PHARMACODYNAMICS AND PHARMACOKINETICS OF DRUGS USED IN PNEUMONIA

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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. 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).*

Key words: *Pneumonia, origin, diagnosis, prevention, prevention, pharmacodynamics of drugs affecting the disease.*

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.

Because, according to clinical and radiological data and using generally accepted microbiological methods, as a rule, it is not possible to reliably determine the etiology of CAP, the basis of treatment is the most is the empirical selection of drugs, taking into account the risk factors for the presence of many pathogens; The effectiveness of the use of β-lactam antibiotics requires compliance with a number of conditions, the basis of which are:

Antibacterial therapy for pneumonia should be early and adequate (the latter refers to the dose, method of administration and duration of use), and should also be adjusted during treatment depending on the clinical effect of the pathogen and sensitivity to the drug. The effectiveness of the treatment depends, first of all, on the correct choice of the antibacterial drug and its compatibility with the etiology of the disease. Currently, the doctor has many different antibacterial drugs in his arsenal, which are very effective for different etiologies of pneumonia.

The presumed etiological variant of pneumonia is the most important guide in choosing the initial antibiotic. The diagnosis of the etiological factor is only indicative and is based on such information as the epidemiological situation, the nature of the background pathology, and the characteristics of the clinical and radiological picture. It should be assumed that the majority of non-pneumococcal pneumonia caused by opportunistic microorganisms is characterized by the clinical course of the disease. Thus, Friedlander's pneumonia usually occurs in people who abuse alcohol for a long time; Pneumonia caused by Haemophilus influenzae - if pneumonia develops in patients with chronic bronchitis and in a patient treated in the hospital, the most likely causative agent is gram-negative flora, in particular, Escherichia coli or Pseudomonas aeruginosa.

When prescribing antibacterial therapy, it is necessary to take into account the possible side effects of drugs and avoid prescribing drugs that cause unwanted effects and worsen the course of the main and concomitant diseases. Hypersensitivity to previously used antibacterial agents should be taken into account. In particular, due to the risk of cross-hypersensitivity, other beta-lactam antibiotics should be prescribed with extreme caution to patients with allergic reactions to penicillin.

If the patient's history contains information about repeated courses of treatment of various diseases with penicillin drugs and other antibiotics, the probability of showing beta-lactamase activity in the representatives of the patient's endogenous microflora increases dramatically.

When choosing an antibacterial drug in patients with pneumonia against the background of chronic kidney failure, the dose of the drug excreted by the kidneys should be reduced in proportion to the glomerular filtration rate or preference should be given to the antibacterial drug metabolized in the liver (erythromycin, clindamycin, metronidazole, cefoperazone). On the contrary, if there are signs of liver pathology, its functional failure, the doses of drugs that are mainly metabolized in the liver should be reduced by 1/3-1/2, or antibacterial drugs (aminoglycosides) that are excreted through the kidneys should be preferred. , fluoroquinolones, cephalosporins, except cefoperazone). If the patient has heart failure or obesity, the excretion of antibacterial drugs from the body is disturbed, their concentration in the blood and the risk of side effects increase, which should be taken into account when choosing an antibacterial drug with long-term pharmacokinetics. (cefoperazone, ceftazidime, roxithromycin, clarithromycin).

The antibiotic to be taken should be characterized by optimal pharmacokinetic parameters: achieving a high tissue concentration, including at the site of inflammation, the maximum possible intervals between drug doses and the need for minimal monitoring. In particular, a pharmacokinetic parameter such as the ability to enter sputum is important in the treatment of patients with pneumonia. In patients with pneumonia, preference should be given to drugs that create high and stable concentrations in sputum. In particular, among aminopenicillins, the concentration of amoxicillin in sputum is twice as high as that of ampicillin when taking drugs in the same doses. In addition, the concentration of amoxicillin in sputum remains at a therapeutic level for a long time. Aminoglycosides do not penetrate the sputum well enough, which is one of the reasons for their incorrect use in this pathology.

It is very difficult to predict the clinical effectiveness of an antibacterial drug in a specific patient, because there are many factors that affect the possible results of antibiotic therapy [10].

These factors can be divided into three groups: macroorganism factors - the human immunological system and its interaction with the pathogen; pharmacodynamic factors of the interaction between an antibacterial drug and a microorganism in the conditions of a macroorganism: bactericidal effect, activity at subinhibitory concentrations, post-antibiotic effect; pharmacokinetic factors.

Adequacy of antibiotic therapy determines recovery time, risk of complications and treatment outcome [1].

Correctly selected antibiotic at the onset of the disease and timely correction of antibacterial therapy over time ensures high efficiency and, most importantly, significantly reduces the cost of treatment. In the treatment of severe pneumonia of local origin, a broad-spectrum antibiotic active against beta-lactamase-producing staphylococci and streptococci, as well as gram-positive microorganisms E. coli, Klebsiella, Enterobacter, H. influenzae, etc. should be prescribed. The initial prescription of extremely strong antibiotics and/or their combinations does not provide advantages, but at the same time increases the risk of selecting problematic microorganisms.

The initial effect of the prescribed antibiotic can be assessed no later than 48 hours, because during the first day the growth and reproduction of sensitive microorganisms is suppressed, then the first positive signs appear in the clinical condition in response to the decrease in intoxication, temperature reaction and laboratory parameters. If it is concluded that the therapy is adequate on the third day of treatment, the course of treatment is continued until the clinical, radiological and laboratory signs of inflammation are normalized. The absence of positive dynamics 72 hours after the start of antibiotic therapy indicates the need to adjust the treatment regimen.

After choosing an antibacterial drug for empiric therapy, it is necessary to determine the optimal method of drug administration, the adequate dose of the drug, adequate monitoring during treatment, and the optimal duration of therapy.

Oral administration of drugs has a number of undoubted advantages over parenteral administration, in particular, it is safer, simpler and cheaper. Parenteral administration of antibacterial agents is indicated in the following cases: for severe or general infection, when it is necessary to quickly achieve the maximum and stable level of drugs in the blood and tissues; when it is difficult or impossible to take drugs orally (patients faint, erratic behavior, damage to the central nervous system, decreased memory or intelligence); for diseases or conditions that cause deterioration of the absorption of drugs in the gastrointestinal tract (severe gastroenteritis, resected stomach or part of the small intestine); in the absence of dosage forms of the selected drug intended for oral administration. In practice, the opportunity to switch to the oral administration of antibiotics appears on average 3-5 days after the start of parenteral treatment.

Preference should be given to agents with different forms of administration (parenteral, oral) using a "staged" therapy scheme.

In most cases, preference should be given to monotherapy, its advantages include adequate interaction of antibacterial drugs, unwanted interactions with other drugs, reduction of the risk of developing toxic events, and simplification of medical work. reducing staff and treatment costs.

According to the recommendation of the European guidelines for the clinical evaluation of anti-infective drugs, it is recommended to continue treatment for 3-5 days after achieving stable normalization of temperature in patients with pneumonia with normal immunity. The duration of antibiotic therapy with this approach is usually 7-10 days. The following point should be considered important: after achieving the initial effect, it is not recommended to change antibiotics within the prescribed period of treatment. The duration of antibacterial therapy for complicated community-acquired pneumonia is determined individually. The main criterion for stopping antibiotic therapy is persistent apyrexia

(3-4 days in a row). Preservation of individual clinical, laboratory and/or radiological symptoms of the disease is not an absolute indicator to continue or change antibacterial therapy.

In most cases, their disappearance occurs by itself or under the influence of symptomatic therapy. If within 48-72 hours after the start of treatment, the continuation or development of clinical manifestations of the disease, the appearance of new focal infiltrative changes in the lungs, the selected antibacterial therapy scheme is considered ineffective. is replaced by an alternative (taking into account the in vitro determination of the sensitivity of the isolated culture of the pathogen to antibiotics).

Patients aged 60 and older and/or concomitant diseases (diabetes, chronic kidney failure, congestive heart failure, chronic liver disease, mental illness, alcoholism, etc.);

patients with clinically severe pneumonia, regardless of age.

In the first group of patients, a clear clinical effect can be achieved by oral administration of antibacterial drugs. Aminopenicillins (amoxicillin is better than ampicillin in terms of pharmacokinetic parameters) and macrolides are recommended as the drugs of choice. To date, differences in the effectiveness of these groups, as well as individual representatives of macrolide antibiotics, have not been identified. Doxycycline is recommended as an alternative.

In the second group of patients, a clear clinical effect can be achieved by oral antibiotic treatment. Since the possibility of the etiological role of gram-negative microorganisms (including those with some mechanisms of resistance development) is increasing in elderly patients or people with concomitant diseases, "protected" aminopenicillins (ampicillin / sulbactam, amoxicillin / clavulanate) or selfosporins. the second type is recommended as a means of selection (cefuroxime axetin). Given the possibility of chlamydia or legionella infection in this group of patients, combined treatment with macrolide antibiotics seems justified.

The drugs of choice in severe community-acquired pneumonia are third-generation cephalosporins without antipseudomonal activity (cefotaxime or ceftriaxone, maximum doses are recommended) together with macrolides (erythromycin, spiramycin) for parenteral administration.

The above combination covers almost the entire spectrum of potential etiological agents of severe community-acquired pneumonia - both "typical" and "atypical".

Chest radiographs of patients with pneumonia

In Russia, severe community-acquired pneumonia is often treated with a combination of β-lactams and aminoglycosides, which is not considered sufficiently proven. Aminoglycoside antibiotics are inactive against pneumococci and atypical pathogens, and have little activity against staphylococci. When arguing about the use of such a combination, they usually mean the possibility of expanding the scope of the combination, demonstrating synergy and overcoming possible resistance. There are objections to each of these arguments.

If gram-negative aerobic microorganisms are sensitive to third-generation cephalosporins, the addition of aminoglycosides does not increase the clinical effect. The idea of a high frequency of synergism between β-lactams and aminoglycosides is somewhat exaggerated.

Resistance of gram-negative aerobic microorganisms to third-generation cephalosporins is now almost always associated with resistance to gentamicin and tobramycin (at least in Moscow).

Thus, it is unrealistic to eliminate possible resistance when using such combinations. An additional argument against the widespread use of aminoglycosides is that their use should be accompanied by monitoring of renal function and hearing.

Thus, it is clear that there is no substantial evidence in favor of the widespread use of aminoglycosides for the empiric treatment of severe community-acquired pneumonia, which, of course, does not exclude their use according to indications.

For many years in our country, intramuscular injection of penicillin was used in the empiric treatment of pneumonia, but the change in the spectrum of pathogens with a high percentage of Haemophilus influenzae, mycoplasma and other bacteria not sensitive to penicillin forced us to reconsider. antibacterial therapy tactics. The emergence of penicillin-resistant strains of pneumococci, as well as the need to administer penicillin every 3-4 hours, requires a change in the first-line drug for the treatment of ambulatory pneumonia.

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БЎШЛИҒИ МУКОЦИЛИАР ТРАНСПОРТИ НАЗОРАТИ ТЎҒРИСИДАГИ ЗАМОНАВИЙ ҚАРАШЛАР (адабиётлар шарҳи). JOURNAL OF BIOMEDICINE AND PRACTICE, 7(2).

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