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Respiratory Viruses; Today's Troubled Agents, Candidates for Marker of Diagnosis and Prognosis

KEYWORDS

S.H Torun	Ayper SOMER	Melis KANTURVARDAR
Istanbul University, Istanbul Medical Faculty, Department of Pediatric Infectious Disease, Istanbul,Turkey	Istanbul University, Istanbul Medical Faculty, Department of Pediatric Infectious Disease, Istanbul,Turkey	Istanbul University, Istanbul Medical Faculty, Department of Microbiology.Department of Microbiology, Virology Unit, Istanbul,Turkey

Selim BADUR	Nuran SALMAN	Ensar YEKELER
Istanbul University, Istanbul Medical Faculty, Department of Microbiology.Department of Microbiology, Virology Unit, Istanbul,Turkey	Istanbul University, Istanbul Medical Faculty, Department of Pediatric Infectious Disease, Istanbul,Turkey	Istanbul University, Istanbul Medical Faculty, Department of Pediatric Radiology,Istanbul,Turkey

ABSTRACT *Objective: The aim was to describe the clinical and epidemiologic characteristics of patients with lower respiratory tract infection (LRTI) who were hospitalized to the Pediatric Infection Department in Istanbul due to respiratory viruses from October 2010 through May 2011.*

Material and Methods: Details of the 156 patients who were hospitalized were recorded. Respiratory viruses were confirmed in specimens using real-time reverse transcriptase-polymerase-chain-reaction (RT PCR) assay.

Results: Respiratory agents were detected in 48 (30.8%) of 156 children with LRTI. Fifty seven patients (36.5%) were female, 99 (63.5%) were male and the median age was 28.2 ±42.1 months. A single agent was identified in 41 (% 85) children, and multiple agents in 7 (%15). Influenza virus was the most common pathogen (31.2%), followed by rinovirus (20.8%), bocavirus (14.5%),coronavirus (10.4%), parainfluenza virus (8.3%), metapneumovirus (8.3%) and respiratory syncytial virus (6.2%). There were no statistically significant differences between the two groups (with isolated virus or no known viral etiology) with respect to symptoms, clinical findings, laboratory work-up, or radiological data except LDH level. Elevated levels of LDH in patients with respiratory virus were statistically significant. In addition, we showed a relationship between patients with the viral infection and peribronchial markings on chest X-ray (p = 0.017, OR 4071 CI :1.290-12, 843) and steroid therapy (p <0.001, OR 7870 CI :2.496-25, 000). Three patients (6.25%) received intensive care support and one patient with congenital metabolic disease who was detected HMPV died.

Conclusions: Diagnosis of respiratory viruses is essential not only for epidemiological data and for antiviral therapy because of easily able to achieve and increased diversity today. With all of influenza is major respiratory virus of LTRI and so vaccine program should evolve influenza vaccine for all children upper 6 months old.

Comminity acquired pneumonia (CAP) in children is still the most important cause of mortality all over the word, especially in developing countries. The overall incidence per 100 was 4 in children aged 0-5 years in industrialized countries, Northern European countries and the United States[1] while in developing countries 21-296 /100 child/year[2]. In our country, according to data from the Ministry of health, CAP is responsible of 48.4 % of deaths under 1 aged and % 42.1 deaths under 1-4 age group[3].

Bacterial pneumonia often occurs in the winter and spring months. Viral Surveillance results of respiratory viruses from all over the world have seasonal distribution., as shown by Figure 1[4]

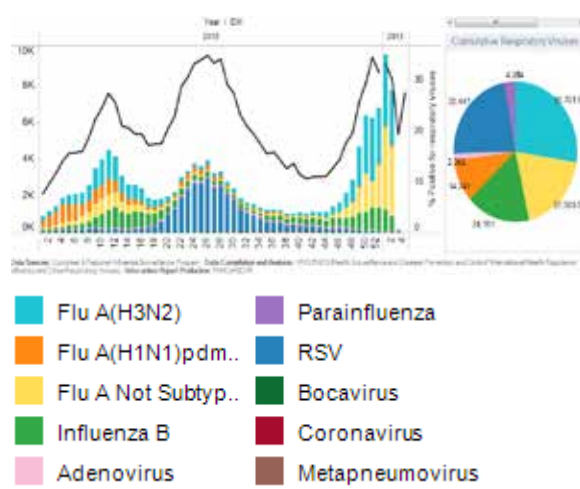

Figure 1; Viral surveillance results of respiratory viruses from all over the world

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World Health Organization (WHO) describes pneumonia as clinical signs accompanied by increased breathing rate, cough or respiratory distress. The purpose of this definitation is provide to access lifesaving antibiotics in developing countries where the incidence of CAP is very high [1,2]. Recently fever and/or acute respiratory symptoms and chest X-ray with parenchymal involment are defined as CAP [13].

Accurate and prompt etiologic diagnosis is limited by inadequate clinical, radiologic, and laboratory diagnostic methods. The aim was to describe the clinical and epidemiologic characteristics of patients with lower respiratory tract infection (LRTI) who were hospitalized to the Pediatric Infection Department in Istanbul due to respiratory viruses from October 2010 through May 2011.

Material and Methods: This study was a prospective, cross-sectional clinical, drug-free, a descriptive research.

Inclusion criteria: Having least two findings of fever, cough, wheezing, tacypnea, dispnea, cyanosis, crackles and bronchial breathing in the last 48 hours and/or chest X-ray with alveolar, lober, interstitial infiltration.Nasopharyngeal swap specimens or tracheal aspirate materal were obtained from patients. Commercial viral transport medium (ViroCult, Medical Wire & Equipment Co., England) was supplied by Ministry of Health and samples were sent to virology Laboratory located at Istanbul Faculty of Medicine. Respiratory viruses were confirmed in specimens using real-time reverse transcriptase-polymerase-chain-reaction (RT PCR) assay. RT-PCR amplification was performed for the detection of , RSV, Influenza A (Inf A), Influenza B (Inf B), Parainfluenza 1(PIV 1), Parainfluenza 2 (PIV 2), Parainfluenza 3 (PIV 3), Rhinovirus, human bocavirus(HBoV), coronavirus (CoV), human metapneumovirus (hMPV). Clinical items, laboratory and radiological findings were investigated in differentiating viral infection. Details of the 156 patients who were hospitalized were recorded.

Pediatric radiologist interpreted X-Ray of patients. Use of antibiotics decision were determined according to clinical, radiogical and laboratory findings that did not rule out to acute bacterial lower respiratory tract infection. Ceftriaxone or apciline-sulbactame were applied. Inhaled steroid (budesonide) and inhaled beta-2-agonist bronchodilator (salbutamol sulphate) treatment were applied to patients with wheezing, shortness of breath, prolonged expiratory time.

The data of all patients were evaluated with a computer package program, SPSS 19.0 for Windows.

Results: Respiratory agents were detected in 48 (30.8%) of 156 children with CAP. Fifty seven patients (36.5%) were female, 99 (63.5%) were male and the median age was 28.2 ±42.1 months. A single agent was identified in 41 (% 85) children, and multiple agents in 7 (%15). Influenza virus was the most common pathogen (n:15), followed by rinovirus (n:8), bocavirus (n:7),coronavirus (n:4), parainfluenza virus (n:4), metapneumovirus (n:2) and respiratory syncytial virus (n:1). Mix agents were RSV+HboV (n:1), HBoV+CoV (n:1), HRV+HboV (n:1), HRV+İNF B (n:2), RSV+HBoV+hMPV (n:1), HRV+hMPV+PİV3 (n:1) (Figure 2).

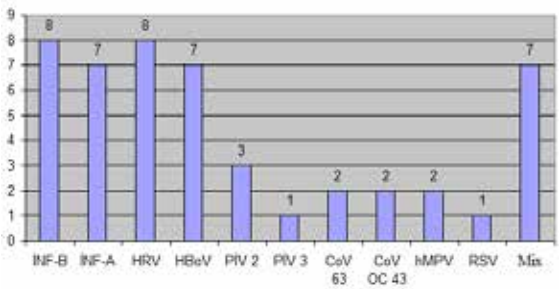

Figure 2: Deteced viral agents

33 of 48 (68.7%). patients were males. The study also investigated the seasonal variation of viruses and peak infection rate occur during january (n: 10), february (n:11) and march. (n:10)(Figure 3). The ratio of patients with chronic disease was 52% (n:25). Asthma, chronic lung disease, primer congenital metabolic disease, bone marrow transplantation/liver transplantation/kidney transplantation, malignency and malnutrutition were underlying diseases. There was no statitiscally significant difference between patients with detected viruses and not detected viruses (p>0.05) (Table 1).

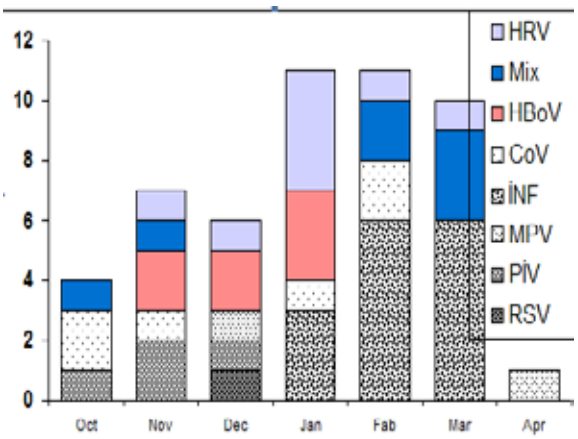

Figure 3: Monthly distribution of viruses

Tablo 1: Comparison of demographic characteristics of patients with detected viruses or not

		No virus (n)	Virus detected (n)	P
Sex	Female	42	15	0.36
	Male	66	33	
Monthly distribution	Jan	13	10	0.344
	Fab	19	11	
	Mar	14	10	
	Apr	10	1	
	May	1	0	
	Oct	14	1	
	Nov	13	3	
	Dec	22	6	
Chronic disease	No	59	23	0.438
	Yes	49	25	

Clinical presentation of patients with detected virüs were cough (n:38), fever (n:34), dirrhea (n:4), vomiting (n:3), cyanosis (n:1), tachypnea (n:27), intercostal withdrawal (n:10), wheezing (n:19) and ral on auscultation (n:20). There was no were statitiscally significant difference between patients with detected viruses and not detected viruses (p>0.05) (Table 2).

Tablo 2 : Characteristics of patients I

		No virus (n)	Virus detected (n)	P
Diarrhea	No	103	44	0.459
	Yes	5	4	
Vomiting	No	101	45	1
	Yes	7	3	
Cyanosis	No	100	47	0.227
	Yes	8	1	
Chest pain	No	103	48	0.154
	Yes	5	0	
Fever	No	43	14	0.202
	Yes	65	34	
Cough	No	30	10	0.359
	Yes	78	38	
Respiratory difficulty	No	62	35	0.047
	Yes	46	13	
Tachypnea	No	50	21	0.768
	Yes	58	27	

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Ral	No	63	28	1
	Yes	45	20	
Intercostal withdrawal	No	79	38	0.423
	Yes	29	10	
Wheezing	No	61	29	0.646
	Yes	47	19	

Laboratory findings is shown as Table 3. High level of LDH and value of low level of CK is statistically meaningful between patients with detected virus and not ($p<0.05$).

Tablo 3: Characteristics of patients II

		No virus (n=108)	Virus detected (n=48)	P
Age	Median±IQR	9±34	14±39	0.059
Duration of hospitalition		6±7	7±6	0.642
Leukocytes (/µL)		9700±6750	9300±7200	0.827
Neutrophil (/µL)		4200±4730	4105±4300	0.858
Lympocyte (/µL)		3200±2275	3210±2030	0.619
C Reactive protein (mg/L)		5.9±24.4	7.45±23.25	0.968
Lactate dehydrogenase (U/L)		552±218	622±161	0.022
Creatinine kinase (U/L)		67±117	36.5±27	0.010
Hypertransemia (U/L)		32±18	31±20.5	0.639
Na (mmol/L)	Mean±SS	136.57±2.63	136.04±2.95	0.263
Ca (mg/dL)		9.11±1.21	9.34±0.66	0.229
P (mg/dL)		4.81±1.09	4.57±1.2	0.238

Na: sodium; Ca: calcium; P:phosphorus.

Radiological findins of patients were hyperaeration (n:29), bronchial infiltration (n:19), peribronchial marking (n:12), atelectasis (n:4) and frosted-glass pattern. There was no were statitiscally significant difference between patients with detected viruses and not detected viruses ($p>0.05$) (Table 4- Pic 1-6).

Table 4.: Radiological findings

		No virus (n=108)	Virus detected (n=48)	P
Atelectasis	No	102	44	0.498
	Yes	6	4	
Frosted-glass pattern	No	100	48	0.108
	Yes	8	1	
Bronchial infiltration	No	82	33	0.347
	Yes	26	15	
Hyperaeration	No	38	19	0.599
	Yes	70	29	
Peribronchial marking	No	64	36	0.059
	Yes	44	12	

Pic 1: X-Ray LTRI* due to CoV NL63

Pic 2: X-Ray LTRI* due to RSV 2

Pic 3: X-Ray LTRI* due to Pİ V3

Pic 4: X-Ray LTRI* due to HMPV

Pic 5: X-Ray LTRI* due to HBoV

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Pic 6: X-Ray LTRI* due to Mix (RSV+HBoV+HMPV)

* LTRI:lower respiratory tract infection

Four of 48 patients required mechanical ventilation. There was no difference between the treatments compared between patients with detected virus or not (p > 0.05) (Table 5).

Table 5: Treatment and Prognosis of the patients

		No virus (n=108)	Virus detected (n=48)	P
Mechanical ventilation	No	92	45	0.131
	Yes	16	3	
Antibiotic	No	14	5	0.654
	Yes	94	43	
Steroid	No	49	16	0.146
	Yes	58	32	
Bronchodilator	No	10	5	0.777
	Yes	98	43	

Logistic regression analysis revealed a significant statistical relationship between patients with detected virus and chronic disease, peribronchial marking, steroid treatment, count of lymphocyte (Table 6).

Tablo 6: Logistic regression analysis

	P	Odds Ratio	Odds Ratio for % 95 CI	
			Lower limit	Upper limit
Chronic disease(Yes)	0.040	3.039	1.050	8.770
Peribronchial marking (Yes)	0.017	4.071	1.290	12.843
Steroid (Yes)	<0.001	7.870	2.496	25.000
Lymphocyte	0.038	1.002	1.000	1.003

Logistic Regression (model: Forward Wald) CI: confidence interval

19 of 156 patients requred mechanical ventilation and six patients died. These patients had underlying disease (n:2 malignency, n:1metabolic disease, n:1 broncho pulmoner disease or were infants (2 and 3 months aged). Patients with metabolic disease were detected hMPV.

The average LDH level was 1123±1862 in patients who died, and it was 593±174 in patients who were healed. This difference was regarded as statistically meaningful (p=0.01, p<0.05).

Discussion:

%75 of CAP cases has been occured in 15 countries from Asia and Africa, where have limited resources for healthcare. Malnutrition and unreachable sanitation are the main critical risk factors for the mortality. In our country according to health minister CAP is one the important cuse of mortality in children of alla ged population[3]. In this study 156 children admitted to an univercity hospital and six patients (3.8 %) were died in eight months. This showed that CAP is still serious problem.

Viral agents play an important role in acute lower respiratory infections and may herald the onset of pneumonia caused by secondary bacterial infections. Although information on the causes of respiratory illness in tropical countries is very scanty, available data indicates about one -third of the cases of respiratory tract infections are due to viruses [5-13]. The present study identified viruses in 30.8% of patients hospitalized for CAP.

As well as bacterial or viral factors in the etiology of CAP is known to play a role and sometimes both bacterial,viral or multiple viral factors are. In Michelow[6] and colleagues's study 34% ratio of bacterial, 16% ratio of single viral, 23% ratio of bacteria and viral, 3% ratio of mix virus, and 21% raito of no pathogens identified factors shown. In this study A single virus was identified in 41 (% 85) children, and multiple viruses in 7 (%15). But in terms of potential mix infection (bacterial+ viral) could not investigated. Because of pneumolysin based PCR or serological assestment for atypical agents would bring additional cost. Hemoculture taken from patients who received antibiotics. It is known that positive hemoculture rate is < %10 in the etiology of CAP[14]. Therewithal patients in this study received antibiotics before admitted to our clinics. And so there was no positive hemoculture in this study.

Recently the etiology of viral agents is determined by similar rates of RSV,PIV,INF. Today new viruses are detected by recent studies such as hMPV,HBoV and new tyoes of CoV. In this study hMPV was found 8.3% and HboV %14.3, CoV % 10.4 etc. The diversity of respiratory viruses in children with CAP requires isolation from others to prevent nosocomial LTRI. Recent studies has shown that LTRI having under five years tend to increase the risk of development of asthma in later of life[15].

Although RSV is known as the single most frequent lower respiratory tract pathogen in infants and young children worldwide. This study showed that RSV is detected 6.2% in children with CAP. Alike in Greece and Japan the ratio of children with detected RSV is very low[7,8]. Ratio of RSV and detected as a agent of a mix infection are thougt to be question that is RSV decresed or diminished living space with global warming?.

There has been a recent resurgence in interest in the relationship between respiratory viruses (RSV..) and the use of the pneumococcal vaccines as an additional measure to prevent

hospitalization due to CAP[16.] Relationship between RSV and invasive pneumococcal disease is not clear. Effects on rates of RSV infection after statewide introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) in 2008 need to investigate.

HRV that is the most reason of cold has been shown to be important in the etiology of LTRI in children with chronic disease or immunsuppressive disease[17,18 ,19.] HRV was detected 20.8 % in this study too. High rates of children with chronic disease in this study might be caused.

Influenza virüs infection,the most common viral infection was detected 31.2 percent as expected. Influenza usually causes a seasonal disease and seen in the northern hemisphere during the winter months between november and april. The influenza vaccine has short duration of protection. However, as shown in this study that influenza infection begining at January influenza vaccine preferably inocculate until january.

There is no specific clinical findings in children with CAP to differentiate the etiology [20,21]. But It is emphasized that the mother's claim of "breathing fast" is a importent clue of hypoxia in children[22]. In this study patients with vomiting, diarrhea, cyonosis, chest pain, cough, tachypnea, wheezing or rales on auscultation were not distinctive difference to etiol-

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ogy. Tachypnea, hypoxemia (pulse transcutaneous saturation ≤92 %), withdrawal, nasal flaring are important in determining the severity of pneumonia. Respiratory distress was less observed in patients with detected virüs in this study. Only 3 patients in need of intensive care (1 month old boy with HRV, 8 months old girl with PIV-3, 14 months olds boy with hMPV and conjenital metabolic disease) is thought to be that respiratory viruses causes less serious disease among children.

Studies were investigated about radiological findings in differentiating the etiology of pnemonia. But none of them showed specific findings that viral or bacterial agents [23],[4]. Alveolar infiltration have been described 74 % of patients with pnemonia confirmed by microbiologically. In addition alveolar lnfiltration was found in 25 % of patients with influenza pnemonia.ın this study hyperaeration, bronchial infiltration, peribronchial marking, atelectasis and frosted-glass pattern were similar findings in children with detected viruses or not. However peribronchial marking was higer than in patients with detected viruses (p=0.017 OR= 4.071 CI: 1.290-12.843).

There are a lot of studies that investigated the role of acute phase reactants in the etiology or severity of CAP [24]. Korppi[25] and colleagues reported that the association of CRP> 80 mg/L WBC > 17000 PCT >0.8 mg/L ESR > 63 mm/h specificity predicts pneumococal infection with 65 %. In this study the relationship between lymphoctes count and detection of virüs was determined as statistically meaningful (p=0.038 OR= 1,002 CI: 1.000-1,003).

Flood[26] and colleagues's meta-analysis of eight studies showed that the value of 40-60 mg/L of CRP is revealed 64 % the positive predictive value and 41 % the prevalence for bacterial pneumonia. In this study CRP, count of lymphocyte, neutrophil and AST was no statistically significant difference between pateints with detected virüs and not. High level of LDH (622±161 N 180-430) and value of low level of CK (36,5±27 U/L N 39-108) is statistically meaningful between patients with detected virus and not ((p=0.022 p<0.05).

A study conducted during the pandemic with (H1N1) virus in Mexico by Padilla[27] et al. laboratory abnormalities reported as LDH elevation (100%), creatine kinase (CK) elevation (62%) and lymphopenia (61%). In another study[28], high CRP (65%), LDH (53%), CK (19%) and aspartate aminotransferase (AST) levels (18%) and lymphopenia (30%) were included. In patients with respiratory difficulty, and with the need of mechanical ventilator support, CRP and LDH elevations were found statistically meaningful. These data suggest that these values could be used as indicators of serious disease in hospitalized patients with H1N1 infection.

Mortality rate of CAP decline 97 % to < 5% in the last 50 years [5]. In this study mortality is 3.8 % (n:6/156). Two of them were receiving chemotherapy due to leukemia, and the others had underlying disease (conjenital metabolic disease, bronchopulmonary dişese) or were 2 and 3 months old. Only one of patients was detected viral agent. Guidelines for diagnosis and treatment of CAP in children highlighted in this study. Promote the use of guidelines and algorithms for diagnosis and treatment of CAP must be explained the importance in every meeting pediatricians.

Conclusion:

The respiratory viruses and it's clinical importance has been investigated and studied on 156 children, which are 0 – 16 ages and have CAP complaints; during the dates between 1st of October / 2010 then 31st of May / 2011. This study has been applied in the Pediatric Infection Department in Medical Faculty of Istanbul University.

Viral agents has been determined on 30,8 % of patients with CAP . %31.2 Influenza viruses (31.2 %), HRV (20.8%),HBoV (14.5 %) and mixt infections (14.5%) HBoV were primary detected in this study, despite of RSV as reported in the literature. These datas shows that the surveillance are more impostant than cross – sectional studies.

The diversity of respiratory viruses in children with CAP requires isolation from others to prevent nosocomial LTRI. Patients with CAP were inverstigated as distinctive clinical, radiolojical and laboratory findings. Though these parameters used very often in daily practice, they were found to be similar as informed in the literature. However elevation of LDH may reflect the severity of the clinic. In addition, we showed a relationship between patients with the viral infection and peribronchial markings on chest X-ray (p = 0.017, OR 4071 CI :1.290-12, 843).

With all of influenza is major respiratory virus of LTRI and so vaccine program should evolve influenza vaccine for all children upper 6 months old.

All over the word respirator viruses leading to serious outbreaks of the economy, health care system in recent years have been indelible mark on everday life. New studies is required for early diagnosis and treatment of CAP.

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