Epidemiology of Common Respiratory Virus in Hospitalized Young Children with Wheezing

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Background: *Acute wheezing episodes are frequently associated with respiratory viral infection in children. Publications worldwide have reported that some respiratory viruses are associated with the induction of acute wheezing. However, epidemiology of this virus in particular in Thailand has so far been limited.*
Objective: *To estimate the frequent of respiratory viruses in hospitalized children with acute wheezing.*
Material and Method: *A prospective study was conducted on children <5 years old, admitted with acute wheezing episodes from June 2014 to September 2015. Viral pathogens (RSV, rhinovirus, influenza virus, enterovirus 68) were detected in nasopharyngeal aspiration by polymerase chain reaction (PCR). Clinical data were prospectively recorded.*
Results: *Among the 74 acute wheezing children, 42 (56.8%) were positive for viral PCR; rhinovirus was the most frequent detected virus (39%), followed by RSV (11%) and enterovirus 68 (5%). Influenza virus was not detectable. No co-viral infections. Rhinovirus infection occurred throughout the year. RSV majority occurred in rainy season. While enterovirus 68 infection occurred in August and December. All patients presented with cough and dyspnea (100%). Fever was found in 67 to 100%. Gastro-intestinal symptoms including vomiting and diarrhea were uncommon. Only 10 to 50% of patients improved after bronchodilator inhaled. Leukocytosis and eosinophil count in rhinovirus was higher than for other respiratory viruses.*
Conclusion: *Viral infections are the common cause of acute wheezing in children. The pattern of infected viral pathogens depends on age, season and year. Rhinovirus and RSV are the most frequently detected viruses. Almost all cases have prodome respiratory symptoms. Rhinovirus may be more related to allergic conditions. However, more research is needed to confirm this finding.*

Keywords: *Respiratory virus, Wheezing, Respiratory syncytial virus (RSV), Rhinovirus, Enterovirus 68*

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Acute viral respiratory infection is one of the leading causes of hospitalization of young children and may be related to a large number of wheezing episode[1]. The common causes of viral induced wheezing in children include respiratory syncytial virus (RSV), rhinovirus, human metapneumovirus and influenza virus[2]. Rhinovirus seems to be the most common respiratory virus associated with acute wheezing in the school-age children, whereas RSV appear to be more frequent in younger children[3]. In addition, the pattern of respiratory viral pathogen is variable and also depends on location, season and year[4,5].

The epidemiology of respiratory viruses in children with acute respiratory tract infections has been documented in various regions[6-8]. However, the role of novel respiratory viruses as a cause of acute wheezing in Thai children has not been well studied. This study was designed to determine the epidemiology and clinical characteristics of respiratory viruses in

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hospitalized young children with acute wheezing.

Material and Method

Participants

Children admitted to Thammasat hospital (Pathumthani, Thailand) with acute wheezing, aged <5 years, from June 2014 to September 2015, were recruited. Approval for the study was granted by the Institutional Ethics Committee of Thammasat Hospital, and informed consent was obtained from all parents before study entry. Patients with underlying chronic disease including congenital heart disease, chronic lung disease, cerebral palsy, immunodeficiency, chronic kidney disease and chronic liver disease were excluded.

Study design

All guardians were asked to complete the case record form (CRF). A physical examination was carried out in all patients. Clinical epidemiological information including bronchodilator response, duration of oxygen supplement, and antibiotic prescription was collected by pediatricians on admission. Nasopharyngeal aspiration samples were obtained within 24 hours of admission by trained nurses.

Laboratory analysis

Total nucleic acid extraction was extracted from 300 ul aliquot of each clinical specimen using the Gene All RibospinvRDII. The influenza virus was detected using a one step multiplex quantitative Real-time polymerase chain reaction (qRT-PCR). RSV, rhinovirus and enterovirus68 were identified using Real-time polymerase chain reaction (RT-PCR)[9,10].

Statistical analysis

Descriptive statistics of the responses were generated. Continuous variables were presented as the mean values and standard deviations (SDs), and categorical variables were presented as numbers and percentages. For categorical data, comparisons between groups were performed using a contingency table with Fisher's exact test. For continuous data, comparison between groups was performed using one-way ANOVA analysis of variant. Multiple comparison tests were performed using Bonferroni method. A $p<0.05$ were considered statistically significant.

Results

Seventy four children with acute wheezing participated in the study including 54 (73%) boys and 20 (27%) girls, with an average age of 2.2±1.2 year. 44 (60%) had a history of previous wheezing. The patient demographic data are shown in Table 1.

Viral findings

Among the 74 children with acute wheezing, 42 (56.8%) were positive for viral PCR; rhinovirus was the most frequent detected virus (39%), followed by RSV (11%) and enterovirus 68 (5%). Influenza virus was not detectable. No co-viral infections were identified in this study. The result is shown in Fig. 1.

Seasonal variations of respiratory virus

Admission for viral-associated wheezing episodes occurred mainly in August. Rhinovirus infection occurred throughout the year. The detection rate of rhinovirus peaked in August and December, respectively. RSV infection majority occurred in the rainy season (July to September). While enterovirus68 infection occurred in August and December. The distribution of viruses by month are shown in Fig. 2.

Clinical characteristics

Among the 74 patients, all presented with cough and dyspnea (100%). Fever was found in 67 to 100%. RSV was associated with higher grade fever than

Table 1. Demographic data

Characteristic	n (%)
Age (years); mean ± SD	2.2±1.2
Age ≤2 years	37 (50)
Boy	54 (73)
Asthma	13 (17.5)
1st episode wheezing	13 (17.5)

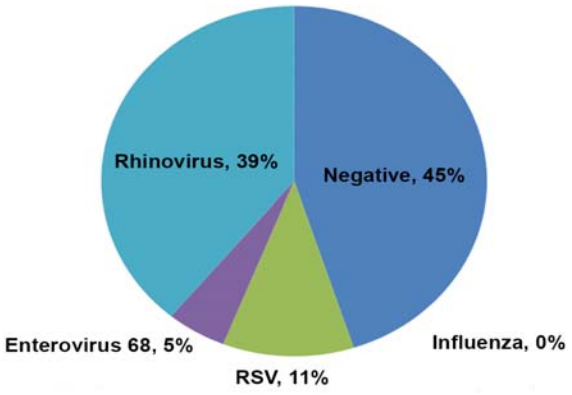

Fig. 1 Percentage of viral detection in virus-positive patients.

other viruses. Gastro-intestinal symptoms including vomiting and diarrhea were uncommon. Only 10 to 50% of patient improved after bronchodilator inhaled. In laboratory tests, leukocytosis and absolute eosinophil count in rhinovirus was higher than other respiratory viruses.

Rhinovirus and RSV were the main pathogens detected in our study. Clinical characteristics in both viruses are compared in Table 2 and 3. Demographic data did not differ between the groups, but the rhinovirus cases were more likely positive for a family history of asthma than the RSV group ($p = 0.027$). RSV positive patients presented with higher grade fever and higher respiratory rates than those with rhinovirus infection. Rhinovirus were more response to bronchodilator inhaled, frequent intubation and prescription of antibiotic therapy, than RSV infection but meant a shorter length of stay. In laboratory tests, higher absolute eosinophil count ($p = 0.014$) and leukocytosis ($p = 0.004$) occurred more frequently in rhinovirus. Clinical characteristics and outcomes of wheezing episodes associated with single viral infection are compared in Table 2 to 4.

Discussion

In this study, the frequency of respiratory viral detection in young children with acute wheezing was 56.8%. This detected rate was similar to that previously reported in China[11-13]. The proportion was relatively lower than those of previous studies in Japan[3,14,15].

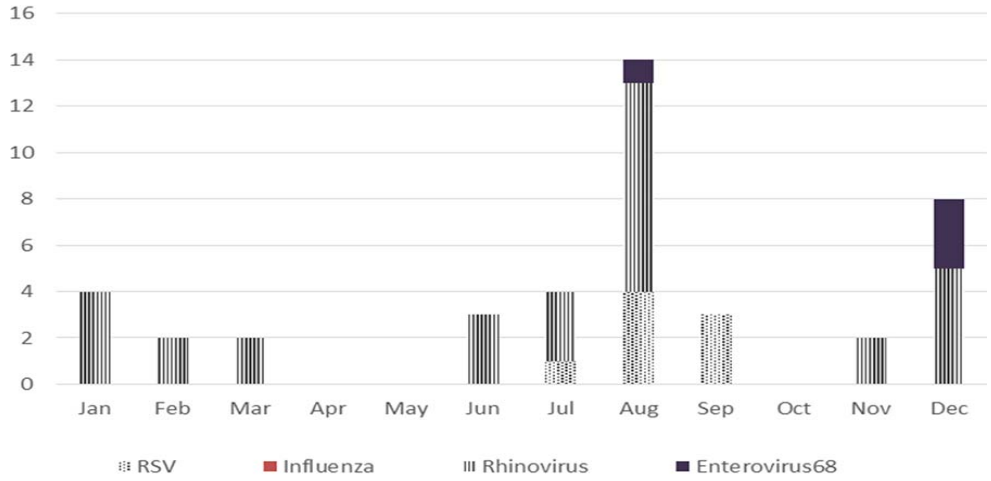

Fig. 2 Seasonal variation of Respiratory viruses.

Table 2. Comparison of clinical characteristics

Total (n = 74)	RSV (n = 8)	Rhinovirus (n = 30)	Enterovirus 68 (n = 4)	No detection (n = 32)	*p*-value
Demographic data					
Boy, n (%)	4 (50)	19 (63)	1 (25)	19 (59)	0.507
Age (years), mean ± SD	2.2±1.4	2.2±1.3	2.5±1.1	2±1.2	0.881
Age <2 year, n (%)	4 (50)	15 (50)	1 (25)	17 (53)	0.871
Asthma, n (%)	1 (13)	6 (20)	3 (75)	3 (9)	0.027
Paternal asthma, n (%)	3 (38)	7 (23)	1 (25)	2 (6)	0.060
Symptom					
Fever, n (%)	7 (88)	20 (67)	4 (100)	26 (81)	0.380
Cough, n (%)	8 (100)	30 (100)	4 (100)	31 (97)	1.000
Rhinitis, n (%)	7 (88)	28 (93)	4 (100)	31 (97)	0.467
Dyspnea, n (%)	8 (100)	29 (97)	4 (100)	29 (91)	0.812
Vomiting, n (%)	5 (63)	6 (20)	1 (25)	12 (38)	0.103
Diarrhea, n (%)	2 (25)	1 (3)	0	4 (13)	0.221

Table 3. Comparison of physical examination and investigation

Total (n = 74)	RSV (n = 8)	Rhinovirus (n =30)	Enterovirus 68 (n = 4)	No detection (n = 32)	*p*-value
BT (°C), mean ± SD	38.6±1.2*	37.6±0.8*	37.6±0.4	38±1	0.039
RR (/min), mean ± SD	49±16 (30 to 80)	44±6 (30 to 60)	49±10 (40 to 62)	43±8 (32 to 66)	0.290
Asthma score, mean ± SD	5±1.5 (3 to 7)	4.9±1.2 (3 to 8)	6.3±2.1 (4 to 8)	4.7±1.6 (2 to 9)	0.234
Bronch. response, n (%)	1 (12.5%)	10 (33.3%)	2 (50%)	7 (21.9%)	0.398
SpO_2, mean ± SD	96.5±1.5	96±1.7	93±6.3	96.3±2.2	0.056
WBC (/mm^3) mean ± SD	9,946±3,401**	16,240±5,305**	15,975±3892	13,134±4,465	0.004
AEoC (/mm^3) mean ± SD	66±84***	426±379***	361±629	199±272	0.014

BT = body temperature; RR = respiratory rate; Bronch. response = bronchodilator response; SpO_2 = oxygen saturation via pulse oximetry; WBC = white blood cell; AEoC = Absolute eosinophil count
* Significant multiple comparison test by Bonferroni = 0.043, ** Significant multiple comparison test by Bonferroni = 0.008, *** Significant multiple comparison test by Bonferroni = 0.048

Table 4. Comparison of outcomes

Total (n = 74)	RSV (n = 8)	Rhinovirus (n = 30)	Enterovirus 68 (n = 4)	No detection (n = 32)	*p*-value
ATB, n (%)	3 (38)	12 (40)	3 (75)	14 (44)	0.649
Intubation, n (%)	0	3 (10)	0	0	0.361
HFNC, n (%)	2 (25)	4 (13)	0	3 (9)	0.606
O_2 use (days, mean ± SD	4±2.8	2.5±2.8	1.5±1.7	1.6±2.3	0.092
LOS (days), mean ± SD	6.6±3.7	4.2±3	3.8±1.7	5.3±2.3	0.111
Mortality, n (%)	0	0	0	0	-

ATB = antibiotic; HFNC = high flow nasal cannulas; O_2 use = oxygen use; LOS = length of stay

This difference might be due to regional variation and testing limitations. We could not perform a full range panel of PCR assays. We only tested for 4 viruses (RSV, rhinovirus, influenza virus, enterovirus 68). Thus, there might be undetected, untested viral pathogens. However, our data shows that viral respiratory infections are the most common cause of acute wheezing in children.

In previous studies, RSV and rhinovirus were the predominant pathogens found in wheezing children[1-3,11-15]. Our data confirms that rhinovirus and RSV play a key role in acute wheezing episodes in children; the prevalence of rhinovirus was close to that in previous studies (39% compare to 28 to 32%) but RSV was detected at lower levels (11% compare to 9 to 40%)[11-15]. In addition, we detected the prevalence of rhinovirus and RSV to be equal in infants <2 year and older children. This contrasts other previous studies where RSV was the most frequently detected, closely followed by rhinovirus, in infants <2 years of age; with rhinovirus the most prevalent in older children[3].

We found some seasonal variation of respiratory viruses. Rhinovirus infection occurred throughout the year, as shown in previous studies[11-16]. The majority of RSV infection occurred in the rainy season, differing from other studies that detected RSV infection mostly in the winter[11-13]. This finding supports that patterns of respiratory viral pathogens are variable, depending on location, region, season and year.

According to previous reports, RSV is one of the future risk of asthma, but other pathogens, such as rhinovirus, may trigger allergic conditions[11-13,15,16]. Our study supported this finding. We found that rhinovirus patients had leukocytosis, high eosinophil count and were more responsive to bronchodilator inhaled. Currently, our results do not show any statistical significance, perhaps due to too few subjects. More research is needed to explain the relation between rhinovirus and allergic conditions.

The limitation in this study deserves further comment. Due to our institutional constraints, a full range PCR for the respiratory viral panel could not be performed. For these reasons, the prevalence of viral identification in wheezing children might be under detected. Second, the bronchodilator response might be interfering with previous allergic conditions of the patients. Thus, more research is essential to better explain reactive airway conditions in the patients.

In summary, hospitalized young children with wheezing are frequently associated with viral infection. The pattern of infected viral pathogens is dependent on age, season and year. Rhinovirus and RSV are the most prevalence viruses in young children with acute wheezing. Almost all cases have prodome respiratory symptoms. Rhinovirus may be more related to allergic conditions. However, more research is needed to confirm this finding.

What is already known on this topic?

Acute wheezing episodes are frequently associated with respiratory viral infection in children. Publications worldwide have reported respiratory viruses are associated with the induction of acute wheezing.

What this study adds?

Viral infections are the common cause of acute wheezing in hospitalized Thai children. The pattern of infected viral pathogens is depending on age, season and year. Rhinovirus and RSV are the most frequently detected viruses. Almost of case have prodome respiratory symptoms. Rhinovirus may be more related to allergic condition.

Acknowledgements

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Potential conflicts of interest

None.

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ระบาดวิทยาของการติดเชื้อไวรัสที่พบบ่อยในผู้ป่วยเด็กเล็กที่รับการรักษาในโรงพยาบาลที่มีภาวะหอบและฟังปอดพบเสียงวี้ด

นิศากร คำจันทร์, อารยา ศรัทธาพุทธ, ภาสกร ศรีทิพย์สุโข, ปรียาพร วิชัยวัฒนา, ยง ภู่วรวรรณ

ภูมิหลัง: *ภาวะหายใจหอบและหายใจเสียงวี้ดในเด็กมักจะสัมพันธ์กับภาวะกับการติดเชื้อไวรัส มีรายงานมากมายพบว่าเชื้อไวรัสกระตุ้นให้เกิดอาการหอบและมีเสียงวี้ดได้ แต่ในประเทศไทยการศึกษาถึงระบาดวิทยาของเชื้อไวรัสในเด็กที่เข้ารับการรักษาตัวในโรงพยาบาลด้วยอาการหอบมีเสียงวี้ดยังมีน้อย*

วัตถุประสงค์: *เพื่อศึกษาถึงระบาดวิทยาและอาการทางคลินิกของผู้ป่วยเด็กเล็กที่เข้ารับการรักษาในโรงพยาบาลด้วยเรื่องหอบและพบเสียงวี้ด*

วัสดุและวิธีการ: *ศึกษาในผู้ป่วยเด็กอายุ <5 ปี ที่เข้ารับการรักษาในโรงพยาบาลธรรมศาสตร์ด้วยเรื่องหอบ และพบเสียงวี้ดในช่วงเดือนมิถุนายน พ.ศ. 2557 ถึง เดือนกันยายน พ.ศ. 2558 โดยเก็บข้อมูลทั่วไป อาการทางคลินิก และผลการรักษาตามแบบสอบถาม นอกจากนี้จะมีการเก็บสารคัดหลั่งจากคอหอยเพื่อส่งตรวจหาเชื้อไวรัสด้วยวิธี PCR ไวรัสที่ตรวจได้แก่ respiratory syncytial virus (RSV), rhinovirus, influenza virus, enterovirus 68 และทำการวิเคราะห์ข้อมูล*

ผลการศึกษา: *มีผู้ป่วยเข้าร่วมการศึกษาทั้งหมด 74 ราย ในจำนวนนี้ตรวจพบเชื้อไวรัสในสิ่งส่งตรวจ 42 ราย (56.8%) เชื้อที่พบมากที่สุดคือ rhinovirus ร้อยละ 39 รองลงมาคือ RSV ร้อยละ 11 enterovirus 68 ร้อยละ 5 ตรวจไม่พบเชื้อ influenza virus และไม่พบมีการติดเชื้อไวรัสร่วมกันในผู้ป่วย พบการติดเชื้อ rhinovirus ได้ตลอดทั้งปีส่วน RSV พบมากช่วงฤดูฝน ในขณะที่ enteroviurs 68 พบช่วงเดือนสิงหาคมและเดือนธันวาคม ผู้ป่วยที่ติดเชื้อไวรัสทั้งหมดจะมีอาการไอและหอบ พบมีไข้ร้อยละ 67 ถึง 100 อาการคลื่นไส้อาเจียนพบได้น้อยและพบว่ามีผู้ป่วยเพียงร้อยละ 10 ถึง 50 ที่ตอบสนองดีต่อการพ่นยาขยายหลอดลม สำหรับผลการตรวจทางห้องปฏิบัติการพบว่าเชื้อ rhinovirus จะพบมีภาวะเม็ดเลือดขาวสูงและพบมี eosinophil ในเลือดสูงกว่าเชื้ออื่น*

สรุป: *การติดเชื้อไวรัสเป็นสาเหตุสำคัญที่พบในเด็กที่เข้ารับการรักษาในโรงพยาบาลด้วยเรื่องหอบและมีเสียงวี้ด โดยเชื้อที่เป็นสาเหตุจะพบแตกต่างกันตามอายุและฤดูกาล เชื้อ rhinovirus และ RSV เป็นเชื้อที่พบบ่อยที่สุด อาการแสดงในผู้ป่วยที่ติดเชื้อไวรัสแต่ละชนิดนั้นคล้ายคลึงกัน คือมีจะมีอาการไข้ไอนำมาก่อนตามด้วยอาการหอบ พบว่าเชื้อ rhinovirus จะมีความสัมพันธ์กับภาวะภูมิแพ้มากกว่าเชื้ออื่น โดยพบมี eosinophil เลือดสูง แต่อย่างไรก็ตามควรมีการศึกษาต่อเพิ่มเติมเพื่อยืนยันผลการศึกษานี้*