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Concerning the Diagnostic and Treatment Problems of Children with Pneumonia

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Article received: 22.11.2014. Accepted for publication: 05.05.2015.

Relevance. *Pneumonia is one of the most prevalent severe and potentially life-threatening diseases in children. Criteria of pneumonia diagnosis and treatment have long and clearly been developed. However, under-diagnosis and irrational therapy are often observed, especially at the outpatient stage.* ***Objective.*** *Comparative analysis of incidence parameters, diagnostic criteria for pneumonia in children listed in Russian and foreign recommendations and their correspondence with the applicable Russian recommendations on diagnosis and treatment of pneumonia in children.* ***Materials and methods.*** *The authors conducted a comparative analysis of the recommendations on diagnosis and treatment of pneumonia in children published recently in a range of countries. They analyzed timeliness of diagnosis and adequacy of therapy at the outpatient stage in 167 hospitalized children with pneumonia. Pneumonia diagnosis was established in accordance with the Russian recommendations and taking into account the WHO recommendations. The authors also used pneumonia diagnosis quality assessment data and data of the expert analysis of radiograms of 679 patients hospitalized in 3 cities (Barnaul, Yekaterinburg and Murmansk) in the course of the PAPIRUS study.* ***Results.*** *The authors revealed a high percentage of late (after the 5th day of disease) hospitalization of children with pneumonia (37% - in 2002-2007, 47% - in 2013-2014) and of late (on the 5th day of disease or later) launch of treatment at the outpatient stage (20% and 34%, respectively). Pneumonic alterations identified in radiograms at 3 regional inpatient hospitals were confirmed by experts in 27% of the cases only.* ***Conclusion.*** *The obtained data indicate both under- and over-diagnosis of pneumonia in children and, thus, the importance of improving pediatricians' knowledge in the sphere of diagnosis and treatment of pneumonia for the delivery of adequate medical care to children at the outpatient stage.*
Keywords: *community-acquired pneumonia, clinical criteria, diagnosis, treatment standards.*

(**For citing:** Bakradze M. D., Gadliya D. D., Rogova O. A., Khokhlova T. A., Tatochenko V. K. Concerning the Diagnostic and Treatment Problems of Children with Pneumonia. *Pediatricheskaya farmakologiya = Pediatric pharmacology*. 2015; 12 (3): 354–359. doi: 10.15690/pf.v12i3.1365)

INTRODUCTION

Pneumonia is one of the most frequent severe diseases in children; it has always attracted attention of pediatricians. However, despite an abundance of studies dedicated thereto (or, possibly, because of this abundance), many aspects of pneumonia are interpreted differently; this creates difficulties and reduces effectiveness of practical work. It is no coincidence that

recommendations on diagnosis and treatment of pneumonia were published within the previous 10 years by professional communities of different countries [1-3]. Analysis of use of these recommendations demonstrates a different and far from 100% implementation of optimal approaches at outpatient and inpatient pediatric establishments [4].
Pneumonia is defined considerably differently in different recommendations; these differences concern both evaluation of a prevalent etiology and approaches to therapy. Underestimation of these differences lead to diagnostic chaos and reflects on determination of the pneumonia morbidity rate.

Diagnosis

Diagnosis of pneumonia in practice is rather complicated as they have to be "singled out" (preferably in the beginning of the disease) in all children suffering from fever. Frequent absence of rales and underestimation of general pneumonia-associated disorders are reasons of underdiagnosis of pneumonia: despite a persistent fever, these children are sometimes diagnosed with acute respiratory viral infections and prescribed antifebrile agents. On the other hand, overestimation of auscultative data by pediatricians, as well as incorrect interpretation of radiographic data, hugely contribute to overdiagnosis of pneumonia. According to a range of private messages, overdiagnosis of pneumonia at inpatient hospitals is promoted by economic aspects of medical standards.

Clinical manifestations

Pic. 1 Pneumococcal strain with reduced sensitivity to antibiotics

Амоксициллин
Пенициллин
Эритро/азитромицин
16-членные макролиды
Котримоксазол
Популяционные исследовния – Р.С. Козлов 2006-2009, Пегас III
Клинические штаммы – Маянский Н.А., 2014

Amoxicillin
Penicillin
Erythromycin/azithromycin
16-membered macrolides
Cotrimoxazole
Population studies – R.S. Kozlov 2006-2009, Pegas III
Clinical strains – N.A. Mayanskiy, 2014

Clinical symptoms of atypical pneumonias described in literature numerous times (persistent temperature reaction without toxicosis, conjunctivitis accompanied by scanty catarrhal syndrome, abundant and asymmetric rales) allow at least suspecting this etiology. Lack of effect of β-lactam use within 1-2 days is the crucial symptom of atypical pneumonia. At the same time,

only an increase in specific antibody titers is a significant laboratory sign of mycoplasmosis and chlamydia infection, whereas in the onset of the disease the absence of such antibodies counts in favor of this etiology. The method of polymerase chain reaction also yield little information, as positive findings, e.g. detection of mycoplasma DNA in the oropharynx, are usually observed in children in the absence of respiratory symptoms (21 and 16.2%, respectively [5]). That is why all published recommendations propose prescribing macrolides only if symptoms of atypical pneumonia are present; in case of doubt, macrolides are recommended only if amoxicillin is ineffective for 24-48 hours. Recommendations of the Russian Federation allow prescribing both drugs, e.g. when patients cannot be followed up.

Correspondence of initial therapy to current etiological structure of pneumonia needs to be analyzed as well as sensitivity of the potential causative agent to antibiotics. Pneumococci are prevalent among bacterial causative agents of pneumonia both before and after pneumococcal vaccination [6, 7]: pneumococci cause up to 50-60% of pneumonias in patients over 5-6 years of age; in other cases pneumonia is induced by atypical causative agents (primarily by *Mycoplasma pneumoniae*, less often – by *Chlamydia pneumoniae*). However, the data on pneumococcal sensitivity in Russia change rapidly. The relative amount of pneumococcal strains with reduced sensitivity to penicillin and macrolides has risen considerably; this makes these preparations hardly suitable for treating pneumonia (see pic. 1).

This article **is aimed at** comparative analysis of pneumonia diagnostic criteria in children given in Russian and foreign recommendations, morbidity rates and their correspondence to the recommendations on diagnosis and treatment of pneumonia in children currently used in Russia.

PATIENTS AND METHODS

The study consisted of 2 stages (in accordance with the aim):

1) comparative analysis of Russian and foreign (US, British, WHO) recommendations on diagnosis and treatment of pneumonia in children published within 5 previous years [2, 3, 8, 9];
2) assessment of timeliness of pneumonia diagnosis in children and adequacy of outpatient therapy.

In order to realize stage 2 medical records of children with pneumonia who applied or were hospitalized to the department of diagnosis and medical rehabilitation at the FSBRI SCCH in 2002-2007 and 2013-2014 (retrospective and prospective analysis). Pneumonia was diagnosed according to the criteria corresponding both to Russian recommendations and recommendations of the World Health Organization (WHO). Children with bronchial asthma and other chronic diseases, which may be complicated by pneumonia, were ruled out from the study. Source documents were examined in order to analyze diagnostic and therapeutic measures implemented to treat children on the outpatient stage.

We also used data of pneumonia diagnosis quality assessment with expert analysis of radiograms of 679 under-5 patients hospitalized to pediatric hospitals of 3 cities (Barnaul, Ekaterinburg, Murmansk). This analysis was conducted in the framework of trial PAPIRUS [10], which involved a multicenter clinical-epidemiological and prospective cohort studies dedicated to appraisal of community-acquired pneumonia and acute otitis media morbidity rates, as well as examination of the role of *Streptococcus pneumoniae* and *Haemophilus influenzae* in etiology of these diseases. Trial PAPIRUS involved all the medical and preventive facilities of the aforementioned cities, where patients with suspected community-acquired pneumonia were hospitalized.

Community-acquired pneumonia project PAPIRUS involved a microbiological blood sample study (hemoculture), analysis of clinical data and C-reactive protein level, interpretation of the chest radiogram.

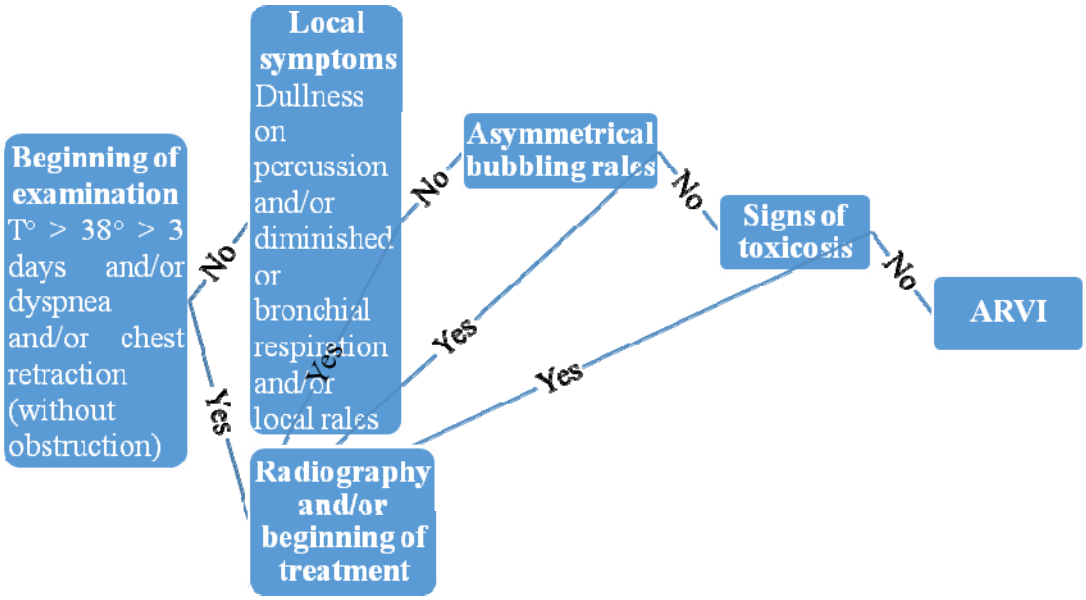
RESULTS

Analysis of contemporary criteria of pneumonia diagnosis recommended by international consensus documents

According to the recommendations on community-acquired pneumonia in children over 3 months of age published by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America [2], diagnostic criteria of the pathology are "presence of signs and symptoms of pneumonia in a previously healthy child". Etiology of most thus diagnosed pneumonias is considered viral. Such an approach may be explained by a tradition of calling bronchiolitis viral pneumonia, as well as by peculiarities of the US healthcare system, where most patients are treated outpatiently and in many cases do not undergo radiography. At the same time, recommendations cite an instruction of the US regulatory bodies [11], according to which antibacterial therapy should be conducted "in the presence of clinical symptoms and signs in combination with radiologic documentation or microbiologic confirmation"; hospitalization of such children is considered reasonable.

The WHO also recommend using clinical criteria of pneumonia when radiography cannot be performed. However, they also list signs and symptoms (cough + dyspnea/tachypnea, expiratory retraction of the lower part of the chest) highly correlating with radiographic criteria of pneumonia and allowing to distinguish primarily bacterial pneumonias from bronchiolitis and other viral diseases of airways [9].

Pic. 2. Algorithm of clinical diagnosis of pneumonia



Note. ARVI – acute respiratory viral infection

In contrast to the approach used in the USA, in Russia, pneumonia has been defined as an "acute infectious disease of pulmonary parenchyma diagnosed with respiratory distress syndrome and/or physical data if the radiogram features infiltrative or nidal alterations" since as early as 1973 [12]. The last condition – the "gold standard" (according to the WHO) of bacterial pneumonia diagnosis – allows excluding other diseases of lower airways (bronchitis, bronchiolitis), which feature viral etiology and usually do not require antibacterial treatment, from the list of conditions defined as "pneumonia". In contrast to the US literature, bronchiolitis is not considered viral pneumonia both in Russia and in Europe.

Russian recommendations allow diagnosing pneumonia at least putatively before performing radiographic examination [8]. Clinical criteria of the WHO were used to design an algorithm of pneumonia diagnosis on the basis of presence of general disorders (pic. 2); its sensitivity is 94% (positive predictive value – 85.2%), specificity – 96% (negative predictive value – 98.5%). The algorithm was published many times, but many pediatricians do not use it.

Clinical signs of pneumonia proposed by the WHO (+ persistent pyretic fever) as pneumonia criteria were also recommended by the British Thoracic Society; they also indicate that bacterial etiology of pneumonia is confirmed by the presence of an infiltrate in the radiogram [3]. Recommendations and pediatric societies of several other countries rely on the same criteria.

We also evaluated and clarified radiographic criteria of pneumonia. According to recommendations of the WHO experts [15], the most characteristic feature of a typical bacterial pneumonia is consolidation of pulmonary tissue – an alveolar infiltrate. Bronchopulmonary picture is not distinguishable due to such a shadow; the infiltrate-adjacent edge of the heart or the diaphragm is poorly contoured; "air bronchogram" is often observed; boundaries by interlobar (and often by intersegment) clefts are usually distinct. Infiltrates and especially consolidation rarely cover less than 1 segment.

Differences in pneumonia are criteria are important for evaluation of morbidity: thus, the morbidity in the USA is 74-92 and 35-52 per 1,000 0-2-year-old and 3-6-year-old children, respectively; however, only 2 out of 1,000 children are hospitalized [2]. However, analysis of effectiveness of pneumococcal vaccination demonstrated that the rate of X-ray-positive pneumonias in the USA is 4.3 per 1,000 under-5 children [16].

The community-acquired pneumonia rate is 1.4 per 1,000 under-16 children and 3.4 per 1,000 under-5 children (using British criteria) [17]. In Germany, these rates of pneumonias "requiring hospitalization" were 3.0 and 6.8, respectively [18].

Analysis of community-acquired pneumonia morbidity in Russia using hospitalization data of 3 Russian regions (PAPIRUS) and radiographic criteria of the WHO demonstrated the following results: 5.3 per 1,000 children aged from 6 months to 5 years [10]. Similar results were observed in Novokuznetsk (2013), where pneumonia patients are rigorously registered: 3.2 in under-1 children, 8.6 in 1-3-year-old children, 4.2 in 4-9-year-old children and 4.7 in under-14 children.

Analysis of antibacterial therapy recommendations

By contrast, recommendations on pneumonia treatment are rather uniform; thus, amoxicillin is indicated for treating airway infections caused by *Streptococcus pyogenes*, *S. pneumoniae* and *H. influenzae*.

According to the WHO [9], a 5-day amoxicillin course (40 mg/kg BID) is recommended for non-severe pneumonia in case no HIV-infection is present. In case of severe pneumonia, treatment should start with administration of ampicillin in the dose of 50 mg/kg and benzylpenicillin in the dose of 50,000 U/kg i/m or i/v every 6 hours for at least 5 days. After the termination of fever and intoxication level reduction the patient is transferred to peroral amoxicillin intake in the dose of 40 mg/kg BID.

The British Thoracic Society [3] recommends amoxicillin for peroral intake as the first-line therapy. Infants do not need amoxicillin to be protected by clavulanic acid, as the national vaccination calendar contains a Haemophilus influenzae vaccination without fail [19].

According to recommendations of the US Pediatric Infectious Diseases Society [2], it is not recommended to treat all community-acquired pneumonias with antibiotics, as diagnostic criteria include viral damage of the pulmonary tissue. Thus, it is recommended to prescribe peroral administration of amoxicillin in the dose of 90 mg/kg (2 intakes) at moderate pneumonia. In case of severe course of pneumonia, the antibacterial drug is administered parenterally; the drug of choice is ampicillin (150-200 mg/kg per day every 6 hours) or penicillin (200,000-250,000 U/kg per day every 4-6 hours).

According to Russian recommendations, amoxicillin treatment in the dose of 50 mg/kg per day is indicated to children over 6 years of age with non-complicated typical pneumonia. Administration of amoxicillin/clavulanate in the dose of 70-100 mg/kg per day is recommended to the under-5 children who have taken the antibiotic before and gone to preschool establishments [8].
All published recommendations propose prescribing macrolides only if symptoms of atypical pneumonia are present; in case of doubt, macrolides are recommended only if amoxicillin is ineffective for 24-48 hours.
Recommendations of the Russian Federation allow prescribing both drugs, e.g. when patients cannot be followed up.

Results of authors' studies

107 children were hospitalized to the department of diagnosis and medical rehabilitation of the FSBRI SSCH due to pneumonia in 2002-2007, in 2013-2014 – 60 children. The maximum incidence rate of typical pneumonia was observed in 1-5-year-old children (61%), of mycoplasma pneumonia – in 3-10-year-old children (67%).
Moreover, the analysis included data of 679 under-5 children from the aforementioned trial (PAPIRUS).
Among the hospitalized children with pneumonia atypical pneumonia was diagnosed in 45% (48 patients) in 2002-2007, 25% (15) – in 2013-2014. Atypical pneumonia has not been registered as a reason for hospitalization in any case.
Analysis of hospitalization term allows talking about underdiagnosis (late diagnosis) of pneumonia in children. According to the authors' clinic's data, in 2002-2007, 37% (39) of the children with pneumonia were admitted on day 5 of the disease or later, in 2013-2014 – 47% (28) (table 1).
As delayed hospitalization was related to ineffectiveness of the previously launched therapy in some patients, we *analyzed outpatient treatment term*: 24 (26%) patients out of 91 started to receive such treatment on day 5 of the disease or later (table 2). It could be assumed that late hospitalization is associated with expectation of therapeutic effect; however, it is not so: 43 (58%) children were admitted to the department also after 5 days of the disease; this may be explained only by underdiagnosis of pneumonia on the outpatient stage. That is why condition of the hospitalized children was significantly worse: pronounced signs of intoxication (food and drink refusal, drowsiness), oxygenation reduction, severe respiratory failure. Children who started the treatment were hospitalized due to therapy ineffectiveness for 2-4 days; some of them were hospitalized immediately after administration of the first antibiotic dose.

Table 1. Day of hospitalization of pneumonia patients

Pneumonia, years	Patients (n)	Day of disease at admission				
		1-2	3-4	5-6	7-9	10-12
Typical, 2002-2007	57	8	27	16	6	0
Typical, 2013-2014	45	10	18	8	7	2
Typical (total)	102	18	45	24	13	2
Atypical, 2002-2007	48	5	26	13	4	0
Atypical, 2013-2014	15	1	3	3	8	0
Atypical (total)	63	6	29	16	12	0

Table 2. Antibacterial therapy beginning on the prehospital stage

Pneumonia	Day of disease			
	1-2	3-4	5-6	≥7
Typical (n = 55)	19	20	11	5
Atypical (n = 36)	15	13	5	3

Table 3. Effectiveness of outpatiently prescribed antibiotics for typical pneumonia

Drug effectiveness	Ceftriaxone	Co-amoxiclav ≥ 45 mg/kg per day	Co-amoxiclav ≤ 45 mg/kg per day	Azithromycin	Cefixime/ceftibuten
Yes	4	2	0	1	2
No	0	0	4	5	5

Overdiagnosis, as well as underdiagnosis, of pneumonia is alarming: some pediatricians consider presence of any rales a sign of pulmonary tissue inflammation. Thus, only 20% of the referring pneumonia diagnoses established in autumn/winter in municipal clinics are confirmed.
Data of the outpatient radiographic examinations of the children subsequently hospitalized to the department of diagnosis and medical rehabilitation with pneumonia (2002-2007, 2013-2014) also confirm the issue of overdiagnosis: negative pictures show only intensification of the bronchovascular picture, peribronchial thickenings, extension of the lung root shadow, segments of hypoventilation etc.
Quality of interpretation of radiograms was assessed within the framework of PAPIRUS [10]: the changes corresponded to the WHO pneumonia criteria only in 27% of case.

Antibacterial therapy analysis

Specialists of the department of diagnosis and medical rehabilitation observe amoxicillin ineffectiveness for treating typical pneumonias, even severe ones, very rarely. The authors' experience shows that sufficient effect of amoxicillin and amoxicillin/clavulanate in children without risk factors of pneumococcal tolerance is achieved with the dose of ca. 50-60 mg/kg per day; if risk factors are present, the recommended dose is according to the WHO (80 mg/kg per day) and leading US clinics (90 mg/kg per day). Unfortunately, pediatricians often follow old instructions, including instructions for use of inhibitor-protected amoxicillin, according whereto the dose is ca. 20-30 mg/kg per day (see instructions of the Drug Tariff of the Russian Federation), which is often ineffective. In children with pneumonia treated at home with amoxicillin/clavulanate to no effect the dose was below 45 mg/kg per day in all cases; dose increase at an inpatient hospital would bring immediate effect. Thus, 43% of the children hospitalized with pneumonia in Kazan were receiving initial treatment with low doses of the aforementioned drugs or other antibiotics on the outpatient stage [20].
Analysis of drug prescriptions on the outpatient stage demonstrated almost complete lack of amoxicillin prescriptions to patients with typical pneumonia; at the same time, macrolide treatment was started in 44% of the cases in 2002-2007 and in 26% of the cases in 2013-2014. High pneumococcal resistance against macrolides in clinical samples has become rather noticeable in everyday practice. We observed lack of effect of outpatient azithromycin course in 5 out of 6 children hospitalized within 2 previous years (table 3). 90% of the children with atypical pneumonias received β-lactam treatment on the outpatient stage in 2013-2014 (in 2002-2007 – 64%), which in many cases lasted 4-6 days; that explains hospitalization of most of them due to the lack of effect.
Considering treatment on the prehospital stage on the whole, we may conclude that an effective (although usually suboptimal) drug in a sufficient dose was prescribed only to 20-25% of the hospitalized children.

DISCUSSION

Analysis of the data on under- and overdiagnosis of pneumonia revealed an almost complete absence of diagnosis of atypical pneumonia and indicated gaps in outpatient pediatricians' knowledge of clinical manifestations of the disease. In particular, such textbook symptoms as local rales and altered respirations are often absent (in 58% of the cases), especially at the most dangerous pneumonias, i.e. pneumococcal pneumonias; neither percussion nor auscultation aid diagnosis [21]. In these cases it is important to check symptoms of condition severity –

persistently increased body temperature > 38 ^{o}C, food and drink refusal, emesis, drowsiness or excitability; these symptoms are usually not listed in guidelines.
Radiographic overdiagnosis of pneumonias dictates the need in introducing stricter rules of chest image description.
The authors' data on high rate of prescription of macrolides to patients with typical pneumonia for initial therapy despite ineffectiveness of these drugs for this form of the disease observed by many authors [22-24] correspond with the data obtained in Moscow (in 33% of the children) and Kazan (in 21% of the children) [7, 20].
Wide use oral cephalosporins, III generation, we observed reflects lack of pediatricians' knowledge even of package leaflets, which clearly state groundlessness of their use at pneumonias.
At polyclinics, amoxicillin is prescribed to less than 10% of patients with pneumonia, amoxicillin/clavulanate – to more than 30% [7]. It may be reasonable to use amoxicillin/clavulanate for severe pneumonia in infants unvaccinated against Haemophilus influenzae; in older children this drug is not more advantageous than amoxicillin due to extreme rarity of hemophilic or any other gram-negative pneumonia.
Analysis demonstrated considerable drawbacks of diagnosis and prescription of timely pneumonia treatment in children. We believe that this is due not only to mistakes of pediatricians, but also to the complexity of organization of quick outpatient examination of acutely ill children; this forces physicians to resort to unreasonable hospitalization. No wonder that inpatient hospitals admit the children whose primary diagnosis of pneumonia is lifted off, while other children remain at home and do not receive timely adequate therapy before their condition aggravates severely.
SCCH pediatricians see the solution in creating conditions for quick examination of acutely ill children with suspected pneumonia either at a polyclinic diagnostic center or at an emergency department on the basis of a pediatric inpatient hospital. The WHO strongly recommends to organize such departments: they have been established at hospitals in many countries, allow hospitalizing children upon indications and help outpatient physicians to properly manage children not requiring hospitalization.
The high level of radiographic overdiagnosis of pneumonias we observed causes high concern, as it virtually voids this method of information value. Training of pediatric radiologists requires serious consideration.

CONFLICT OF INTEREST

The authors of this article have declared absence of reportable financial support / conflict of interest.

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