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How to distinguish a bacterial infection from a viral one and how to treat it

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The article is dedicated to the most relevant issue of childhood – febricities, the causes of which and, subsequently, correct patient management tactics are difficult to determine. The authors present not only their own experience of clinical and laboratory differential diagnostics of viral and bacterial infections, but also the world literature data. Low bacterial infection risk criteria, which allow avoiding the prescription of antibacterial drugs, are listed. Special attention is given to the most important inflammation markers at various febrile diseases and signs of a severe bacterial infection and fever without an apparent infection's nidus. The authors recommend using express tests to confirm the presence of a bacterial infection. Indications to antibacterial therapy prescription are analyzed.
Keywords: *fever, bacterial infection, viral infection, differential diagnosis, treatment principles, children.*

The problem of diagnostics of infectious diseases in pediatrics has been present for many centuries. Most acute diseases in children are accompanied by fever, which helps to suspect an infection, although it is not sufficient to determine whether the infection is viral or bacterial. Fever is what the parents fear most; it is a frequent and often the only cause for hospitalization (which is often ungrounded). Most parents believe that it is important only to bring the temperature the down, but doctors should not follow this opinion.

The temperature level does not always correlate with the disease severity. E.g., non-life-threatening respiratory viral infections are often accompanied by a higher temperature than a life-threatening pneumonia. For a modern pediatrician, it is not so much the body temperature rise level as its cause that is important in case of fever, because it is possible to prescribe etiotropic therapy at a bacterial infection and influenza, while most viral infections should be treated with pathogenetic drugs or, in most cases, only with symptomatic drugs.

Apart from fever, many infections have their characteristic clinical symptoms, which allow determining etiology rather accurately. Among them are the main "children's" exanthematic infections, pertussis, diphtheria, inflammatory diseases of a range of organs (acute otitis media, lymphadenitis, hepatitis). A range of infections is easily diagnosed with blood and urine analyses (e.g., urinary tract infections) or express tests. At present, it is possible to conduct express diagnostics of streptococcal tonsillitis, influenza, adeno- and rotavirus gastroenterites. Shortage of information and slow introduction of express tests in the wide use are serious problems. Differential diagnostics of viral and bacterial diseases based on the clinical data is often complicated due to the similarity of their clinical manifestations (e.g., in case of a respiratory pathology). It is also difficult to establish diagnosis "bacteremia", as it often lacks any symptoms apart from fever. This is a serious problem, as bacteremia often precedes development of such severe invasive bacterial infections (SBI) as meningococcal, pneumococcal and type b hemophilic infections.

Difficulty of clinical diagnostics of bacterial infections (not more than 5-10% in the structure of acute fevers) force doctors to prescribe antibiotics "just in case". In practice, antibacterial

therapy is often received by patients with respiratory viral infections and their characteristic clinical symptoms, while children with bacteremia lacking catarrh and visible organ disorders are often left without it. Moreover, they are often prescribed the drugs that are less active against most infections, the drugs that belong to the third or even fourth choice drugs for many nosologies, e.g., macrolides or adequate antibiotics for certain diseases given in small and ineffective doses. It is also observed that pediatricians prescribing antibiotics "just in case" lose their level of proficiency and are often unable to prescribe them in the indicated cases.

The so called inflammatory markers help to distinguish between viral and bacterial infections: leukocytosis, C-reactive protein (CRP), procalcitonin (PCT). However, the literature sources cite data, which do not allow an unambiguous interpretation of an increase in the level of these markers as a sign of bacterial inflammation.

Thus, it has been shown that neither leukocytosis level nor the total amount of neutrophils is a reliable marker of bacterial infections in patients with hyperpyrexia [1].

Only leukocytosis of more than $30x10^9$/l may indicate a severe bacterial infection in children of the first months of life with respiratory syncytial viral bronchiolitis [2]. B. Gomez et al. showed in their study that the PCT level ≥0.5ng/ml is associated with invasive bacterial infections (RR=21.7), while its level <0.5ng/ml reduces the chance of SBI down to 0.5%. The PCT level >2ng/ml increases the chance of an invasive bacterial infection only up to 19.3%.

Inflammatory markers. First of all, we defined the marker thresholds, i.e. the marker levels that are most likely to occur at bacterial infections. The range of inflammatory marker levels at respiratory infections is given in tb. 1. Despite the widespread opinion, a typical bacterial pneumonia is characterized by leukocytosis $>15x10^9$/l (not $>10x10^9$/l, as was considered before); levels of neutrophilia in general ($>10x10^9$/l) and of stab neutrophils ($>1.5x10^9$/l) are higher than the threshold level. A typical bacterial infection is unlikely when the levels of CRP <30mg/l, of PCT - <2ng/ml. Inflammatory marker level at atypical pneumoniae is similar to the one at acute respiratory viral infections (ARVI), although lower marker levels do not rule out the possibility of a bacterial infection. According to our data, the leukocytosis level did not exceed $15x10^9$/l in 41% of patients with typical pneumonia; these results do not differ from the figures obtained at ARVI, bronchitis and croup. Levels of leukocytes, CRP and PCT did not increase in a significant number of patients with acute otitis media. In exactly the same way, most patients with urinary tract infections have a low marker level; sharp level increase indicates affection of renal parenchyma.

Table 1. Level of inflammatory markers at respiratory diseases (%)

Leukocytosis, $x10^9$/l	**<10**	**10-15**	**>15**
ARVI, bronchitis	69	28	2
Pneumonia (typical)	12	29	59
For pneumonia in comparison with ARVI and bronchitis		PPV NPV	88% 87%
CRP, mg/l	**<15**	**15-30**	**>30**
ARVI, bronchitis	81	17	2
Pneumonia (typical)	0	0	100
For pneumonia in comparison with ARVI and bronchitis		PPV[1] NPV[2]	97% 100%
PCT, ng/ml	**<0.5**	**0.5-2**	**>2**
ARVI, bronchitis	81	19	0
Pneumonia (typical)	0	4	96
For pneumonia in comparison with ARVI and bronchitis		PPV[1] NPV[1]	100% 97%

Note. [1] – positive predictive value indicates the diagnosis probability in case the marker is positive; [2] – negative predictive value indicates the alternative diagnosis probability in case the marker is negative; ARVI – acute respiratory viral infection, CRP – C-reactive protein, PCT – procalcitonin.

Moderate PCT increase may also be observed at respiratory viral infections, internal hemorrhage and convulsions. E.V. Starovoytova demonstrated at our clinic that the PCT level >2ng/l has higher specificity (92%) and positive predictive value (PPV – 85%) than CRP and leukocytosis; however, there are exceptions in respect of procalcitonin as well [3].

Clinical differentiation of acute viral and bacterial infections. This clinical differentiation is based on a range of facts, proved and tested in special studies. Thus, prevalence of viral etiology of such diseases as rhinitis, nasopharyngitis, laryngitis (including laryngitis with croup syndrome), bronchitis and bronchiolitis was proved [4]. As mixed viral-bacterial infections rarely act as an etiologic factor at these diseases, we abandoned the routine prescription of antibiotics to patients suffering from these diseases without additional clinical signs (most often, otitis) or in case of doubt (e.g., in case of temperature $\geq 38^{o}$ lasting ≥ 3 days) and without results of the study that would indicate the possibility of a bacterial infection. A share of children with the aforementioned diagnoses (who receive antibiotics) at our clinic is 3-8%.

Catarrhal phenomena rather count against a bacterial infection. Out of 1,420 children with acute fever admitted to our hospital in the last 2 years catarrhal phenomena were manifested in 70%; only 23% of these patients needed antibiotics. At the same time, feverish children without catarrh (30%) needed antibiotics in 77% of cases. It was in this group that children with late onset of antibacterial treatment due to the lack of the disease symptoms other than fever would appear.

Low bacterial infection **risk** (Rochester) criteria are widely used in the therapeutic practice around the world; they allow avoiding prescription of antibiotics to children of 0-3 months of age (and especially in the older children) with the temperature $>38^{o}$:

- term infants who had not been receiving antibiotics before this disease;
- no physical symptoms of a bacterial infection (otitis, pneumonia, meningitis);
- leukocytosis – $5\text{-}15 \times 10^{9}$/l, amount of stab neutrophils – $<1.5 \times 10^{9}$/l;
- less than 10 leukocytes per HPF in uropsammus.

A bacterial infection was revealed only in 0.67% of all children of 0-3 months of age who had sought medical attention and met these criteria; this is 30 times as rare as in children with high SBI risk criteria [5].

Diagnosis otitis at examination of children with affection of **only the upper respiratory tract** is not difficult (pediatricians have to master the otoscopy technique, otherwise all the patients will have to be examined by an otolaryngologist). According to the modern recommendations, children under 2 years of age with diagnosis “Acute otitis media” undoubtedly need an antibiotic. Expectant management is possible with older children with the same diagnosis – the decision about the antibiotic prescription should be made within 72 hours while controlling the otoscopic presentation in dynamics. However, in case of this type of management, otalgia persists for 2 days in 46% of children in comparison with 18% of children treated with amoxicillin/clavulanate [6].

When treating acute otitis media, it is most often indicated to take in amoxicillin (dose ≈50mg/kg per day, 2 intakes); the dose is doubled in countries with high pneumococcal resistance level. Amoxicillin/clavulanate in the same dose is prescribed to children admitting preschool institutions or to those children who have recently been treated with any antibiotic in order to overcome possible *Haemophilus influenzae* resistance. *Azithromycin and cefixime are not recommended for acute* otitis media due to the higher pneumococcal resistance [7].

Differential diagnostics of acute tonsillites poses a serious problem: they almost always have viral etiology in children under 3 years of age. According to our data, the group A β-hemolytic streptococcus (GAS) is a causative agent of acute tonsillites in children of 4-12 years of age in ¼ of the cases, in the older children – in half of the cases; these results correspond to the literature data. Bacteriological test of palatine tonsillar material is the “gold standard” of diagnostics of acute bacterial tonsillites; at present, an alternative to cultural study method is the use of express

tests to diagnose BAS-tonsillites (we use Streptatest at our clinic). However, intense catarrh and conjunctivitis at acute tonsillitis, as well as diagnostics of infectious mononucleosis, allow not prescribing antibiotics to patients. It is indicated to use amoxicillin or cefalexin for BAS-tonsillitis OD or BID for 10 days in children under 2 years of age, for 7 days – in the older children [8, 9].

It has been proved that the marker level often exceeds the stated threshold at acute viral tonsillites (tb. 2); this reduces positive and, to a lesser extent, negative predictive value. When in case of Epstein-Barr virus infection doctors may be guided by leukocytosis (which may be high, though it is usually lymphocytic), in case of tonsillites caused by respiratory viruses (e.g., adenovirus) and bacteria (streptococcus) leukocytosis may be neutrophilic and even with left deviation. That is why the following figures appear to be more specific for diagnostics of bacterial tonsillitis: leukocytosis >20x10^9/l, CRP >100mg/l, PCT >10ng/l; these figures are not frequent (low sensitivity) [9].

Table 2. Level of inflammatory markers at acute tonsillites (%)

Leukocytosis, x10^9/l	**<10**	**10-15**	**>15**
Viral (adeno- - 70%)	37	39	24
Epstein-Barr virus	27	29	44
Bacterial	20	43	32
For bacterial tonsillitis in comparison with viral tonsillitis		PPV NPV	31% 75%
CRP, mg/l	**<15**	**30-60**	**>60**
Viral (adeno- - 70%)	43	25	32
Epstein-Barr virus	58	25	17
Bacterial	28	21	53
For bacterial tonsillitis in comparison with viral tonsillitis		PPV NPV	38% 86%
PCT, ng/ml	**<0.5**	**0.5-2**	**>2**
Viral (adeno- - 70%)	30	37	30
Epstein-Barr virus	15	25	60
Bacterial	8	7	85
For bacterial tonsillitis in comparison with viral tonsillitis		PPV NPV	57% 48%

Note. CRP – C-reactive protein, PCT – procalcitonin, PPV – positive predictive value, NPV – negative predictive value.

Acute rhinosinusitis is caused by viruses in 95% of cases; persistence or aggravation of symptoms (nasal congestion, pain in the region of paranasal sinuses, fever or buccal and/or palpebral edema (which is sometimes confused with periostitis or Quincke's edema)) indicate the development of bacterial process (usually – 10-12 days after the onset of ARVI). In case of bacterial sinusitis, antibacterial therapy of 10-14 days or, in range of cases, more is indicated; complicated sinusitis requires massive therapy (ceftriaxone or cefazolin with aminoglycoside) [10].

Latent pneumonia (no dyspnea and physical signs), urinary tract infection or bacteremia may occur in a feverish child with signs of upper respiratory tract catarrh; these diseases may be suspected due to the appearance of SBI signs (see below) and temperature stability. In this case the studies, including the study of the aforementioned markers, have to be more in-depth; it is also strongly recommended to conduct total analysis, urine culture and chest radiography.

Signs of the **lower respiratory tract affection** (dyspnea, respiratory obstruction and suppression, dullness on percussion and local rales) indicate the possibility of a bacterial pneumonia.

Inspiratory stridor is characteristic of croup, expiratory respiratory obstruction – obstructive syndrome – is characteristic of bronchitis, bronchiolitis and bronchial asthma. As has been mentioned above, these diseases do not require prescription of antibiotics in most cases. These assertions are based on the large amount of controlled studied, including our studies; this allows treating children with the lower respiratory tract affection usually with symptomatic means only.
Croup has to be differentiated from bacterial epiglottitis; the latter is characterized by SBI symptoms, odynophagia and lack of cough and hoarseness). Ceftriaxone or amoxicillin/clavulanate should be administered parenterally under suspicion of epiglottitis; intubation of the patient may be required [7].
Auscultative presentation of a typical pneumonia (most often pneumococcal pneumonia) is highly specific (local alteration of percussion sound and breathing, fine rales) though not very sensitive: rales are often not audible in the disease onset; this may results in under-diagnosis of pneumonia. Dyspnea, durable fever, "grunting" respiration (not to be confused with obstruction), retraction of tractable regions of chest and SBI signs should be taken into account at radiographic diagnosis verification. The studies of the World Health Organization (WHO) showed that the account of general disorders allows establishing diagnosis "pneumonia" clearer than using a stethoscope.
Do scattered dry and moist rales characteristic of bronchitis rule out the possibility of pneumonia? Not always, as pneumonia caused *Mycoplasma pneumoniae* (atypical pneumonia) is characterized by a bronchitic presentation. Persistent febrile temperature typical of this infection helps to establish diagnosis; however, the lack of intense toxemia accompanying this symptom results in the late ambulation, scanty catarrh with conjunctival hyperemia and asymmetry of rales (more rales in the pulmonary tissue infiltration zone). Infiltration stain in this case is often very slight and sometimes non-existent; according to our classification, in this case we may speak of the mycoplasma bronchitis. Rising antibody titer in the paired sera confirms diagnosis "mycoplasma infection"; detection of mycoplasma using a polymerase chain reaction is unreliable, as its carriage is revealed in more than 20% of healthy children [11]. Detection of IgM antibodies in mycoplasma may also be associated with the previous infection.
The WHO suggests the following criteria of pneumonia severity. Pneumonia may be considered severe in case the child has physical signs of pneumonia with the appearance of central cyanosis, other symptoms of severe respiratory compromise and liquid refusal. Severe pneumonia is accompanied by retraction of subcostal and intercostal areas and nasal flaring [12].
Amoxicillin is the main drug for community-acquired non-complicated non-severe pneumoniae. The Who recommends using it in the dose of 80mg/kg per day in 2 intakes; the daily dosage should not be less than 50mg/kg in any case. Lack of effect within 24-48 hours indicates the replacement of the drug by macrolide or addition of macrolide to the therapy, as the probability of atypical pneumonia is high in this case. If clinical signs indicate the possibility of mycoplasmosis, therapy should be started with macrolide: we prefer josamycin (Wilprafen Solutab), as it is the most active drug against pneumococcus, which is crucial in case of faulty diagnosis or mixed infection. Severe pneumoniae require parenteral administration of drugs active against pneumococcus and Haemophilus influenzae Type B (the latter – in children under 5 years of age (amoxicillin/clavulanate, 2^{nd}-3^{rd} generation cephalosporins)) [13].
Severe bacterial infection (SBI) is a generally accepted term both for invasive (bacteriemic) infections and life-threatening acute diseases. We revealed SBI in 20% of feverish children of 0-3 years of age (tb. 3) with fever within the range of 38.5-39.5^{o}C. These children require urgent diagnostics and treatment.
Children's appearance and behavior assessment are considerably more important for the SBI diagnostics than their temperature. The signs conductive to the possibility of intoxication severity assessment in feverish children include:

- sharp aggravation of the general condition, reduction in the child's activity;
- irritability (cry at a touch);
- flaccidity, sleepiness (longer sleep);

- no eye contact with the child at examination;
- food and liquid refusal;
- painful bright light.

Given these signs, SBI are diagnosed in 75-80% of patients before conducting laboratory analyses [14].

Table 3. Severe bacterial infection rate among the feverish children of 0-3 years of age who sought medical attention at the inpatient hospital (RAMS SCCH, Moscow) and the emergency department [Canada; by Manzano S. et al. *Arch Dis Child*. 2011; 96; 440]

Infections		**Moscow, n=859 (%)**	**Canada, n=328 (%)**
Viral infections		598 (70)	-
Bacterial infections:		84 (10)	-
	Streptococcal tonsillitis	20 (2.4)	
	Otitis	64 (7.6)	
SBI:		177 (20.4)	54 (16)
	Pneumonia	30 (3.5)	4 (1.2)
	Meningococcemia	2 (0.2)	
	Febrile UTI	105 (12.2)	48 (14.6)
	Bacteremia	40 (4.7)	2 (0.6)

Note. SBI – severe bacterial infections, UTI – urinary tract infection.

The following should also be taken into consideration at the disease severity evaluation:

- degree of tachycardia, muting of heart sounds;
- hypo- or hyperventilation;
- disturbed microcirculation, peripheral cyanosis, delay in the nail bed capillary filling;
- incessant emesis;
- dehydration signs.

Special attention should be given to the anxiety of parents, insistent demands of active medical aid or hospitalization. Such “anxious parents”, who insist on the severity of one or another disorder (e.g., sharp behavior alteration, sparing of a limb etc.), should be distinguished from parents who deem any temperature higher than normal dangerous for their children.

Various signs, which allow suspecting localization of the infection, may be distinguished in some children with SBI at admission to inpatient hospital. However, a significant number of patients have neither catarrh nor other symptoms apart from fever at examination. In this case we may speak of a fever without an apparent source (FWAS).

Fever without an apparent source is not rare; it occurs at least in 15-25% of children of 0-3 years of age at the moment of ambulation. There is no doubt that the FWAS rate depends on the diagnostic facilities as well: specific diagnosis is established in 1/3 of children after otoscopy, urine analysis and radiography (according to indications) in the admission department. Thus, we revealed otitis, pneumonia and urinary tract infection in 17%, 6% and 18% of patients out of the 183 children with fever and without catarrh or other symptoms. 62% of the remaining 108 (59%) patients are children with viral infections (enterovirus, herpes simplex virus type 1 and 2, herpesvirus type 6) without any characteristic clinical signs in the first days of disease. According to the recently published article, viral infections (mainly herpesvirus type 6, adeno- and enteroviruses) were revealed in 70% of children with FWAS [15].

These viral infections do not entail dangerous consequences, while 38% of children with FWAS have latent bacteremia, which may cause the development of an SBI. It is most often caused by pneumococcus; more rarely – by Haemophilus influenzae, meningococcus, colon bacillus. Asymptomatic bacteremia development risk is the highest in the first months of life and reduces at the age of 1-3 years. Bacteremia is the presence of bacteria in blood without organ affection (unlike sepsis). Bacteremia is only rarely revealed by blood culture on the early stage;

identification of a blood bacterial culture is usually possible in case of sepsis or any other SBI development.
In the absence of symptoms in children with FWAS it is possible to differentiate between viral and bacterial infection using the aforementioned severity criteria and inflammatory markers. Tb. 4 demonstrates that though leukocytosis and CRP levels are sufficiently informative, they are inferior to PCT in this respect, as PCT ≥2ng/ml (usually – higher than 10) almost always indicates the presence of bacteremia. Out of 68 children with viral FWAS, antibiotics were prescribed to 12 children with high CRP and/or leukocytosis, who did not undergo a PCT test [15].

Table 4. Level of inflammatory markers (%) in children with fever without an apparent source

Inflammatory marker levels	**Leukocytosis, x10^9**		**CRP, mg/l**		**PCT, ng/ml**
	10-15	**>15**	**30-60**	**>60**	**>2**
Viral	9	6	12	6	0
Bacteremia	25	70	23	73	100
PPV	-	88%	-	89%	100%
NPV	-	84%	-	88%	100%

Note. CRP – C-reactive protein, PCT – procalcitonin, PPV – positive predictive value, NPV – negative predictive value.

Children with bacteremia require an urgent intravenous administration of a wide action spectrum antibiotic – ceftriaxone (80mg/kg per day) or amoxicillin/clavulanate (80-100mg/kg per day). This usually leads to the temperate reduction within several hours after the beginning of the treatment. However, these drugs should be supplemented by aminoglycoside (e.g., amikacin in the dose of 15mg/kg OD) in certain children with gram-negative bacteremia (usually in case of pyelonephritis). In children of 0-2 months of age cephalosporins are combined with ampicillin (200mg/kg per day) due to the possibility of infection with listeria or enterococcus, which are resistant to cephalosporins [16].
Thus, on the basis of our own and literature data, we adhere to the following recommendations on the management of children with FWAS:

- leukocytosis >15x10^9/l, total amount of neutrophils >10x10^9/l or of stab neutrophils >1.5x10^9/l may indicate bacteremia; antibiotics are indicated; expectant management may be justified in “non-toxic looking” children with normal procalcitonin level;
- in case of leukocytosis <15x10^9/l and total amount of neutrophils <10x10^9/l or of stab neutrophils <1.5x10^9/l, the CRP (over 70mg/l) and/or procalcitonin (over 2ng/ml) level increase may indicate the antibacterial therapy.
- singular antibiotic administration with the subsequent condition assessment is indicated for children with fever >40^{o}C (0-2 months of age - >39^{o}C), the amount of leukocytes 10-15x10^9/l and of CRP 30x70mg/l and in case it is difficult to provide adequate supervision of patients;
- in the absence of bacterial inflammatory markers – symptomatic therapy.

Prevention. Vaccination against influenza does not only reduces influenza morbidity, but also reduces the FWAS rate. Tb. 3 presents the comparative analysis of our data and the Canadian data, which demonstrate that cohort immunization against pneumococcus and *Haemophilus influenzae* type b reduced the rate of bacteremia and SBI among feverish children. Vaccination against these infections made bacteremia so rare, that the reasonability of blood culture in children with FWAS is doubtful, as they are positive only in 10% of cases.

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