromycin has the best effect against S. aureus), lincosamides; Moxifloxacin has the highest antistaphylococcal activity among fluoroquinolones. Methicillin-resistant strains of S. aureus (MRSA) are not specific for CAP, but can be isolated from patients with cystic fibrosis (often associated with P. aeruginosa) (VE Nonikov et al., 1993). Glycopeptides (vancomycin), oxazolidinones (linezolid) and rifampicin (80% of cases) are active against MRSA.

In the treatment of mycoplasma pneumonia, the macrolides and tetracyclines with the greatest natural activity against M. pneumoniae are used, and the new fluoroquinolones used against this pathogen are more active than the previous fluoroquinolones. M. pneumoniae is naturally resistant to β-lactam antibiotics because it lacks the cell wall and its component, peptidoglycan, which is the target of β-lactams. C. pneumoniae is also resistant to β-lactams and aminoglycosides, and the drugs of choice for the treatment of chlamydial CAP are macrolide antibiotics and tetracyclines. Legionella spp. - a gram-negative microorganism with mainly intracellular localization, is the causative agent of CAP with a severe course.

The drug of choice for the treatment of Legionella pneumonia is erythromycin, which is often used in combination with rifampicin.

Early and newer fluoroquinolones are also highly effective drugs in the treatment of Legionella pneumonia. Other macrolides are also effective (especially clarithromycin and azithromycin, which produce high concentrations in bronchial secretions). K. pneumoniae is rare, usually found in patients with severe comorbidities (diabetes, heart failure, liver cirrhosis, etc.). III-IV generation cephalosporins, carbapenems and fluoroquinolones have the highest natural activity against this pathogen. P. aeruginosa plays a minimal role in CAP and rarely occurs in bronchiectatic and immunosuppressive patients (eg, glucocorticoid therapy), heroin addicts, and cystic fibrosis (often associated with S. aureus, Candida fungi) can cause illness.).Some β-lactams (piperacillin/tazobactam, ceftazidime, cefoperazone, cefepime, imipenem, meropenem), aminoglycosides and fluoroquinolones (the most active ones are ciprofloxacin and moxifloxacin) are active against Pseudomonas aeruginosa.

Currently, one of the most urgent problems of modern medicine is the rational use of antimicrobial drugs (AMP). Interest in this problem is associated with a number of important circumstances. First, antibiotics are one of the most frequently prescribed drugs both in outpatient practice [1] and in hospitals [2], often irrationally and without appropriate indications. Second, antibiotic therapy is an expensive method of treatment, accounting for 50% of the costs of medical institutions [3] and taking a leading place in the composition of outpatient costs of infectious diseases. In addition, over time, the use of antibacterial drugs is accompanied by a decrease in their activity due to the development of resistance of microorganisms to them. Accordingly, the term "rational antibacterial therapy" for various infectious diseases is understood as achieving the predicted treatment result with the lowest economic costs and the lowest risk of selecting resistant strains of microorganisms [4].

Today, the guidelines and principles of antibacterial therapy are clearly described in the pages of many international and local recommendations for the treatment of patients with respiratory tract infections (RTI) [5-8]. However, the availability of the most up-to-date recommendations does not guarantee their practical use, and mistakes related to an irrational approach to the use of antibiotics in RTIs are often encountered in daily practice. It should be noted that errors in antibacterial therapy of IDPs have the largest share of all treatment errors made in pulmonology practice. At the same time, the incorrect prescription of antibiotics has a decisive effect on the outcome of the disease, the economic component of treatment, and leads to the selection of antibiotic-resistant strains of pathogens [9,10].

The main errors in antimicrobial therapy [11,12] include:

1) unjustified antibiotic prescription;

2) wrong choice of medicine;

3) antibiotic selection without taking into account the regional characteristics of current pathogen resistance;

4) insufficient dosage regimen;

5) unreasonable or irrational combination of drugs;

6) incorrect assessment of treatment efficiency criteria;

7) unreasonable duration of antibacterial therapy.

Thus, during a multicenter pharmacoepidemiological study, the practice of treating acute respiratory viral infections (ARVI) in children was evaluated [13]. Antimicrobial therapy was indicated in 52% of outpatients. It is noted that 8.2% of patients experienced various adverse events during treatment. In the study of VK. Tatochenko and others. [14] analyzed 1469 episodes of acute respiratory illness (ARI) in children between 1998 and 2001. It is known that the frequency of prescribing antibiotics for ARVI by local pediatricians is 26-36% [10]. A pharmacoepidemiological study of the current practice of treatment of ARVI in conscripted military personnel in the troops of the Moscow Military District showed that in 74.2% of cases aminopenicillins were prescribed at the beginning of treatment [15]. However, it should be noted that the practice of prescribing antibiotics for ARVI in childhood is widespread throughout the world. For example, the frequency of their use in Canada is 14% [16], in France - 24% [17], in the USA - 25% [18]. In China, 97% of children with acute respiratory infections who contact a healthcare professional receive antimicrobial therapy [19].

Thus, it should be recognized that the current practice of ambulatory treatment of OB in adults includes the prescription of broad-spectrum antibacterial drugs in most cases (85.7%). At the same time, the frequency of prescribing antimicrobial therapy was high in all outpatient medical institutions, regardless of their geographic location. It is clear that the practice of widespread use of antimicrobial agents for diseases of mainly viral etiology is incorrect and only leads to an increase in the number of adverse events, the "increase" in the cost of treatment, and with the increase in the number of can be. antibiotic-resistant strains of microorganisms.

In the analysis of outpatient treatment of adult patients with acute tonsillopharyngitis (ATP) aggravated by chronic bronchitis and acute otitis media (AOM), a high frequency of use of antibacterial therapy was noted - in 95, 84 and 79% of cases, respectively [20] –22]. At the same time, the percentage of bacterial pathogens in ATF does not exceed 30%, and the treatment of patients with mild forms of AOM includes prescribing antibiotics only in the presence of persistent symptoms against the background of adequate symptomatic therapy.

Another serious problem that often occurs in the treatment of IDPs is the irrational tactics of antibacterial therapy. According to a number of large-scale, multicenter pharmacoepidemiological studies conducted in Russian polyclinics, the choice of antibacterial drugs for tonsillopharyngitis, AOM, acute sinusitis in most cases is the range of the most relevant pathogens, without taking into account modern data done. their resistance to antibiotics, as well as the pharmacokinetics and safety profile of the drugs [20-21,23]. For example, in the treatment of acute sinusitis only 18% of cases recommended by experts, and in 82% of cases antibiotics that have lost their clinical significance (co-trimoxazole, doxycycline) were used. 23]. Antibiotics were used in patients with ATF, whose activity did not allow the necessary destruction of group A β-hemolytic streptococci (doxycycline, ciprofloxacin, etc.).

Currently, the pages of local recommendations for the management of patients with community-acquired pneumonia (CAP) focus on the analysis of the most common errors in antibacterial therapy for this disease.

In a multicenter prospective pharmacoepidemiological study conducted in 2007, the current practice of antibiotic therapy in patients with SAP was further analyzed [7].

In addition to the recommended drugs (amoxicillin, amoxicillin/clavulanate, macrolide antibiotics), cefazolin and ciprofloxacin (drugs with low pneumococcal activity) took an important part in the prescriptions; There was a high frequency of prescribing third-generation parenteral cephalosporins (cefotaxime, ceftriaxone). At the same time, widespread unreasonable use of "early" fluoroquinolones (ciprofloxacin) may be accompanied by the formation of antibiotic-resistant strains of microorganisms, including new representatives of this class of antibiotics (levofloxacin, moxifloxacin). In 2007, the composition of AMPs used for the initial monotherapy of CAP in the outpatient setting is presented in Figure 2.

Currently, the following approach is presented in the pages of local recommendations [7] for ambulatory treatment of patients with SAP. In the case of non-severe pneumonia in patients without concomitant diseases and who have not received it in the last 3 months. Antibacterial drugs Adequate clinical effect can be obtained by using amoxicillin or macrolide antibiotics with improved pharmacokinetic properties (azithromycin, clarithromycin) (Table 2). On the contrary, the patient has concomitant diseases (chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), congestive heart failure, liver disease, alcohol abuse, drug addiction, underweight) and / or received in the last 3 months if antibacterial drugs (the risk of identifying pathogens resistant to antibiotics, the proliferation of gram-negative microorganisms, it is recommended to prescribe aminopenicillins "protected" from co-infection); In particular, taking into account the possible contribution of pathogens such as Chlamydophila and Mycoplasma pneumoniae to the etiology of pneumonia, combined therapy can be prescribed: "protected" aminopenicillin + macrolide (Table 2). An alternative to this approach for the treatment of non-severe CAP with risk factors for treatment failure may be the use of "inhaled" fluoroquinolones.

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