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# Pharmacoepidemiological Effects of Antibacterial Drugs for Community-Acquired Pneumonia in Children of Different Ages in a Modern Interpretation

**Kodirova Shakhlo Salokhitdinovna**
Assistant, Department of Pediatrics, Samarkand State Medical University

***Abstract:*** The article presents the main goals of antibiotic therapy and its indications in acute respiratory viral infections. Literature data on the modern spectrum of pathogens of bacterial foci of the lower respiratory tract (bacterial bronchitis and pneumonia) in children are presented. The spectrum and mechanisms of antibiotic resistance of isolated pathogens are listed. A brief overview of the pharmacological properties and sensitivity of antibacterial drugs of the main groups recommended for the treatment of lower respiratory tract diseases in children is given - semi-synthetic aminopenicillins, drugs protected by inhibitors, cephalosporins, macrolides. Local algorithms of antibacterial therapy for bronchitis and pneumonia are presented, which are based on the principles of evidence-based medicine. The advantages of the soluble oral form of antibacterial drugs - Solutab dispersible tablets, which have high bioavailability, efficacy and safety, are named.

***Key words:*** early diagnosis of Mycoplasma pneumoniae, pneumoniae, Haemophilus influenzae.

## Login

As is known, antibacterial therapy is used for inflammatory diseases of an infectious nature. The triumphant march of antibiotics began in the 1940s and 1970-90s. The whole world has become accustomed to the use of many modern antimicrobial drugs - aminopenicillins protected by inhibitors, III- It marked the introduction of fourth-generation cephalosporins, carbapenems, fluoroquinolones, macrolides, and others into clinical practice.

Antibiotics are used in various fields of medicine all over the world. Their choice is huge. The International Alliance for the Rational Use of Antibiotics (APUA) has registered more than 600 trade names on the world market. In Russia, about 200 (excluding generic names) are used. Nevertheless, the development of new antibiotics continues. True, over the past decade, the pharmaceutical industry has registered and brought to the market only a few.

One of the current problems associated with antibacterial therapy is the widespread practice of unjustified frequent use of antibiotics. According to many studies, up to 75% of patients with acute respiratory infections (ARI), while the viral nature of ARI accounts for 85-95%. Antimicrobial drugs are often prescribed without appropriate indications and are used irrationally (without taking into account the spectrum of the most important pathogens and information on antibiotic resistance, pharmacokinetics and safety profile). In addition, parenteral antibiotics are often prescribed unjustified to outpatients, which makes it difficult to adhere to the drug regimen and reduces patient compliance with treatment [2].

Another problem, as shown by the results of pharmacoepidemiological studies [3], is the widespread practice of self-medication, purchasing antibacterial agents in pharmacy chains without first consulting a doctor.

**Diagnostic check**

The emergence of new drugs, new information about the clinical and pharmacological properties of previously known drugs, and the dynamics of resistance of key microorganisms to antibacterial drugs require a change in approaches to the treatment of infectious diseases.

There are two approaches to treatment - etiotropic and empirical. In both outpatient and inpatient settings, the clinician usually uses the empirical approach.

Russian recommendations for antibacterial therapy [2, 4-10], reflecting current international trends and treatment standards, are based on evidence from meta-analyses of multicenter clinical trials. They identify priority drugs (selected drugs) that should be prescribed first and alternative drugs that should be used in case of ineffectiveness or poor tolerability of the selected drug, or if it is impossible to prescribe it.

The choice of antibacterial therapy is based primarily on the diagnosis. It is also necessary to know the spectrum of pathogens most often detected in this pathology, the presence of underlying diseases in the patient, information about previous antibacterial therapy for this treatment, as well as the specific characteristics of the drugs (efficacy, safety, the possibility of compliance with the regimen or the use of the drug, which is especially necessary in pediatric practice). The clinician, who focuses primarily on the effectiveness of the treatment, must always rely on a high level of compliance with the treatment by the patient himself.

Lower respiratory tract infections in children include acute bronchitis and pneumonia. Acute bronchitis is usually caused by respiratory viruses and does not require antibiotic therapy. Bacterial bronchitis is often considered a complication against the background of severe bronchial obstruction (foreign aspiration, stenosing laryngotracheitis), hereditary lung diseases (cystic fibrosis), or bronchial malformations. In children with frequent illnesses, which changes the microbial picture of the nasopharyngeal mucosa, there is a mixed viral-bacterial nature of bronchitis. In pediatric practice, the etiological spectrum of acute bacterial bronchitis is mainly represented by Streptococcus pneumoniae (45-50%), Haemophilus influenzae (17%), less often Moraxella catarrhalis, and intracellular pathogens Mycoplasma pneumoniae , pneumoniae (%17) and pneumonia (%17). [11].

Pneumonia, according to modern views, represents a group of acute infectious diseases that differ in etiology, pathogenesis and morphological features [12-14]. According to official statistics, the incidence of pneumonia in different age groups is about 4%, which, most likely, does not reflect the real picture. Pneumonia is a life-threatening condition. In Russia, about 1000 children die from community-acquired pneumonia per year, and from 1% to 5% are treated at home [15]. From a practical point of view, it is important to divide pneumonia into community-acquired and nosocomial (hospital-acquired). In daily practice, doctors mainly encounter community-acquired pneumonia, in which a child becomes infected in normal conditions (outside a medical institution). The etiology of community-acquired pneumonia largely depends on the child's age, time of year and premorbid background. Community-acquired pneumonia is mainly the result of activation of the bacterial microflora of the child's oropharynx. External infection is less common.

Community-acquired pneumonia in children under 6 months of age often develops against the background of cystic fibrosis, habitual food aspiration, primary immunodeficiency and is caused by gram-negative intestinal flora ( Escherichia coli , Klebsiella pneumoniae ) and Staphylococcus aureus . Atypical pneumonia caused by Chlamydia trachomatis is more common (the child is infected intrapartum, the disease manifests itself after 1.5-2 months). Pneumonia in premature infants can be caused by opportunistic microflora and Pneumocystis carinii . In children who have become ill as a result of contact with a patient with ARVI, pneumonia can be caused by typical pneumotropic flora S. pneumoniae and H. influenzae (10%). The main causative agent of community-acquired pneumonia in children aged 6 months and older at all ages is S. pneumoniae (35–50%), less frequently H. influenzae (7–10%), and M. catarrhalis (5–10%). In school-aged

children, the incidence of atypical pneumonia caused by M. pneumoniae and C. pneumoniae is increasing (15–32%) [12–14].

The prognosis of bacterial respiratory infections depends to a large extent on timely and adequate antibiotic therapy. Diagnostic studies (X-rays, laboratory tests) should not lead to the initiation of antibacterial treatment without delay. Current recommendations call for early antibiotic administration: in the first four hours in outpatient settings, and immediately after admission to the hospital in patients hospitalized for community-acquired pneumonia.

**Increasing resistance of microorganisms as a result of aggressive antibiotic therapy**

The causative agent of community-acquired pneumonia is usually highly susceptible to antibacterial drugs. The increasing resistance of microorganisms to antibacterial drugs is of great concern to clinicians [16]. The emergence and development of resistance is a natural response to the widespread, sometimes aggressive use of antimicrobial drugs. The result is the mutation of microorganisms, the selection and reproduction of resistant strains. Infections caused by resistant strains are more severe, often require hospitalization, and worsen the prognosis of the disease. The susceptibility of pathogens to antibiotics depends on both their genetic characteristics and previous contact with antibiotics. The mechanisms of defense of microorganisms against antibiotics are diverse [3, 17]. The most relevant mechanism of resistance for the group of beta-lactam antibiotics is their inactivation by hydrolysis of one of the bonds of the beta-lactam ring by beta-lactamase enzymes. To date, 500 beta-lactamases of four molecular classes are known. Despite the widespread distribution of bacteria producing beta-lactamases, they do not pose a serious problem for treatment with modern beta-lactam antibiotics - aminopenicillins and carbapenems - protected by cephalosporins of the III-IV generation. These groups of drugs are not susceptible to hydrolysis. Another mechanism of resistance to beta-lactams is a change in the target of action, namely a decrease in affinity for proteins involved in bacterial cell wall synthesis (BCW), resulting in an increase in the minimum inhibitory concentration (MIC) and a decrease in the effectiveness of beta-lactams. Resistance of pneumococci to beta-lactams occurs due to mutations in the KSB genes. H. influenzae and M. catarrhalis

Resistance to beta-lactams is associated with the production of beta-lactamases. However, H. influenzae strains have a target of action with one modification - beta-lactamase-negative ampicillin resistant, respectively, resistant to inhibitor-protected beta-lactams. The main target of macrolide action is the 50S subunit of the bacterial ribosome. The antimicrobial effect is associated with the disruption of protein synthesis in the ribosomes of the microbial cell. Most gram-positive and gram-negative bacteria are protected from macrolide antibiotics by modifying the target of action, mainly as a result of its methylation. In addition, 16-membered macrolides are most protected from various types of methylases of certain bacteria. The genes for these enzymes are localized on plasmids, which contributes to the destructive spread of resistance. In recent years, selective resistance to 14- and 15-membered macrolides has increased. Restricting the use of drugs has little effect in combating plasmid-borne spread of resistance.

**Choosing drugs for initial therapy**

Due to the catastrophic decline in the susceptibility of microorganisms to current antimicrobial drugs, certain rules for prescribing antibiotics should be followed to prevent the selection of multidrug-resistant strains of microorganisms. Particular attention should be paid to the choice of drug for empirical initial therapy, the dosage regimen, and the patient's compliance with medical instructions.

Local recommendations for the selection of the initial antibacterial drug in the treatment of lower respiratory tract diseases in children have been developed taking into account the age of the child and the form of the disease [1-10]. Semi-synthetic aminopenicillins, drugs protected by inhibitors and macrolides are recognized as the first-choice drugs. Antibacterial therapy should begin with the oral form of amoxicillin, which is effective against the main causative agent of bacterial bronchitis and community-acquired pneumonia S. pneumoniae. According to the data of the local large-scale

study PeGAS (1999-2009) [18, 19] in Russia, 99.6% of S. pneumoniae strains are susceptible to amoxicillin. Therefore, in most cases, the choice of therapy is effective and sufficient. Beta-lactams protected by inhibitors have no advantage, since streptococci do not produce beta-lactamases. High activity against the main pathogens S. pneumoniae , H. influenzae (strains that do not produce beta-lactamases), low levels of secondary resistance, good safety profile, proven efficacy in controlled clinical studies, optimal price / effectiveness ratio make amoxicillin in Russia the drug of choice, that is, the initial drug for most bacterial infections of the upper and lower respiratory tract. The usual dose for children is 30-60 mg / kg per day, divided into two or three doses.

Indications for initial monotherapy with macrolides are beta-lactam intolerance, atypical infection, and mixed infection. In the latter case, a combination of macrolides and beta-lactams is possible [20, 21]. The advantages of modern macrolide antibiotics include the rapid achievement of high drug concentrations in the focus of inflammation, several times higher than serum concentrations, and their effect on biofilms with suppression of bacterial adhesion. Macrolides are able to stimulate certain components of the immune system. By the way, among the macrolides used in Russia, josamycin (Vilprafen) has the highest activity against S. pneumoniae. Currently, macrolides are considered the safest group of antibiotics.

If the child has ENT pathology or chronic bronchopulmonary diseases, as well as a course of antibiotic therapy within the previous three months, protected aminopenicillins of the II-III generation or cephalosporins that are effective against pneumococcus and hemophilic rod are prescribed. A combination of modern macrolides and beta-lactams is indicated.

In the event of bacterial superinfection against the background of influenza, it is indicated to start antibiotic therapy with a course of beta-lactams (aminopenicillins, cephalosporins of the II-IV generations).

The effectiveness of antibiotic therapy is assessed by the improvement of the general condition after 36-48 hours, the appearance of appetite, a decrease in body temperature, a decrease in shortness of breath, and the absence of negative dynamics in radiological data. The effect of treatment occurs quickly, usually in 85-90% of cases. If treatment with the initially selected antibiotic is ineffective, it should be replaced with a drug selected from another group or alternative drugs of the 2nd and 3rd line, which are the most expensive and sometimes have a lower safety profile.

In cases of severe illness or when oral antibiotics are not possible (often temporary) (vomiting, cough due to intoxication), stepwise therapy is recommended. This therapy involves a two-stage administration of the antibiotic, starting with parenteral administration (intravenous drip, intramuscular injection) with a transition to oral administration after the patient's clinical condition has stabilized. The optimal option for stepwise therapy is the sequential use of two dosage forms of the same antibiotic (for parenteral and oral administration) [22-24]. In pediatrics, the economic benefit and psychological relief for the patient are obvious.

Note: Penicillins and cephalosporins are drugs with a time-dependent antimicrobial effect. That is, it is important to maintain a concentration in the blood serum and at the site of infection that is 3-4 times higher than the MIC for 40-60% of the time interval between doses. Moreover, increasing the concentration (dose) of the antibiotic does not affect its effectiveness. In this regard, it is very important to adhere to the drug intake and dosage regimen [3].

**The bioavailability of a drug is an important pharmacokinetic parameter**

For oral antimicrobial drugs, such a pharmacokinetic parameter as bioavailability is important. Modern dosage forms are characterized by high bioavailability. Thus, if the bioavailability of amoxicillin in tablets or capsules is about 75-80%, then in a special soluble form of Solutab it exceeds 90% [25]. Innovative technologies are used in the production of Solutab dispersible tablets: first, the active substance is contained in microgranules, then a tablet is formed from the microgranules, which completely dissolve (due to nanofiltration, there are no impurities in the active substance antibiotic). Microgranules protect the drug from the effects of hydrochloric acid in the stomach. The release of the antibiotic from microgranules occurs only in the small intestine

when exposed to alkaline juice. The released microgranules are evenly distributed over the surface of the intestinal epithelium and provide the maximum absorption area. Due to the rapid and complete absorption of the antibiotic, it practically does not remain in the intestines, which significantly reduces its irritating effect on the mucous membrane. Moreover, the vital activity of normal microflora is not inhibited.

The controlled release of the antibiotic in the intestines ensures taste masking, and the quality of the flavors reduces the likelihood of developing allergic reactions, which is important when treating children.

The dispersible tablet contains a minimal amount of filler and does not contain sugar or gluten, which does not limit antibacterial therapy in children with underlying pathology. The complete and time-stable dissolution of the Solutab dispersible tablet in a glass of water at room temperature (50–55 seconds) allows the patient to visually verify the authenticity of the antibiotic when preparing the solution, which serves as a guarantee of quality.

The advantage of the Solutab dispersible tablet dosage form is that it provides a variety of administration methods depending on the situation, the patient's age and personal preferences, which increases compliance with therapy. The Solutab dispersible tablet can be swallowed whole, broken into pieces, chewed, prepared into syrup or dissolved in water to form a pleasant-tasting suspension. Regardless of the chosen route of administration, the pharmacokinetic properties and clinical efficacy of the drug remain unchanged, since the adsorbed dose corresponds to the dose taken.

Amoxicillin is absorbed in the intestine by 93%. The addition of potassium clavulanate effectively protects amoxicillin. Clavulanic acid is an unstable molecule, and when stored in a dissolved state, its concentration decreases [26, 27], which reduces the protective effect of amoxicillin in the drug against beta-lactamases. Solutab technology has improved the pharmacokinetic parameters of amoxicillin and clavulanic acid: bioavailability is increased, absorption variability is reduced. In addition, due to the low residual concentration of the active substance in the intestine and the minimal residence time of amoxicillin and potassium clavulanate, Flemoclav Solutab is well tolerated and has little effect on the normal intestinal microflora. The effectiveness of Flemoclav Solutab reaches 95.9%, the number of adverse reactions is half that of standard forms of amoxicillin / clavulanate.

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