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ORIGINAL ARTICLE

Clinical Signs and Diagnostic Tests in Acute Respiratory Infections

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Abstract
Objectives To evaluate clinical manifestations of acute respiratory system infectious diseases and specific tests for causative agents in pediatric patients.
Methods The authors evaluated children aged 0–16 y with clinical symptoms of acute respiratory tract infections who were administered rapid strep A test and/or throat culture test and/or respiratory viral panel test, from February 2012 through January 2013 at pediatric department of Acıbadem Maslak Hospital, Turkey.
Results A total of 1654 patients were evaluated; 45.9 % were girls, 54.1 % were boys. Absence of cough and presence of headache were higher in the patients >6 y of age (p 0.0001, p 0.002 respectively). Positive respiratory viral panel test was higher in the patients <2 y of age (p 0.002). Both positive rapid strep A test and positive throat culture test were higher in the patients >6 y of age (p 0.0001). Positivity of rapid strep A or throat culture test were not observed in children <2 y of age.
Conclusions A clinician should mostly consider viral infections in the etiology of acute respiratory infections in children under 2 y of age and there is no need to rush for the use antibiotherapy. Bacterial etiology should be frequently considered after 6 y of age and rapid use of antibiotheraphy is essential to avoid the complications.

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Keywords Clinical signs · Diagnostic tests · Beta hemolytic streptococcus · Children

Abbreviations

GAS	Group A beta hemolytic streptococcus
RSV	Respiratory syncytial virus
vPIVs	Parainfluenza viruses
IFVs	Influenza viruses
EVs	Enteroviruses
ADVs	Adenoviruses
HRVs	Human rhinoviruses
hMPV	Human metapneumovirus
HCoVs	Human coronaviruses

Introduction

Infectious diseases are common in childhood. Acute respiratory tract infections are the most common cause with high mortality and complication rates. The most common agents for acute respiratory tract infection are viruses [1] and include respiratory syncytial virus (RSV), parainfluenza viruses (PIVs), influenza viruses (IFVs), enteroviruses (EVs), adenoviruses (ADVs), human rhinoviruses (HRVs), human metapneumovirus (hMPV) and human coronaviruses (HCoVs) 229E, OC43, NL63, and HKU1. Coronaviruses NL63, HKU1 and human bocavirus, WU and KI polyomaviruses are the other viruses that cause serious respiratory tract infections [2]. Although viruses are the most common causes of acute respiratory tract infections, main etiological diagnosis is often missed and unnecessary or inappropriate antibiotic use is seen in more than 50 % of acute respiratory tract infections worldwide [3]. This leads to development of serious outcomes such as high resistance rates or multidrug

resistance along with drug side effects in the children infected with virus [3, 4]. There are many pathogens causing similar clinical manifestations suggestive of acute respiratory tract infection [3]. Group A beta hemolytic streptococcus (GAS) is the most frequent bacterial agent in the etiology of acute respiratory tract, accounting for 15–30 % of acute pharyngitis cases especially in the children [5]. Clinical manifestations of GAS respiratory tract infection are mostly presence of sore throat and fever and absence of cough [5]. Clinical manifestations like cough, nasal discharge, and diarrhea are more suggestive of viral causes [5]. Clinical differentiation between viral and bacterial etiology is important for performing appropriate laboratory test, treatment and follow-up. In the index study, the authors investigated clinical manifestations and laboratory tests of these two most common etiological causes seen in the children.

The authors investigated the results of respiratory viral panel test (RVPT) (Mutiplex PCR panel) for the diagnosis of frequently isolated viral etiologic groups: RSV, PIVs, IFVs, ADVs, HRVs, hMPV and HCoVs with the results of rapid strep A (RSA) antigen detection test and throat culture test for the diagnosis of GAS.

Material and Methods

The authors retrospectively evaluated 1654 patients aged 0–16 y with clinical presentation of acute respiratory system infection such as: fever [>38 °C (tympanic)], nasal discharge, cough, rash, sore throat, hoarseness, hyperemia of oropharyngeal region, hyperemic and hypertrophic tonsils, retropharyngeal secretions who presented at Acibadem Maslak Hospital from February 2012 through January 2013. With these clinical findings RVPT, RSA and throat culture tests were performed. Admission date, date of birth, gender, complaints and season of infection were recorded.

Tests and results were performed in SPSS database. In this study, NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program was used for the statistical analysis.

During the evaluation of the study data, regarding the comparisons of descriptive statistical methods (frequency and percentage distribution) as well as qualitative data, Chi-square test and Fisher's exact tests were used. Sensitivity, specificity, positive predictive value, negative predictive value and LR + (Likelihood Ratio) values were calculated for the reliability of diagnostic methods. The results obtained from the study were evaluated at a significance level of $p < 0.05$ and within 95 % confidence interval.

Results

RSA test, throat culture test and RVPT were performed in the patients presenting with symptoms of acute respiratory tract infection. The patients' gender, age, clinical signs (fever, cough, sore throat, headache, rash, nausea, vomiting, hoarseness, ear pain, abdominal pain and foot-knee-leg pain) and season of getting infected are shown in Table 1.

Of the total patients, 45.9 % ($n = 759$) were girls and 54.1 % ($n = 895$) were boys. Patients were classified according to the age groups: < 2 y, between 2 and 6 y and >6 y. There was no difference between the age groups with respect to gender ($p = 0.886$) and no difference between the genders with respect to winter, spring, summer and autumn seasons ($p = 0.808$).

RVPT and RSA tests were performed simultaneously in 10.3 % ($n = 4$) < 2-y-old, 53.8 % ($n = 21$) 2–6 y old and 35.9 % ($n = 14$) > 6-y-old. RVPT and throat culture tests were performed simultaneously in 18.6 % ($n = 11$) < 2-y-old, 52.5 % ($n = 31$) 2–6 y old and 28.8 % ($n = 17$) > 6-y-old children. Throat culture test and RSA test were performed simultaneously in 4.6 % ($n = 22$) < 2-y-old, 45.5 % ($n = 218$) 2–6 y old and 49.9 % ($n = 239$) > 6-y-old children. Distribution of the tests according to the age groups is shown in Table 2.

The number of tests performed due to the complaint of fever were higher in 2–6 y age group as compared to the patients in <2 y and >6 y age groups (p 0.0001). The number of tests performed due to the complaint of cough were less in >6 y age group as compared to <2-y-old and 2–6 y age groups (p 0.0001). The tests performed due to the complaint of sore throat were less in <2 y age group as compared to 2–6 y and >6 y age groups (p 0.0001). Also the number of tests performed due to the complaint of headache were higher in >6 y age group as compared to <2 y and 2–6 y age groups (p 0.002). No difference was observed between the number of tests performed in <2 y, 2–6 y and >6 y age groups due to the complaints of foot-knee-leg pain, nausea-vomiting, nasal discharge, nasal congestion, rash, fatigue, abdominal pain, hoarseness and ear pain ($p > 0.05$). Complaint of fever in the patients in whom the test was performed in the spring and winter months was found to be higher than those in whom the test was done in the summer and autumn months (p 0.005). Absence of cough in the patients in whom the test was performed in the spring and winter months was found to be higher than those in whom the test was performed in the summer and autumn months (p 0.0001). No difference was observed between distribution of presence of sore throat, headache, nasal congestion, rash, hoarseness and ear pain with respect to the winter, spring, summer and autumn seasons ($p > 0.05$). Presence of fatigue in the patients in whom the test was performed in the winter months was found to be higher than those in whom the test was performed in the summer, spring and autumn months (p 0.012).

Table 1 Distribution of patients according to the age group, gender, season of getting infected and complaints

	<2 y (N = 127) n(%)		2–6 y (N = 752) n(%)		> 6 y (N = 775) n(%)		*P*
Gender							
Boy	56	(44.09)	343	(45.61)	360	(46.45)	0.886
Girl	71	(55.91)	409	(54.39)	415	(53.55)	
Season							
Winter	43	(33.86)	220	(29.26)	216	(27.87)	0.0001
Spring	38	(29.92)	298	(39.63)	381	(49.16)	
Summer	25	(19.69)	103	(13.70)	70	(9.03)	
Autumn	21	(16.54)	131	(17.42)	108	(13.94)	
Fever	82	(64.57)	555	(73.80)	485	(62.58)	0.0001
Cough	47	(37.01)	274	(36.44)	212	(27.35)	0.0001
Sore throat	5	(3.94)	182	(24.20)	342	(44.13)	0.0001
Foot-Knee-Leg pain	0	(0.00)	10	(1.33)	12	(1.55)	0.369
Headache	0	(0.00)	10	(1.33)	29	(3.74)	0.002
Nausea-Vomiting	6	(4.72)	27	(3.59)	42	(5.42)	0.228
Nasal discharge	10	(7.87)	60	(7.98)	53	(6.84)	0.684
Nasal congestion	1	(0.79)	8	(1.06)	9	(1.16)	0.928
Rash	10	(7.87)	31	(4.12)	27	(3.48)	0.069
Fatigue	0	(0.00)	7	(0.93)	16	(2.06)	0.063
Abdominal pain	0	(0.00)	15	(1.99)	21	(2.71)	0.137
Hoarseness	1	(0.79)	3	(0.40)	4	(0.52)	0.830
Ear pain	0	(0.00)	7	(0.93)	7	(0.90)	0.555

Positive RSA test was not observed in <2 y age group and the number of patients with positive RSA test was higher in >6 y age as compared to 2–6 y age group (p 0.0001). Positive throat culture test was not observed in <2 y age group and the number of patients with positive throat culture test were found to be higher in >6 y age group as compared to 2–6 y age group (p 0.0001). Number of patients with positive RVPT were higher in <2 y age group as compared to 2–6 y and >6 y age groups (p 0.002).

Positive RSA test and throat culture test in the winter and spring months were higher than in summer and autumn months (p 0.001, p 0.008 respectively). Distributions of tests according to the complaints are shown in Table 3.

No difference was observed between distribution of positive RVPT in winter, spring, summer and autumn season groups (p 0.135).

The number of patients with RSA test (+) in >6 y age group were higher than those in RSA test (−) group (p 0.0001).

No difference was observed between distribution of gender of RSA test group (−) and rapid strep A test (+) groups (p 0.770). The number of patients with fever in the RSA test (+) group were higher than those in RSA test (−) group (p 0.022). The number of patients with cough in the RSA test (+) group were less than those in RSA test (−) group (p 0.001). The number of patients with sore throat in the RSA test (+) group were higher than those in RSA (−) group (p 0.0001).

Table 2 Distribution of the tests according to the age groups

Test	<2 y n(%)	2–6 y n(%)	>6 y n(%)	Total
Rapid Strep A				
Negative	62 (100.00)	456 (89.24)	413 (76.91)	931 (83.87)
Positive	0 (0.00)	55 (10.76)	124 (23.09)	179 (16.13)
Throat Culture				
Negative	52 (100.00)	374 (88.42)	330 (72.37)	756 (81.20)
Positive	0 (0.00)	49 (11.58)	126 (27.63)	175 (18.80)
Respiratory Viral Panel				
Negative	19 (39.58)	55 (62.50)	40 (72.73)	114 (59.69)
Positive	29 (60.42)	33 (37.50)	15 (27.27)	77 (40.31)

Table 3 Distribution of tests according to the complaints

Complaint	Rapid Strep A test n(%)	Throat Culture test n(%)	Respiratory Viral Panel test n(%)
Fever	816(73.5)	602(64.7)	140(73.3)
Cough	332(29.9)	321(34.5)	96(50.3)
Sore throat	363(32.7)	359(38.6)	21(11.0)
Foot-Knee-Leg pain	14(1.3)	12(1.3)	0(0)
Headache	29(2.6)	23(2.5)	1(0.5)
Nausea-Vomiting	54(4.9)	33(3.5)	10(5.2)
Nasal discharge	82(7.4)	82(8.8)	15(7.9)
Nasal congestion	12(1.1)	8(0.9)	0(0)
Rash	49(4.4)	35(3.8)	5(2.6)
Fatigue	17(1.5)	13(1.4)	2(1.0)
Abdominal pain	24(2.2)	15(1.6)	0(0)
Hoarseness	3(0.3)	7(0.8)	0(0)
Ear pain	6(0.5)	8(0.9)	0(0)

No difference was observed between distribution of foot-knee-leg pain, headache, nausea-vomiting, nasal discharge, nasal congestion, rash, fatigue, abdominal pain, hoarseness and ear pain in the RSA test (−) group and the RSA test (+) groups ($p > 0.05$).

In the >6 y age group number of patients with throat culture (+) were higher than those in throat culture (−) (p 0.0001).

No difference was observed between distribution of gender in the throat culture (−) and the throat culture (+) groups (p 0.423). The number of patients with detection of infection in winter and spring months in the throat culture (+) group were higher than those in the throat culture (−) group (p 0.008).

Presence of cough in the throat culture (+) group was less than the throat culture (−) group (p 0.001).

Sore throat in the throat culture (+) group was higher than the throat culture (−) group (p 0.0001).

No difference was observed between distribution of fever, foot-knee-leg pain, headache, nausea-vomiting, nasal discharge, nasal congestion, rash, fatigue, abdominal pain, hoarseness and ear pain in the throat culture (+) group and throat culture (−) groups ($p > 0.05$). Positive RSA test in the throat culture (+) group was higher than the throat culture (−) group (p 0.0001).

In <2 y age group, number of patients with RVPT (+) were higher than those with RVPT (−) (p 0.002).

No difference was observed between the distribution of gender in RVPT (−) and RVPT (+) groups (p 0.994).

No difference was observed between distribution of season, fever, cough, sore throat, headache, nausea-vomiting, nasal discharge, rash and fatigue in RVPT (−) and RVPT (+) groups ($p > 0.05$).

According to throat culture, specificity, sensitivity, positive predictive value, negative predictive value and LR(+) values of the results of RSA test were found to be 0.50, 0.98, 0.85, 0.88 and 20.83, respectively. In a patient positive with RSA test, the likelihood of positivity of throat culture is 20.83-fold higher than in a patient with negative RSA test.

According to throat culture, specificity, sensitivity, positive predictive value, negative predictive value and LR(+) values of the results of RVPT were found to be 0.17, 0.64, 0.14, 0.87 and 0.46, respectively. In a patient positive with RVPT, the likelihood of positivity of throat culture is 0.46-fold higher than in a patient with negative RVPT (it is not successful since it is not more than 2).

Discussion

RVPT and RSA tests were performed simultaneously in 10.3 % (n = 4) < 2-y-old, 53.8 % (n = 21) 2–6 y old and 35.9 % (n = 14) > 6-y-old patients; RVPT and throat culture tests were performed simultaneously in 18.6 % (n = 11) < 2-y-old, 52.5 % (n = 31) 2–6 y old and 28.8 % (n = 17) > 6-y-old patients; throat culture test and RSA tests were performed simultaneously in 4.6 % (n = 22) < 2-y-old, 45.5 % (n = 218) 2–6 y old and 49.9 % (n = 239) > 6-y-old. It shows that according to the patient's complaints, clinician could choose one or two tests for diagnosis.

Viruses cause most common acute respiratory system infections but GAS causes 37 % of all cases of acute respiratory system infections in children older than 5 y. Streptococcal acute respiratory system infections have a peak incidence in the early school years and are uncommon before 3 y of age [6].

It was found that the ratio of the patients in whom the test was performed due to the complaint of fever was higher in 2–6 y age than the patients in <2 y and >6 y age groups. While the ratio of the patients in whom the test was performed due to the complaint of cough was significantly less in >6 y age group; the ratio of the patients in whom the test was performed due to the complaint of headache was higher in >6 y age group. The authors found that the number of patients in whom the test was performed due to the complaint of sore throat were less in <2 y age group as compared to those in >6 y age group. The ratio of patients with positive RSA test and positive throat culture test was higher in >6 y age group. Also the ratio of patients with complaint of cough and sore throat were low and high respectively in the patients with positive RSA and positive throat culture test. GAS is seen frequently during the winter and spring months especially in 5–15 y age groups [8]. The number of patients with positive GAS tests were higher in the winter and spring months. While viruses are responsible for 95 % cases of sore throat in <5 y age children, they are responsible for 70 % cases of sore throat in 5–15 y age group. The

most common bacterial cause of sore throat is GAS. One-third cause of sore throat in children 5–15 y of age is GAS [9]. Absence of cough, headache, myalgia, fever >38 °C has sensitivity of 51–79 %, 48 %, 49 % and 22–58 % respectively for GAS respiratory system infections [6]. The clinical presentations of GAS and viral acute respiratory system infections show considerable overlap and no single element of the patient's history or physical examination reliably confirms or excludes GAS acute respiratory system infection [6]. Most of the American authors suggest the necessity of microbiological confirmation for the diagnosis of GAS; clinical criteria can help a clinician to select patients who need to be tested [7].

Also in the index study, the authors found the ratio of positive RSA test and throat culture test in the winter and spring months to be higher in >6 y age group. They found the ratio of positive RSA test and positive throat culture test in the summer, autumn months to be lower in >6 age group. While complaints of fever and sore throat are more suggestive of GAS infection, symptoms like cough, nasal discharge, diarrhea and conjunctivitis are suggestive of viral causes [5, 8, 9]. Complaints like headache, nausea, vomiting and abdominal pain may accompany GAS infection especially in the children [8]. In the index study, the authors found no difference between the distribution of nausea, vomiting, nasal discharge, nasal congestion, hoarseness, headache, foot-knee-leg pain, rash, fatigue, abdominal pain and ear pain in the groups with positive RSA test and positive throat culture test.

It was observed that GAS infection is higher in >6 y age group and again in this age group complaints of fever and sore throat are at the forefront and complaint of cough is lower. The authors found the presence of positive RSA test in the group with positive throat culture to be higher than the group with negative throat culture test. They found no positive RSA test or throat culture test in children <2 y age group. GAS infection is not seen frequently in <3 y age group. However, the authors found positive RVPT to be higher in <2 y age group than in 2–6 y and >6 y age groups.

No statistically significant difference was found between distribution of positive RVPT in the winter, spring, summer and autumn seasons. Viral infections may show seasonal variance and peaks. However, there is no certain information regarding seasonal distribution of viral infection; viral infections vary according to the seasons, trophic-nontrophic regions and geographic locations [10].

No difference was found between the distribution of genders in the RVPT negative and RVPT positive groups. There was no difference between distribution of fever, cough, sore throat, headache, nausea-vomiting, nasal discharge, nasal congestion, rash and fatigue in the RVPT negative and RVPT positive groups. Although the complaints like fever, cough, nasal discharge and nasal congestion are suggestive of a viral etiology but they are not specific. Some clinical symptoms are non-specific and variable in viral infections [11]. Rapid and precise determination of viral etiology in a laboratory test is necessary to initiate appropriate antiviral therapy, reduce the requirement of additional diagnostic studies and to limit unnecessary use of antibiotics in clinical therapy and also helps in epidemiological evaluation [12]. Considering and verifying the viral etiology is important for the treatment and prevention or epidemiological tracking of the disease.

Currently, population of viral infection is changing and new viral agents causing serious infections are seen. According to the etiology, it is necessary to administer the required therapy to prevent the spread of the disease and to protect the patient. Also if the pathogen is viral, unnecessary antibiotherapy would be prevented.

Conclusions

In patients of <2 y age group with acute respiratory tract infection symptoms and presenting with any complaint, primarily a viral etiology should be considered and should not be hurried for antibiotherapy. Viral etiology should be investigated and if it is necessary, antiviral therapy should be administered and the necessary precautions should be taken according to the viral etiology to prevent the contamination. In the patients of >6 y age group presenting with complaints of presence of fever, sore throat and absence of cough, primarily GAS infection should be considered and it should be confirmed with rapid strep A test and/or throat culture test and antibiotherapy should not be delayed.

Compliance with Ethical Standards

Contributions RD: Conceptualized and designed the study, designed the data collection instruments and coordinated and supervised data collection and drafted the manuscript and approved the final manuscript. SK: Designed the study, coordinated and reviewed and revised the manuscript. RD will act as guarantor for this paper.

Conflict of Interest None.

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