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Pharmacoepidemiological Basis of Antibacterial Drugs in Pneumonia outside the Hospital

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Abstract: The etiology of CAP is directly related to the normal microflora of the "non-sterile" parts of the upper respiratory tract (oral cavity, nose, oropharynx and nasopharynx). Of the many types of microorganisms that colonize the upper respiratory tract, only a few can cause an inflammatory reaction by penetrating the respiratory parts of the lungs, even with a minimal violation of protective mechanisms. Typical bacterial pathogens of SAP.

Key words: Legionella, Mycoplasma pneumoniae, Moraxella (Branhamella) catarrhalis, Haemophilus influenzae, Streptococcus pneumoniae.

- Streptococcus pneumoniae - gram-positive cocci, the most common cause of pneumonia in all age groups (30% or more of all cases);
- Haemophilus influenzae - gram-positive bacilli responsible for the development of pneumonia in 5-18% of adults, often in smokers and patients with chronic obstructive bronchitis;
- Moraxella (Branhamella) catarrhalis - Gram-negative coccobacilli, an insignificant cause of pneumonia (in 1-2% of patients), usually of etiological significance in patients accompanied by chronic obstructive bronchitis.

Other frequently identified etiological agents of CAP differ from the microorganisms listed above with slightly different pathogenicity and biological characteristics. Asymptomatic colonization of the upper respiratory tract by these microorganisms is unlikely.

Since the 1940s, the term "atypical pneumonia" has been used to refer to interstitial or segmental lung disease that is milder than typical pneumococcal lobar pneumonia. Later, pneumonia with an unusual clinical appearance, which can occur in a muted form or with a clear intoxication syndrome, began to be considered atypical. In some cases, atypical pneumonia is also understood as viral pneumonia in the countries of Indochina, but in clinical practice, pneumonia caused mainly by microorganisms of intracellular localization: mycoplasma, chlamydia and legionella is of great importance.

The main methods of infection by microorganisms in SAP caused by atypical pathogens are aspiration of the contents of the oropharynx and inhalation of microbial aerosol in Legionella pneumonia. Under normal conditions, a number of microorganisms, such as S. pneumoniae, can colonize the oropharynx, but the lower respiratory tract remains sterile. Microaspiration of oropharyngeal secretions is a physiological phenomenon observed in 70% of healthy people, mainly during sleep. At the same time, the coordinated work of mucociliary cleaning, lactoferrin, lysozyme, interferon, and the bactericidal effect of class A secretory immunoglobulin found in bronchial secretions prevent the adhesion and colonization of microorganisms and the subsequent development of CAP.

Let's look at some biological features of atypical CAP triggers.

Mycoplasma pneumoniae is a microorganism without an outer membrane, which determines its natural resistance to β-lactam antibiotics; it is characterized by close contact with the membrane of eukaryotic cells (membranotropic pathogen), intracellular localization is possible.

Chlamydia pneumoniae is a microorganism that is only an intracellular parasite, similar in structure to gram-positive bacteria; causes pneumonia, usually not severe, in 2-8% of cases. Information is collected on the frequent isolation of this microorganism together with other "lung" pathogens.

Microorganisms of the genus Legionella are gram-negative bacilli that are obligate pathogens. Legionella spp. (mainly Legionella pneumophila) is a rare causative agent of SAP (2-10%), but Legionella pneumonia is the second most common cause of death (after pneumococcus).

The frequency of mycoplasma pneumonia increases during epidemics, which are repeated every 4-5 years, and in the autumn-winter period, pneumonia may account for an average of 20% of the total number. This pathogen is more likely to cause disease in young people. The clinical presentation usually includes fever, pharyngitis, myalgia, asthenia, and extrapulmonary complications. The disease can heal on its own within 1-2 weeks, but often lasts 4-6 weeks. and is accompanied by all its characteristic manifestations, including cough with mucous sputum. Cultural diagnosis of mycoplasma infection is difficult. The diagnosis can be confirmed by detecting a 4-fold seroconversion of mycoplasma-specific IgM antibodies using the Elisa test.

Pneumonia caused by chlamydia became known relatively recently. Cl. pneumoniae causes infection in at least 10% of young patients. The clinical presentation of this infection includes pharyngitis and laryngitis, in addition to the specific manifestations of bronchitis and pneumonia. Common symptoms are hoarseness, low-grade fever, and a persistent cough that is often dry and sputum is usually non-mucous and purulent. In patients with bronchial asthma, chlamydia infection often leads to exacerbation of asthma attacks. Bronchial inflammation caused by chlamydia usually occurs in young patients and is rarely observed in old age. The diagnosis can be confirmed by seroconversion data, the Elisa test is the most modern. Currently, polymerase chain reaction (PCR) is used to diagnose mycoplasma and chlamydia infections.

Pneumonia caused by L. pneumophila is not a common cause of SAP, but is usually characterized by a severe course, development of a systemic inflammatory response, and extrapulmonary symptoms. Rifampicin, often used in combination with macrolides, has the highest natural activity against Legionella. Atypical CAP

clinical and radiological signs Large multicenter studies based on the principles of evidence-based medicine have reliably shown that in many cases it is not possible to speak sufficiently based on the analysis of the clinical and radiological appearance of the disease. Level of confidence in the probable etiology of CAP. In particular, the division of CAP into typical (for example, pneumococcal) and atypical (mycoplasma or chlamydia) is not of particular clinical importance, because it does not affect the choice of the initial antibiotic for empiric therapy. At the same time, some features of atypical CAP were noted: the formation of destroyed spaces in the lungs that are not typical for pneumococcal, mycoplasma and chlamydial pneumonia, on the contrary, staphylococcal infection, aerobic gram-negative enterobacteria and anaerobes shows; reticulonodular infiltration in the basal parts of the lungs is characteristic of mycoplasma pneumonia (in 20% of cases, mycoplasma pneumonia may be accompanied by focal confluent infiltration in the projection of several segments or even lobes). Laboratory diagnosis of atypical CAP

Serological diagnosis of infections caused by M. pneumoniae, C. pneumoniae and Legionella spp is not included among mandatory research methods, as the need for repeated sampling of blood serum in the acute period of the disease and in the recovery period is taken into account. a few weeks from the onset of the disease), the epidemiological level of the diagnosis, not the clinical one. Recently, the enzyme-linked immunosorbent test has become widespread - with the detection of a specific soluble antigen of L. pneumophila (serotype 1) in urine, but in our country the use of these rapid diagnostic methods is used only in certain clinics. centers.

Currently, the PCR method is promising, it is used to diagnose pathogens such as Cl. pneumoniae and M. pneumoniae. However, the role of the PCR method in diagnosis has not yet been determined and it cannot be recommended for widespread clinical practice.

In foreign medical practice, there is the following algorithm for laboratory diagnosis of SAP caused by atypical pathogens: when the patient is admitted to the hospital, a blood serum sample should be taken and kept frozen for serological examination. In severe CAP, ineffectiveness of β-lactam antibiotics, the presence of epidemiological risk factors, as well as in other cases where a precise etiological diagnosis is necessary, a repeated serum sample is taken and examined after 7-10 days. simultaneous detection of increased antibody titers to "atypical" (legionella, mycoplasma, chlamydia, etc.) pathogens. For the same indications and if available, additional diagnostic methods are used, including detection of Legionella antigen in urine, PCR (according to the recommendations of the British Thoracic Society).

Treatment of atypical CAP

In our country, despite the widespread introduction of standards for the treatment of SAP at the outpatient stage, a very high percentage of hospitalization of patients remains - 50% of patients who are sick at home are admitted to inpatient treatment. This is almost double the global figure. Such a negative situation may occur for the following reasons:

- availability and availability of a large number of non-prescription drugs in the pharmacy network, patients can take them as an alternative to antibiotics;
- stereotypes established among local therapists for the treatment of pneumonia and compliance with modern recommendations [3].

The analysis of empirical antibacterial therapy for CAP on the example of a multidisciplinary medical institution in Moscow showed that the financial costs of patients whose AT met modern recommendations were much lower than the costs of patients whose treatment did not meet modern standards and recommendations. [4]. Penicillin, amoxicillin, cefazolin, gentamicin and lincomycin are unreasonably often prescribed by many local doctors. It was found that in the treatment of SAP, gentamicin was prescribed in 40% of cases, cefazolin at a daily dose of 2.0 g/day in 30%, amoxicillin in 16%, and a combination of amoxicillin and cefazolin. only in 14% of cases. In addition, monotherapy with "traditional" APs was prescribed in 86% of cases (Figure 1).

Currently, the variety of forms of release of modern drugs allows the doctor and the patient to have the opportunity to choose the most convenient drugs from a practical point of view. Among antibacterial drugs, macrolides are in wide demand in the retail and hospital sectors of the pharmaceutical market [7,8]. Ease of use, broad spectrum of antibacterial activity, bactericidal effect, clinical effectiveness, possibility of use in many infectious diseases, relatively favorable safety profile and pharmacoeconomic component of the treatment process, due to its availability in the pharmacy sector for the end user. (RX drug group), drugs of this category are included in the top 10 sales of Russia.

In this regard, when choosing a particular drug, it should be taken into account that the price of azithromycin in the modern pharmaceutical market is very diverse: from expensive original drugs to cheaper generics, some of which are also of good quality [10]. This ensures the availability of drugs of this group for all segments of the population. In recent years, the emergence of many generic drugs of azithromycin has led to a decrease in the course of treatment and the widespread use of this drug in outpatient practice. However, when prescribing treatment for a patient, the doctor pays attention not only to the price of the drug, but also to the personal experience of its use. One of the popular antibiotics in Russia is Azitral® produced by the pharmaceutical company Shreya Life Sciences Pvt. Ltd." (India).

Azithromycin drugs are characterized by the presence of various dosage forms on the market, including 250 and 500 mg capsules (Table 1). This is due to the wide antibacterial spectrum and the low level of resistance of pathogens to it (for example, in Russia, in contrast to the countries of

Western Europe, the USA and Southeast Asia, a favorable situation remains with the sensitivity of pneumococci to macrolides, and today they are cell is almost the only group of antibiotics to which infectious agents are highly sensitive). Therefore, due to its pharmacokinetics (high pulmonary deposition) and good tolerance, azithromycin is the drug of choice for the treatment of "atypical" (mycoplasma, legionella, chlamydia) pneumonia, which accounts for more than 30% of cases. All cases of CAP.

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.

One of the most important problems of antimicrobial therapy is the widespread practice of using antimicrobial agents without appropriate indications. According to pharmacoepidemiological studies, 20 to 50% of antibiotic prescriptions worldwide are inappropriate, and such prescriptions are often used for community-acquired URTIs. This problem is also relevant for Russia.

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].

The average age of the patients included in the study was 39.8±5.7 years, most of them were men - 74%, women - 26%. Antibiotics were used in 85.7% (490 patients with OB) of 572 cases of pharmacotherapy for OB. Thus, in Nizhny Novgorod (n=237) AMP was prescribed in 84% of cases, in St. Petersburg (n=200) and Moscow (n=108) in 88.5 and 81.5% of cases, respectively. All patients with OB in Kazan (n=27) were treated with antibacterial therapy. The most commonly used AMPs were the following groups: macrolides in 45.8% of cases, "inhibitor-protected" penicillins - in 43.7%, fluoroquinolones (ciprofloxacin) - in 4.9% (Figure 1). The use of doxycycline was less frequently reported - 1.6% of cases, amoxicillin - 1.8%, ampicillin - 2.2%. Among macrolide antibiotics, azithromycin was prescribed most often - in 33.7% of cases, clarithromycin and erythromycin were used less often - in 8.6 and 3.5% of cases, respectively.

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. It is known that a serious error in the treatment of CAP in outpatient practice is the use of gentamicin, co-trimoxazole, ciprofloxacin (Table 1) [7].

According to large-scale pharmacoepidemiological studies devoted to the analysis of pharmacotherapy of CAP in different cities of the Russian Federation, gross errors in the treatment of CAP both in outpatient practice and in the hospital remain [7,12,24-27]. It should be noted that such monitoring studies are of particular interest, as they allow the analysis of changing stereotypes among doctors in the selection of AMP, as well as the evaluation of the effectiveness of administrative and educational measures aimed at optimizing therapy. Thus, in 2003–2004 compared to 1998. A significant increase in the use of amoxicillin (from 1.2 to 24%), a simultaneous decrease in the use of ampicillin, frequent prescription of macrolides - from 12.5 to 21.4%. Overall, the frequency of use of gentamicin (from 29.3 to 4.1%) and co-trimoxazole (from 22.7 to 1.2%) decreased significantly between 2003 and 2004. At the same time, there was a significant increase in the use of ciprofloxacin - from 1.4% in 1998 to 10.1% in 2003. The

prescription of AMP combinations for non-severe forms of SAP decreased from 16.4% (1998) to 7.7% (1998). 2003-2004), but in most cases the choice of AMP for combination therapy remained. illogical. Combinations of aminopenicillins and ciprofloxacin with gentamicin have often been used. The frequency of parenteral antibiotic use for non-severe CAP averaged 29%.

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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