ETIOTROPIC TREATMENT OF PNEUMONIA IN CHILDREN AT THE CURRENT STAGE

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Annotation.

Etiotropic treatment of any disease requires, first of all, knowledge of the pathogen and its sensitivity to antibiotics. Since, when meeting with an acute patient, the doctor cannot delay the start of treatment until these issues are clarified, his empirical prescriptions should be carried out taking into account the likelihood of a particular pathogen and its sensitivity. Recent work has shown that the accuracy of the empirical choice of an antimicrobial drug can be very high (80-70%) when taking into account a number of obvious factors [1].

When addressing this issue, one should first of all take into account where the pneumonia developed, since in terms of etiology, community-acquired ("home-acquired", community-acquired) pneumonia is fundamentally different from hospital-acquired pneumonia. The latter also includes cases of pneumonia developing in a child recently (less than 7 days) discharged from the hospital, as well as in a child receiving antibiotics at home. A special case is pneumonia in people with immunodeficiency, which is distinguished by both its particular severity with "common" pathogens and the participation of opportunistic flora. The Classification of Nonspecific Respiratory Diseases in Children [2] lists the probable causative of pneumonia of these main groups, however, to narrow the range of possible causative agents, it is advisable to supplement these data with two other characteristics - age and the nature of pneumonia.

Community-acquired pneumonia

Pneumonia is common in children of all ages, but their etiology can differ significantly. Taking into account age allows you to significantly narrow the range of likely pathogens of pneumonia and thereby increase the accuracy of the empirical choice of antibiotic.

The choice of drug is greatly influenced by the type of pneumonia, determined by fairly clear clinical and (or) radiological criteria. In children in the first 6 months of life, it is easy to distinguish pneumonia that occurs without fever (afebrile) from "classic" pneumonia, accompanied by febrility; Radiologically, the latter appear as focal, segmental or confluent, while afebrile forms typically have diffuse damage to both lungs. At an older age, it is also easy to distinguish atypical forms, accompanied by an abundance of wheezing (previously called bronchopneumonia) and inhomogeneous changes on the radiograph, from pneumonia with pronounced

percussion changes in the absence or a small amount of wheezing and homogeneous focal , segmental or lobar shadows on the radiograph. In the 0-6 month age group, about 50% of pneumonias are of nosocomial origin, while community-acquired pneumonia is relatively rare [3]. They are usually associated with infection from a sibling or an adult and develop against the background of a respiratory viral infection, which obviously facilitates bacterial invasion. In 1/4 of children, pneumonia is associated with dysphagia and reflux, leading to habitual aspiration of food; in 7-10%, pneumonia is the first manifestation of a systemic disease, for example, primary immunodeficiency or cystic fibrosis. The causative agents are usually Staphylococcus aureus and Escherichia coli, less commonly Moraxella (Branchamella) catharalis. In children with habitual aspiration of food, in more than half of the cases, other representatives of the intestinal flora are also isolated, often with multiple resistance. In the first half of the year, the role of pathogens that cause pneumonia due to infection in the perinatal period is significant (18% in Moscow). Among them, chlamydial pneumonia is most often diagnosed, which occurs as afebrile, with diffuse changes on the radiograph. In rare cases, children born prematurely have a similar course of pneumocystis; In very premature infants, pneumonia caused by ureaplasma and Mycoplasma hominis has also been described, the diagnosis of which, however, has not been developed. In the second half of life, chlamydial pneumonia practically does not occur; aspiration pneumonia is less common, but nosocomial diseases continue to occupy a significant place (about 25%). Children 6 months - 4 years. In the case of community-acquired bacterial pneumonia, both according to our data [1] and according to joint studies in different cities of the country [4], the most common pathogen is pneumococcus. Pneumococcus is also the leader in older children, but the identification of this age group is justified by the fact that it is in this group that pneumonia caused by Haemophylus influenzae b is observed. An increase in the incidence of pneumococcal pneumonia begins at the end of the first year of life, which coincides with a drop to the lowest levels of titers of anti-pneumococcal antibodies received transplacentally by children [5]. During the 1st-3rd year of life, the incidence of pneumococcal pneumonia is maximum (13-25 per 1000 children per year), and among pneumonias complicated by destruction of lung tissue, pneumococcal pneumonia also predominates. The severity of such pneumonia may be associated with the virulence of the serotype (3, 5, 9), as well as with the absence of type-specific antibodies in the patient before the disease.

Table 1. Choice of starting antibiotic for nosocomial pneumonia

Therapy before pneumonia	Probable causative agent	Recommended drugs

Not conducted	Pneumococcus, mycoplasma	Penicillin, ampicillin intramuscularly or macrolide (midecamycin, etc.)
Penicillin, ampicillin	Staphylococcus, mycoplasma	Oxacillin, lincomycin, 1st generation cephalosporin or macrolide
1st generation cephalosporin, oxacillin, lincomycin	*E. coli* , other Gram-negative flora, resistant staphylococcus	*Amoxicillin/clavulanate* ; gentamicin or other aminoglycoside, 2nd-3rd generation cephalosporins, carbapenems, ticarcillin/, clavulanate, vancomycin
Gentamicin, other aminoglycosides	Pneumococcus, gram-negative flora, resistant staphylococcus	Penicillin, ampicillin, if there is no effect - ureidopenicillins, rifampicin, carbapenems, *ticarcillin/clavulanate* , vancomycin, aminoglycosides in high doses*
Aminoglycosides + cephalosporins 2-3rd generations	Resistant gram-negative flora, resistant staphylococcus	Carbapenems, *ticarcillin/clavulanate* , vancomycin, ureidopenicillins, rifampin, high-dose aminoglycosides*
** Gentamicin up to 15 mg/kg/day or amikacin 30-50 mg/kg/day*		

In combination with pneumococcus, non-capsular form *of Haemophylus influenzae is often encountered* , and although its role as a causative agent of pneumonia is not entirely clear, it is also desirable to take into account its sensitivity. Capsular form of *Haemophylus influenzae* type b is apparently not so common in the middle zone, but in Central Asia it causes more than 20% of destructive forms of pneumonia in young children. The significance of *Mycoplasma pneumoniae* as a causative agent of pneumonia in young children is apparently small, but this possibility should be taken into account during epidemic seasons (August-November). In preschool and especially school age, the significance of mycoplasmas increases, causing, according to estimates, about half of all pneumonias. In adolescents, the possible role of

Chlamidia pneumoniae as a causative agent of pneumonia (usually occurring with pronounced changes in the pharynx and, typically, with cervical non-purulent lymphadenitis) should be taken into account.

Hospital-acquired pneumonia

Hospital-acquired pneumonia is caused either by "hospital" strains of pathogens, usually highly resistant to antibiotics (staphylococci, klebsiella, pseudomonas, proteus), or by the autoflora of the patient himself. Their development is facilitated by antibacterial therapy administered to the patient, since it suppresses the usual pneumotropic flora, to which the child has a certain degree of immunity. As a result, this opens the way for the colonization of the lower sections of the respiratory tract by flora alien to it (usually intestinal).

Pneumonia in immunocompromised individuals

In humoral forms of immunodeficiency (usually primary), pneumonia is caused by the same pneumotropic flora as in healthy children, but, for obvious reasons, it is more severe and tends to recur. In patients with cellular forms of immunodeficiency, pneumocystis pneumonia is common (especially common in HIV infection), and less common (in transplant recipients) is pneumonia caused by cytomegalovirus. It is also necessary to keep in mind the forms caused by fungi or mycobacteria (BCG, Micobacteria avium).

Sensitivity of pneumotropic flora

Community-acquired pneumonia. Until recently, most pneumotropic strains circulating among the population were sensitive to the corresponding antibiotics. However, recently in many countries of the world there has been an increase in the resistance of pneumococci circulating among the population to penicillin [6,7], often also to macrolides, which is associated with the unjustifiably wide use of antibiotics, especially for ARVI. All penicillins, macrolides, lincomycin, rifampicin and cephalosporins are highly active against this pathogen, and gentamicin and other aminoglycosides are practically inactive. The sensitivity of pneumococcus to tetracycline is low, which does not allow creating a sufficiently high level of it in the blood and tissues.

Based on our own 15-year observations, we can say that the sensitivity of both capsular and non-capsular *Hemophylus influenzae* also remains at a sufficiently high level. Thus, 92, 77 and 98% of strains are sensitive to ampicillin, erythromycin and azithromycin, 91-96% to doxycycline and tetracycline, 97-100% to all aminoglycosides, 2nd and 3rd generation cephalosporins, rifampicin. However, with respect to this pathogen, we observe a decrease in sensitivity to penicillin (from 96 to 63%), cephalexin (from 63 to 12%), cefazolin (from 78 to 50%). *Hemophylus influenzae* is poorly sensitive to lincomycin, oxacillin, oleandomycin; roxithromycin and midecamycin suppress the growth of only 35-50% of strains of this pathogen.

Hemolytic streptococcus group A is highly sensitive to all antibiotics except aminoglycosides, streptococci of other groups are sensitive to oxacillin, 2nd and 3rd generation cephalosporins, lincomycin and rifampicin and somewhat less sensitive to other penicillins and macrolides. *Moraxella catharalis* is sensitive to macrolides, cephalosporins, aminoglycosides, rifampicin and is slightly sensitive to penicillins (except augmentin).

Table 2. Choice of drug for the treatment of community-acquired pneumonia

Age, shape	**Etiology**	**Starter drug**	**Replacement in case of inefficiency**
1-6 months, febrile , with infiltrative shadow	Staphylococcus, E. coli, etc. Gram-negative flora	Ampicillin with oxacillin, 3rd generation cephalosporin	Gentamicin with 1st generation cephalosporin; lincomycin
1-6 months, afebrile with diffuse process on radiograph	Chlamydia, less commonly pneumocystis, ureaplasma	Macrolides (midecamycin, etc.)	Cotrimoxazole
6 months-4 years, uncomplicated, homogeneous shadow on radiograph	Streptococcus pneumoniae, possibly also Haemophilus influenzae	Orally, penicillins (amoxicillin); macrolides; 1st generation cephalosporins	Orally: amoxicillin/clavulanate; 2nd-3rd generation cephalosporins. Parenterally: penicillin; chloramphenicol; 2nd-3rd generation cephalosporins.
4-15 years, uncomplicated, homogeneous shadow on radiograph	Pneumococcus;	Orally penicillins; macrolides; 1st generation cephalosporins	Parenteral penicillin; lincomycin; chloramphenicol
4-15 years, uncomplicated,	Mycoplasma, chlamydia pneumonia	Macrolide inside	Other macrolide; parenteral lincomycin

non-homogeneous shadow on radiograph			
6 months-15 years, complicated by pleurisy or destruction	Pneumococcus; rare: Haemophilus influenzae type B (up to 5 years), streptococcus (>6 years)	Parenteral penicillins; lincomycin; chloramphenicol	Cephalosporins of the 2nd-3rd generation (for hemophilus infection)

According to our clinical observations, erythromycin and other macrolides are quite active against mycoplasmas, and the same drugs, as well as co-trimoxazole, are active against chlamydia.

Evaluation of effectiveness

Evaluation of the effectiveness of the drugs administered to the patient is the only way to decide whether it makes sense to continue treatment with an empirically selected drug or whether it should be changed. With a full effect, the temperature decreases within 24-48 hours, the general condition improves, pneumonic changes decrease or, at least, do not increase (the number of wheezes may increase). In these cases, no drug change is required, and it is better to replace the parenteral drug with an oral one.

In some cases, the results of treatment may be less noticeable due to the persistence of temperature and intoxication. If this is due to the presence of a destructive focus in the lung, a drop in temperature can be expected only after its emptying (through the bronchus or into the pleural cavity). With the development of an immunopathological complication (metapneumonic pleurisy), febrile temperature ("germ-free fever") can last for a week. Nevertheless, in these cases it is important to identify signs of a partial effect (improvement of condition and appetite, reduction of pneumonic infiltration, reduction of pleural exudate cytosis, etc.) and, refraining from unnecessary change of the drug, continue treatment, it is also better to replace parenteral drugs with oral ones. The lack of effect - maintenance of temperature and increase in pneumonic infiltration - allows to exclude the etiology that the doctor assumed when choosing this drug, and to prescribe an alternative scheme. Replacement or, at least, addition of a new antibacterial agent should be carried out after 36-48 hours (and in extremely severe infections - after 24 hours).

Selecting a specific antibacterial drug

We have about 200 antibacterial drugs available, sold under more than 600 brand names. In such a situation, the physician should be guided by the choice of drug, in

addition to its expected efficacy and potential toxicity for the child, convenience of use for the patient and cost.

Our observations have shown that the majority of uncomplicated community-acquired pneumonias can be cured with oral drugs of first choice, so that only in 10-15% of cases is it necessary to replace the empirically selected drug. In more severe cases, it is recommended to start treatment with a parenteral drug with a transition to an oral one when the effect is achieved. Newer drugs with a broader antimicrobial spectrum have to be selected for initial therapy only for the treatment of hospital-acquired pneumonia. The use of such often expensive drugs in most cases of community-acquired pneumonia is not required, especially since their widespread use contributes to the development of resistance of the pneumotropic flora circulating among the population. In young children, the most convenient oral forms are syrups, suspensions and solutions, which allow the required dose to be easily administered. However, these forms are more expensive, and not all of them are included in the lists for free treatment. Therefore, their use should be proportionate to the available financial resources. Provides general recommendations for choosing groups of drugs for the treatment **of community-acquired pneumonia** . As can be seen from the table, parenteral drugs are initially recommended to be administered only to children in the first 6 months of life and to older children with complicated forms. In all other cases, preference is given to oral drugs. It is important that the prescribed drug acts on coccal flora as the most likely in pneumonia; therefore, for example, prescribing one aminoglycoside is a gross mistake, since drugs of this group do not suppress the growth of pneumococcus. The leading factor in choosing a starting drug for **nosocomial pneumonia** is the treatment carried out before the onset of the disease; It is obvious that the pathogen of such pneumonia (whether we know it or not) will be resistant to the drugs of the group with which it was treated. Provides recommendations using this approach.

Penicillins occupy one of the leading places among drugs for the treatment of pneumonia: penicillin and ampicillin parenterally, benzathine-phenoxymethyl-penicillin and amoxicillin orally have proven their high efficiency. Oxacillin, on the contrary, should be used only against staphylococcus, since it has almost no effect on Haemophilus influenzae. For children recently treated with antibiotics, it is better to prescribe the so-called protected penicillins, for example, amoxicillin/clavulanate, which is resistant to lactamase due to the presence of clavulanic acid. Penicillins have a bactericidal effect on coccal flora that is slightly dependent on its concentration in tissues [8], so the doses of these drugs, as a rule, should not exceed 50-100 mg / kg / day, and if there is no effect, it is better to switch to parenteral drugs (penicillin, chloramphenicol, cephalosporins of the 2nd-3rd generations). When using sufficiently high single doses, penicillins accumulate well in tissues, which ensures the

maintenance of a bacteriostatic concentration for 8-12 hours, and this allows them to be administered no more than 2 times a day. **Carbenicillin and ureidopenicillins** (piperacillin, mezlocillin) are used in high doses (400-500 mg/kg/day) only for hospital-acquired infections. The same applies to **aztreonam, ticarcillin, carbapenems** (meropenem and imipenem).

Macrolides have high activity against both gram-positive and gram-negative coccal and bacterial flora, as well as against mycoplasmas and chlamydia (midecamycin is active against *Mycoplasma hominis*). This is especially valuable in the empirical selection of a drug for the treatment of pneumonia when the type of pathogen is not certain. They accumulate well in neutrophils, where they remain for a long time, exerting their bactericidal effect. The bactericidal activity of these drugs, as well as penicillins, depends little on their concentration in tissues [8], so that, given their moderately long post-antibiotic effect, they can be administered 2 times a day (azithromycin - 1 time per day).

Erythromycin base often causes dyspeptic phenomena, syrups with erythromycin esters (stearate, estolate, etc.) are more acceptable (but not in price). Oleandomycin causes fewer side effects, but does not affect Haemophilus influenzae. Josamycin, midecamycin, roxithromycin are effective against most forms. Erythromycin and azithromycin are most reliable in suppressing the growth *of Hemophylus influenzae* , but the latter is more expensive than other macrolides.

Lincomycin and clindomycin have pronounced activity against staphylococci and other gram-positive cocci, anaerobic cocci and bacteria, and also to some extent against mycoplasmas. Haemophilus influenzae is resistant to these drugs, which reduces their "universality".

Cephalosporins have no advantages over penicillins for community-acquired (sensitive) coccal flora; the use of oral forms of 1st generation cephalosporins is justified by their ease of use and relatively low cost, but they do not act on Haemophilus influenzae, mycoplasma and chlamydia, which reduces their attractiveness. Parenteral 1st generation cephalosporins (cefazolin) suppress the growth of penicillin-resistant (but not methicillin-resistant) staphylococci and are used in combination with gentamicin for severe pneumonia of unknown etiology. 2nd-3rd generation cephalosporins may be unreliable for coccal infection; they are used if a gram-negative pathogen is suspected. Ceftriaxone has a broader spectrum of action and is administered once a day. Ceftazidime and cefperazone should be reserved for pneumonia of Pseudomonas aeruginosa etiology. The pharmacodynamics of cephalosporins are similar to those of penicillins (bactericidal activity independent of concentration), so there is no point in increasing their doses and frequency of administration (more than 2 times, and for ceftriaxone - more than 1 time per day).

Aminoglycosides are active against gram-negative flora and staphylococci, but do not act on pneumococci, which makes them unsuitable for empirical monotherapy of acute pneumonia. In combination with b-lactam drugs (penicillins, cephalosporins), they are used to treat severe pneumonias in which there is reason to think about gram-negative etiology. These drugs have maximum concentration-dependent bactericidal activity and a long post-antibiotic effect, which allows them to be administered rarely - 2 or even 1 time per day. The use of high doses of aminoglycosides in severe cases of refractory hospital-acquired pneumonia (most often of Klebsiella etiology), indicated in is aimed at exceeding the expected level of resistance of the pathogen, which often gives a life-saving effect.

Cotrimoxazole has a broad spectrum of activity (cocci, some intestinal bacteria, chlamydia, pneumocystis), which makes the drug attractive at a low price. But the increasing resistance of pneumococci and hemophilus to it (L.S. Strachunsky - oral communication) forces one to treat it with caution.

Metronidazole is bactericidal against anaerobes, including bacteroids, and has no effect on other pneumotropic pathogens.

Rifampicin is active against staphylococci, pneumococci and Haemophilus influenzae, including those resistant to other drugs. Its use should be limited to cases of hospital-acquired infection, which helps prevent the spread of resistant flora.

Tetracyclines are not used in children under 8 years of age due to their effect on tooth enamel and bone tissue. Due to the resistance of many cocci to these drugs, they are used mainly to treat mycoplasmosis in adolescents.

Fluoroquinolones (ciprofloxacin and ofloxacin) are used only in adults and are not recommended for children due to the possible effect on growth cartilage (in an experiment). These drugs are permissible for use in children only in the most severe resistant infections, in particular pseudomonas (for example, in patients with cystic fibrosis).

Levomycetin causes irreversible aplastic anemia regardless of the dose and duration of administration. In this regard, it is recommended to prescribe it only in critical situations for the treatment of severe infections caused by *H. influenzae* or multidrug-resistant Pseudomonas aeruginosa.

Duration of therapy

Therapy should be continued until the pathogen is suppressed and eliminated by immunological mechanisms. The general opinion of most researchers is that in pneumonia, treatment should be continued for at least 2-3 days after the effect is achieved (temperature drops, progression of the process stops, etc.). As indicated, after signs of effectiveness appear, it is worth switching to oral administration of drugs. In most cases, mild pneumonia is treated for 4-6 days, complicated pneumonia - 8-12

days; the experience of shorter courses of therapy (for example, 2-3 days for pneumococcal pneumonia [9]) should hardly be extended to widespread practice.

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