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REVIEWS

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Differential diagnosis of respiratory viral infections in children during the COVID-19 pandemic

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary **Background.** Respiratory tract infections (RTIs) constitute the most common reason for pediatric patients to report to primary care facilities. Additionally, RTIs are also a significant problem among hospitalized patients. Due to the lack of specificity in the observed symptoms, RTIs cause both diagnostic and therapeutic difficulties.

Objectives. The aim of our study was to explain the causes of RTIs in the pediatric population and to provide guidelines to facilitate diagnosis.

Material and methods. In the study, the authors analyzed available literature dealing with the possibility of laboratory diagnosis and the results of treatment used in children with RTIs.

Results. In pediatric patients, RTIs are mainly caused by viruses and occur seasonally during the autumn-winter period. There are certain factors, such as physiological distinctness resulting from developmental immaturity of the body, genetically determined diseases and specific diseases occurring during childhood, which contribute to the incidence of RTIs. Moreover, factors depending on the mother and the growth environment also significantly affect the incidence of RTIs in children.

Conclusions. Available knowledge concerning the seasonality of the occurrence of individual pathogens and the differences in symptoms may facilitate an initial diagnosis. However, lower respiratory tract infections, and severe infections in particular, require the use of specific diagnostic tests which allow for both the identification of the etiological factors and the implementation of targeted treatment. The COVID-19 pandemic has highlighted the difficulties in the diagnosis and therapy of RTIs in pediatric patients, as well as the need to develop more sensitive diagnostic tools and a more effective treatment.

Key words: infections, respiratory tract diseases, viruses, SARS-CoV-2, COVID-19, human influenza, rhinovirus, hypersensitivity.

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Respiratory tract infections (RTIs) constitute both the most common reasons (about 70%) for reporting to a primary care physician and a frequent cause (about 20%) for hospitalization of children and adults [1, 2]. The frequency of the appearance of RTIs varies depending on the age of the patient and concomitant risk factors.

The most important symptoms of RTIs include: runny nose, sore throat, cough, fever, lack of appetite or weakness [3]. Due to the lack of specificity in the observed symptoms, the identification of the main cause of the appearance of RTIs is difficult. Some of the pathogens responsible for the appearance of RTIs are epidemiologically seasonal or/and provide a common clinical picture facilitating diagnosis [3]. The choice of an appropriate therapeutic procedure should be preceded by the best possible diagnosis, in particular in the case of severe infections [1, 4–6].

The aim of the publication was to develop a diagnostic guideline for viral respiratory infections in children. The authors analyzed available literature dealing with the possibility of a laboratory diagnosis and the results of treatment used in children with RTIs. The authors' intention was to develop a set of clear and simple guidelines aiding practicing doctors in the process of making a diagnosis and choices for treatment. In our work, we analyzed typical causes and features of clinical symptoms of diseases in children in clear and understandable tables. We also showed available tests that should be used to improve the diagnosis of viral diseases in the pediatric population.

Viral respiratory infections in children

RTIs in children are most often caused by viruses, accounting for 85–90% of all respiratory infections [5, 7]. In the Northern Hemisphere, depending on the age, the socio-economic status of the patient and the time of year, as well as different viruses, may be responsible for the appearance of RTIs (Table 1). Data collected in different regions of the world (Australia, South-East Asia, South America) show that in children aged 6 months to 10 years and treated as an outpatient for RTIs, the following constitute the most common reason for RTIs: human rhinoviruses (hRV) – 41.5%, influenza viruses (IV) – 15.8%, human adenoviruses (hAdV) – 9.8%, human parainfluenza viruses (hPIV) and respiratory syncytial virus (RSV) – both 9.7%, human coronaviruses (hCoV) – 5.6%, human metapneumovirus (hMPV) – 5.5% and human bocavirus (hBoV) – 2.0% [8]. On the other hand, a study conducted on outpatient pediatric patients in Italy indicated the following: RSV – 27.1%, hAdV – 23.6%, hCoV – 15.3%, IV – 11.5%, hBoV – 9.4%, hPIV – 6.6%, hMPV – 4.4% and human enteroviruses (hEV) – 2.1% [9]. The most commonly appearing viruses causing RTIs in hospitalized children (there are large differences between individual studies) are the following: RSV, hAdV, hRV, IV, PIV type 1, 2, 3, hCoV, hMPV and hBoV [10–12]. The incubation time for infections caused by individual viruses ranges from 1 to 15 days, and so far, only two vaccines against two viruses and three specific antiviral drugs are available (Table 1).

Table 1. Viruses causing RTIs in children, vaccines and antiviral drugs [5, 7, with our modification]

Viruses	Time of year*	Incubation (days)	Vaccines	Specific antiviral drugs
Human rhinoviruses (hRV)	March–October	1–2	–	–
Coronaviruses (SARS-CoV-1, MERS-CoV, SARS-CoV-2)	October–June (whole year)	2–5	+ (SARS-CoV-2)	during trials
Influenza viruses (IV)	November–March	1–4 (6)	+	+
Human parainfluenza viruses (hPIV)	autumn	2–6	–	–
Human adenoviruses (hAdV)	whole year	4–5	–	–
Human metapneumovirus (hMPV)	winter–spring	2–3	–	–
Coxsackieviruses	summer–autumn	3–5	–	–
Human bocavirus (hBoV)	winter–spring	?	–	–
Respiratory syncytial virus	November–April	2–8	–	during trials
Human herpesvirus 6 (hHSV-6)	spring–autumn	5–15	–	+

* Northern Hemisphere temperate zone.

Table 2. Factors determining a higher incidence of RTIs in children

Child-related factors	Maternal factors	Environmental factors	Medical care-related factors
Low birth weight and prematurity	short period of breastfeeding	low socio-economic status, poor housing conditions, contact with moisture	abuse of antibiotic therapy
Genetic diseases (cystic fibrosis, ciliary mobility disorders, deficiency of α1-antitrypsin)	the use of stimulants, e.g. tobacco, alcohol	exposure to tobacco smoke and air pollution	lack of preventive vaccinations
Anatomical differences, a small distance between the nasal and oral cavities and the lower respiratory tract	lack of proper diet, malnutrition during pregnancy and lactation	having an older sibling	insufficient prevention of infections
Limited possibilities of expectoration		staying in large groups without the possibility of isolation (nursery, kindergarten, school)	
Immature immune system			
Predisposition to foreign body aspiration to the respiratory tract			
Gastroesophageal reflux			
Food and respiratory allergy			

In the Northern Hemisphere, the intensification of the incidence of RTIs, and upper respiratory tract infections (URTIs) in particular, is usually observed seasonally in the autumn–winter and early-spring periods [4, 5]. RTIs caused by hEV and hCoV do not show marked seasonality, and rhinoviral etiology is dominant in late summer [2, 13]. Moreover, there is a possibility of the appearance of simultaneous co-infections caused by various viruses, as well as the existence of the carrier of various viruses, especially in the case of the upper respiratory tract [5, 13, 14]. Due to the possibility of its severe clinical course and high infectivity, the SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) pandemic requires that COVID-19 (Coronavirus Disease 2019) patients should be separated from patients with viral infections of a different etiology.

Factors contributing to respiratory tract infections in children

RTIs are more common in children than in adults for numerous reasons (Table 2). Knowledge of these reasons allows one to determine indications for a possible extension of diagnosis and to refer these patients to a specialist pulmonologist or clinical immunologist in the case of the appearance of atypical and disturbing symptoms which are unusual for the developmental age [15–20].

Epidemiological and clinical characteristics of selected viral RTIs in children

Influenza

Influenza is caused by viruses belonging to the Orthomyxoviridae family. Based on the differences in the organization of the genome, several types of influenza viruses (IV) have been identified. The most widespread human influenza virus is the influenza A virus, which is epidemic. Influenza is less frequently caused by the influenza B virus, while the type C virus is responsible for respiratory infections with a mild course [21]. Most influenza cases occur seasonally from autumn to spring, and the incubation period of the disease is 2 to 4 days (Table 1). Flu symptoms appear suddenly and include: high fever above 38°C, chills, muscle ache and headache, malaise, non-productive cough, less frequently chest pain and abdominal pain, nausea and vomiting [22–26]. Symptoms usually appear simultaneously in the first days of the illness, and in many cases, they are self-limiting within a week. However, the occurrence of complications during the course of the disease and after are more and more commonly observed, and they include pneumonia, bronchitis, middle ear inflammation, myositis, meningitis and even death [27]. It should be remembered that infection caused by the influenza virus and other viruses may exacerbate the course

of chronic diseases such as asthma [28, 29]. In addition, influenza takes the form of an annual epidemic and causes infections in many people, resulting both in numerous school absences in the case of pediatric patients and sick leaves in adults. Therefore, the role of the use of oseltamivir in the treatment of patients with influenza, as well as in the prevention of diseases in people exposed to contact, has been emphasized for several years. There are a few types of vaccines available as well [30].

RSV infections

The respiratory syncytial virus (RSV) belongs to the Paramyxoviridae family and is responsible for human respiratory tract infections all over the world. In adults and older children, RSV infection is clinically associated with upper respiratory symptoms, while in infants, RSV causes bronchiolitis and lower respiratory tract illness that can progresses to pneumonia [31].

Coughing and wheezing are common with RSV and rhinovirus type C respiratory infections and can be difficult to distinguish from non-infectious (allergenic) asthma exacerbations, especially when the course of disease is without a fever. However, the age of the patient is an important feature that differentiates these disease: RSV infections with obstruction of the lower respiratory tract (bronchiolitis) are more common in younger children (mainly between the age of 6 weeks and 6 months), while allergic asthma exacerbations are usually observed in preschool and school children (Table 3).

RSV infections and the exacerbations of asthma (caused by intense contact with the allergen the child is allergic to) may occur simultaneously. Interestingly, there is even data indicating that the first episode of asthma may be related to an RSV infection. In such cases, bearing in mind that RSV (and RV) infections may develop into pneumonia, respiratory disorders, apnea and, in rare cases, can lead to death, the testing for RSV infection is the decisive diagnostic element and enables the implementation of appropriate treatment [2, 13, 18, 31–33]. In the case of an infection caused by several viruses, no more severe course of the disease should be expected, since the co-infection with RSV, hRV and IV usually leads to a reduction in growth of the second virus [2, 34, 35].

hMPV infections

hMPV causes about 7% of RTIs in children, both hospitalized and treated as an outpatient, aged 1–5 [36]. As with RSV and influenza viruses, it occurs seasonally, in late winter and spring [37]. In premature babies and children with reduced immunity, the infection is severe and requires hospitalization. The peak age of hospitalization of infants with hMPV is 6–12 months, and the clinical course of the infection is similar to that of RSV infection [38].

hBoV infections

It is estimated that in terms of the number of cases and after RSV and hMPV, hBoV is the third pathogen causing RTIs in children 5 years of age or less (mainly those between 3 months and 3 years of age) [39]. The incidence of hBoV types 1–4 in children is 10–30% [40]. Although the majority of hBoV cases occur in the winter months, it is common throughout the year. The symptoms are non-specific, but the most common symptoms in the course of the disease are the following: cough, runny nose, fever, difficulties in breathing, conjunctivitis, erythema, rash, nausea and sore throat [41].

SARS-CoV-2 infections

Since 2019, the differential diagnosis of RTIs should take into account infections caused by SARS-CoV-2. In the pediatric COVID-19 population, the disease caused by coronavirus usually presents as mild upper respiratory tract infections (URTIs) and/or lower respiratory tract infections (LRTIs) with a cough, rhinitis, sore throat and mild fever [42–44]. Less frequent are vomiting, diarrhea, loss of smell and taste and cardiovascular symptoms (chest pain, myocarditis, arrhythmia) [45–47]. It is uncommon for the symptoms to appear simultaneously, and they usually appear over the course of the disease on consecutive days. After the patient's condition has improved for several days, another deterioration can be expected. Coughing and weakness may persist for several weeks after recovery from the illness. A few cases of children developing multiple organ failure, acute respiratory distress syndrome (ARDS) and isolated cases of death in the course of COVID-19 have been reported [42–48].

Table 3 shows the frequency of COVID-19 symptoms in children based on available publications. Less severe symptoms in the pediatric population, as well as more frequent asymptomatic SARS-CoV-2 infections when compared to the adult population, are probably associated with a lower expression of ACE2 receptors (Angiotensin Converting Enzyme 2) in the epithelium of the oral cavity, nasal passages and lower respiratory tract, as well as a higher concentration of ACE2 in the blood, which further reduces the possibility of the virus binding to ACE2 receptors [47]. Factors that increase the risk of a severe course of COVID-19 in children include an age below 30 days, male gender, chronic diseases of the nervous, cardiac, respiratory and urinary systems, immunosuppression, obesity and co-infection with the influenza virus or RSV [27].

Table 3. Symptoms of viral RTIs and allergic rhinitis in children [48–52, with our modification]

Clinical feature	COVID-19	Influenza	Viral * rhinitis and pharyngitis	RSV infection	Allergic rhinitis (exacerbation)
Runny nose	rarely	often	often	sometimes	very often
Nasal congestion	sometimes	sometimes	often	often	often
Sneezing	rarely	sometimes	often	rarely	often, in peals ≥ 3
Loss of smell	sometimes (children rarely)	sometimes	sometimes	rarely	sometimes
Nasal itching	rarely	sometimes	rarely	rarely	very often
Conjunctivitis	sometimes	sometimes	rarely	rarely	often (seasonal rhinitis)
Cough	often	often	often	often	quite often
Shortness of breath (dyspnea)	sometimes	rarely	rarely	often	–
Additional auscultatory phenomena	often	rarely	never	often	never

Table 3. Symptoms of viral RTIs and allergic rhinitis in children [48–52, with our modification]

Clinical feature	COVID-19	Influenza	Viral * rhinitis and pharyngitis	RSV infection	Allergic rhinitis (exacerbation)
Fever	often (< 38°C)	often (> 38°C)	sometimes	sometimes	never
Myalgia	sometimes	often	rarely	sometimes	never
Malaise	often	sometimes	often	sometimes	sometimes
Sore throat	sometimes	quite often	often	rarely	sometimes (mild)
Throat or palate itching	never	never	never	rarely	sometimes
Diarrhea	rarely	sometimes	rarely	rarely	–
Duration of symptoms	7–16 days	5–10 days	3–14 days	4–11 days	weeks, months
Age	in each age	in each age	in each age	under 3 years	adolescent and adult
Another	sudden onset	sudden onset	slowly onset	bronchiolitis, appetite decreased	positive allergy interview, slow, lengthy process

* hRV and other viruses causing the common cold.

Differential diagnosis of acute RTIs

Acute infection of the nasal mucosa and paranasal sinuses, pharyngitis and tonsillitis, otitis, laryngitis and tracheitis belong to the URTI group – the group of the most common diseases in pediatrics (especially in children 1–6 years of age), although they are also of interest to an ENT specialist, an allergist or an immunologist [2, 34, 53]. In children, URTIs usually have an acute and short course, sometimes recurrent (> 2–6 episodes per year, depending on the age and the disease), usually without permanent consequences [20, 53].

If the patient presents a number of various upper respiratory symptoms, we are in fact faced with at least three questions:

1. Is it a URTI or an exacerbation of allergic rhinitis (AR)?
2. What kind (clinical form) of URTIs are we dealing with?
3. What is the etiological factor of the URTI?

A carefully collected medical history is helpful in the process of a differential diagnosis (Table 3, 4). For example, the following symptoms indicate an allergic background of symptoms in the form of AR occurring seasonally during the pollination of wind-pollinated plants to allergens to which the patient is allergic: sneezing in series, itching of the nose, itching and tearing of the conjunctiva or rhinorrhea [16, 24]. A physical examination of patients with AR will show congested conjunctivitis, shadows under the eyes, transverse nasal crease, pale blue staining and swelling of the nasal auricles in the anterior rhinoscopy [24, 54].

The occurrence of fever, mucopurulent secretion in the nasal canals, enlarged lymph nodes and a sudden onset of the disease will suggest an infectious etiology (Table 3). In contrast, viral tonsillitis is often accompanied by conjunctival, laryngeal, nasal and sinus symptoms, muscle and joint pains and abdominal pain with diarrhea. A physical examination will show typical bubbles on the mucous membrane of the soft palate and, in the history, a slow increase in symptoms. However, sudden onset, difficulty in swallowing, fibrous deposits or purulent secretion on the tonsils suggest bacterial etiology [4, 33, 55]. The differentiation of etiology in different clinical forms of URTIs in children has been collected in Table 4.

The usefulness of CRP and/or procalcitonin determinations in the differential diagnosis of viral and bacterial URTIs in children is still questionable. In light of the latest meta-analyses, the determination of CRP or procalcitonin may be useful in primary health care or HEDs (hospital emergency departments) to make the right decision concerning antibiotic therapy in patients with acute forms of respiratory tract infections [56, 57]. However, the interpretation of these proteins seems to be increasingly subjective. Therefore, there have been attempts to obtain more objective markers of inflammation, such as proteins related to TNF (*tumor necrosis factor*) and interferon γ [58].

Table 4. Symptoms indicating viral or bacterial infection [52, our modification]

Disease	Viral ethology	Bacterial ethology	Tests
Acute pharyngitis	cough, runny nose	without cough lymphadenopathy	throat swab, rapid strep a antigen test
Acute otitis media	duration < 48 hours	duration > 48 hours in children < 1 year high fever, vomiting	tests not necessary
Acute rhinitis and sinusitis	duration < 7 days	duration > 10 days, worsening in 5–7 days pain and facial swelling	tests not necessary

Infections of the lower respiratory tract (LRTI), especially of the bronchi and lungs, constitute a more likely cause of hospitalization than URTIs and may lead to permanent complications, such as impaired ventilation or the development of asthma [4, 49]. Among the etiological factors of LRTIs in children, viruses also predominate, and the course of the infection is often self-limiting. However, due to the recommended implementation of causal treatment in the case of bacterial diseases and influenza and the increased risk of permanent complications, causal diagnosis should be undertaken much more often than in the case of URTIs [3, 5, 16, 18]. The best samples from the lower respiratory tract are obtained with the use of bronchoscopy, which is very infrequent in children. It is replaced with an easily accessible nasopharyngeal swab. Importantly, when interpreting the results, the possibility of carrying non-pathogenic viruses/bacteria should be considered [59].

Due to the difficulties or even inability to establish the etiology of RTIs based on a medical interview and physical examination, it is necessary to conduct additional tests, even in the primary health care facility. Over the last 20 years, great progress has been made in the diagnosis of viral RTIs, which is mainly related to the introduction and increase in use of methods based on the amplification of viral nucleic acids and antigen tests.

Diagnostic tests helpful in the differential diagnosis of viral RTIs are divided into 3 main groups [60]:

Antigenic (strip, cassette): immunofluorescent, enzyme immunoassay, e.g. ELISA and immunochromatographic tests – to detect the presence of virus antigens in the tested material.

Genetic (molecular) – most often the RT-PCR method (reverse transcriptase polymerase chain reaction) – detecting the genetic material of the virus in the tested sample.

Serological: qualitative, semi-quantitative or quantitative assessment of the concentration of IgG and/or IgM in the blood.

The research materials include: nose or throat swab, bronchoalveolar lavage fluid, tracheal or bronchial aspirate. The advantages and disadvantages of diagnostic tests most often used in the diagnosis of viral RTs are presented in Table 5 [60].

The most popular tests aiding rapid identification of the pathogen are antigen tests, used as well as screening tests. The result is usually obtained within 10–30 minutes after the performance of the test. Such tests should be widely used by family doctors and pediatricians in primary care facilities and in emergency departments of hospitals. They differ in sensitivity and specificity. For example, in the case of rapid tests for detecting influenza A or B antigens, the sensitivity differs depending on the manufacturer from 53–54%, with a specificity of 98%. The sensitivity of the test usually decreases with the duration of the infection [61].

When IV, RSV or hAdV infections are suspected, a negative result should be confirmed by the method recognized as the golden standard, i.e. PCR (or RT-PCR). Particularly in the case of hospitalized patients, molecular tests identifying a given pathogen should be performed. Using the available tests, it is possible to obtain the results within 15–30 minutes from the start of the test, and their sensitivity is 95–99%. The documented sensitivity tests should be used to minimize the possibility of a false result [62]. One study evaluated immunochromatic rapid antigen tests for COVID-19 - Ag Respi-Strip (Coris BioConcept, Gembloux, Belgium). However, their sensitivity turned out to be very low – 30–50% compared to RT-PCR [63, 64). Currently, the so-called golden standard for testing for URTIs is a nasopharyngeal swab (Figure 1).

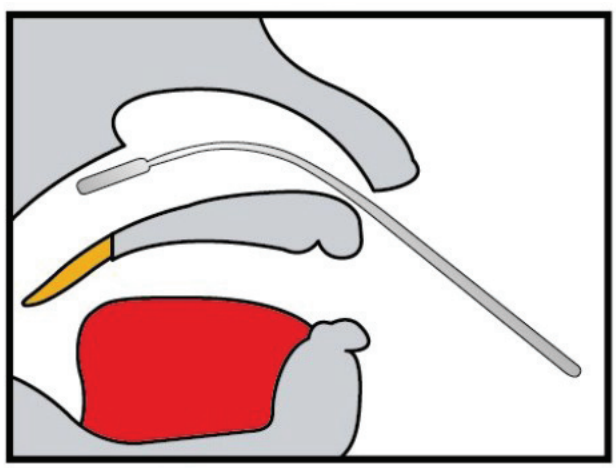

Figure 1. Taking a nasopharyngeal swab

Alternatively, a nasal swab and/or deep throat swab (positive opinion of the Polish National Institute of Hygiene for 2018 nose and throat swabs) can be taken. Importantly, the same swab brush should always be used to take the swab from both nostrils to increase the likelihood of detection of the RNA virus. The test result is also influenced by the time of sample delivery to the laboratory and the sample storage conditions. Moreover, performance of the test and interpretation of the result should be performed by the same person.

There are serological tests available on the market examining the level of IgA, IgM and IgG antibodies directed against SARS-CoV-2. The WHO permits the application of these methods as a supplementary diagnosis method. The validity of blood serological tests is related to the fact that some patients experience a decrease in RT-PCR sensitivity after about a week after the onset of symptoms. The first antibodies may appear as early as 10 days after the onset of symptoms of the disease.

Table 5. Advantages and disadvantages of diagnostic tests most often used in the diagnosis of viral RTs

Type of test	Advantages	Disadvantages
Antigenic	ease of execution (Primary Health Care, HED), screening test, simple apparatus, short execution time – approx. 15–20 minutes, cost of a single test approx. 10–15 times lower than RT-PCR	smaller sensitivity vs RT-PCR
Genetic RT-PCR	the most sensitive and specific test (gold standard), determination of the number of copies or units of the virus in the appropriate serum volume, evaluation of the virus variant (mutations or characteristic sequences in the genome), the presence of a small virus titre (copies) is sufficient	requires experienced personnel and specialized laboratory, high cost, long testing time (1–4 hours)
Serological	assessment of population immunity, useful in epidemiological studies and confirmation of the disease in a patient without clinical symptoms	the need to collect blood serum, supplementary test

Conclusions

Infections of the respiratory tract in children are still an important diagnostic and therapeutic problem in primary health care, especially during the COVID-19 pandemic. The unspecific history and symptomatology of the majority of viral RTIs require diagnostic tests. The available knowledge concerning the seasonality of the occurrence of individual pathogens and the differences in the symptoms may facilitate initial diagnosis. However, lower respiratory tract infections, and severe ones in particular, require the use of specific diagnostic tests which allow for both the identification of the etiological factors and the implementation of targeted treatment. There is an urgent need to introduce rapid antigen tests to help determine the etiology of RTIs (especially LRTIs) in children, mainly for influenza, RSV, RV and SARS-CoV-2. Due to the COVID-19 pandemic, rapid progress in virological diagnostics and vaccinology should be expected, along with the availability of new antiviral drugs.

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Tables: 4
Figures: 1
References: 65

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