Prevalence of respiratory viruses in wheezing children not older than 24 months of age

Martín Bedolla-Barajas[1], Hilda Montero[2], Jaime Morales-Romero[2], Adriana Landa-Cardeña[2], Jahaziel Díaz[2], Netzahualpilli Delgado-Figueroa[1] and Luis Gustavo Orozco-Alatorre[1]

[1]Nuevo Hospital Civil de Guadalajara Dr. Juan I. Menchaca, Guadalajara, Jalisco, Mexico; [2]Instituto de Salud Pública, Universidad Veracruzana, Xalapa, Veracruz, Mexico

Abstract

Introduction: *Wheezing in children not older than 24 months of age is a frequent event, and viruses are usually the causative agents. The aim of the study was to estimate the prevalence of respiratory viruses in wheezing children who were not older than 24 months of age and who had no history of asthma.* **Methods:** *Fifty-five Mexican children were included in an analytical cross-sectional study. Nasal secretions were obtained by using sterile rayon-tipped applicators to identify the virus by polymerase chain reaction or reverse transcription-polymerase chain reaction: adenovirus, bocavirus, human rhinovirus, influenza virus type A, human metapneumovirus, parainfluenza, rhinovirus, and respiratory syncytial virus. The prevalence of viral etiology was estimated by dividing the frequency of the identified virus by the number of participants. Ninety-five percent confidence intervals for proportions were calculated.* **Results:** *Most of the patients were male (35/55, 63.6%). The average time of evolution of wheezing episode was 3 days. The third part of enrolled population were receiving antibiotics. Respiratory viruses were detected in 33 (60%; 95% CI: 46.8-71.9%) out of 55 cases, and viral coinfection was detected in five cases (9.1%; 95% CI: 3.5-19.9%). Human metapneumovirus was the most frequently identified virus (23.6%), followed by bocavirus (14.5%), respiratory syncytial virus and rhinovirus (12.7% each), and to a lesser extent influenza virus type A and parainfluenza. Rhinovirus was the predominant virus in outpatient children (28.6%). In the inpatient emergency room and inhalotherapy room, human metapneumovirus predominated (41.2 and 16.1%, respectively).* **Conclusion:** *bocavirus and human metapneumovirus were the most frequently identified viruses in Mexican children who were < 2 years of age, suffered from wheezing, and had no history of asthma.*

KEY WORDS: *Virus. Wheezing. Children. Respiratory. Virus. Asthma.*

Resumen

Introducción: *Las sibilancias en niños ≤ 24 meses de edad son un evento frecuente, y los virus son los agentes que más comúnmente las ocasionan.* **Objetivo:** *Estimar las prevalencias de los virus respiratorios en niños de hasta 24 meses de edad con sibilancias y sin antecedentes de asma.* **Métodos:** *En un estudio de corte transversal y analítico se incluyeron 55 niños mexicanos con sibilancias y sin antecedentes personales de asma que acudieron a un hospital de segundo nivel de atención. Se obtuvieron secreciones nasales usando aplicadores estériles con punta de rayón para identificar, mediante reacción en cadena de la polimerasa (PCR) o PCR en tiempo real, adenovirus, bocavirus (hBoV), rinovirus (hRV) influenza tipo A (IF), metaneumovirus (hMPV), parainfluenza (PIF) y virus sincitial respiratorio (VSR). La prevalencia de la etiología viral se estimó dividiendo la frecuencia del virus identificado por el número de participantes. Se calcularon los intervalos de confianza al 95% (IC 95%) para proporciones.* **Resultados:** *Predominaron los hombres: 35/55 (63.6%). La evolución promedio del episodio de sibilancias fue de 3 días. La tercera parte estaba recibiendo antibióticos. Se detectaron virus respiratorios en*

Correspondencia:
Martín Bedolla-Barajas
Salvador de Quevedo y Zubieta, 750
Col. La Perla
C.P. 44340, Guadalajara, Jal., México
E-mail: drmbedbar@gmail.com

Fecha de recepción en versión modificada: 20-07-2016
Fecha de aceptación: 25-07-2016

Gac Med Mex. 2017;153:329-34
Contents available at PubMed
www.anmm.org.mx

33/55 casos (60%; IC 95%: 46.8-1.9%), coinfección viral en 5 (9.1%; IC95%:3.5-19.9%). El hMPV fue el virus más frecuentemente identificado (23.6%), luego el hBoV (14.5%), el VSR y el hRV (12.7% cada uno), y en menor grado estuvieron IF y PIF. Los hRV fueron los virus predominantes en niños outpatient *(28.6%); en* Inpatient emergency room *y en* Inpatient Inhaloterapy room *predominaron los hMPV (41.2% y 16.1%, respectivamente).* **Conclusión:** *hMPV y hBoV fueron los virus más frecuentemente identificados en niños mexicanos con edad ≤ 24 meses, con sibilancias y sin antecedentes de asma.*

PALABRAS CLAVE: *Virus. Sibilancias. Niños. Respiratorio. Virus. Asma.*

Introduction

In childhood, respiratory infections are a common event. So, it is not uncommon for a child to have six to eight episodes a year, and of these, 57-89% were reported to have a viral etiology[1,2].

Wheezing has been related to a decrease in the diameter of the bronchus, mainly related to inflammation of the epithelium or smooth muscle contraction. During the first few years of life, the frequency of at least one acute episode of wheezing varies between 30-50%[3-5] and tends to be higher in populations with a low income[6]. Sociodemographic and environmental factors influence wheezing incidence in the population.

Diverse causes are related to the presence of acute wheezing in childhood and these include viruses, asthma, gastroesophageal reflux disease, and bacterial agents. However, respiratory viruses are noteworthy for their great diversity, seasonal and geographical variation, and the ability to produce different degrees of severity of the disease.

When wheezing is related to a viral infection, the most frequently identified agents are the following: human metapneumovirus (hMPV), human adenovirus (hAD), respiratory syncytial virus (RSV), human rhinovirus (hRV), human bocavirus (hBoV), influenza virus (IF), parainfluenza virus (PIF), and human coronavirus[2,7-9].

In Mexico, little is known about viral agents associated with acute wheezing in children. So this study aims to determine the prevalence of respiratory viruses in children who are not older than 24 months and suffer from wheezing.

Methods

Setting

The selection of children was made from the pediatric emergency department of a secondary care university hospital located in Guadalajara city, Mexico and that provides medical care to people without social security.

Design and patients

To carry out this work, an analytical cross-sectional study was designed. Patients were consecutively recruited from December 2012 to April 2013. In total, 62 children with wheezing were selected; of these, 55 were < 24 months of age.

Procedures

The identification of wheezing was made by the pediatrician who provided treatment to the child at that time. Then, through an interview, one of the parents or guardians of children answered a structured questionnaire that included questions about age, sex, personal history of asthma, maternal history of breastfeeding, and the time of evolution of the disease.

Children were categorized by the following features: (i) the presence or absence of a virus in secretions; (ii) the site where they were recruited: emergency room consult (outpatient), inpatient in the emergency department (inpatient at emergency room), and inpatient in inhalotherapy service (inpatient at inhalotherapy room); and (iii) the severity of the episode was determined by peripheral capillary oxygen saturation (SpO2): mild (at least 96%), moderate (92-95%), and severe (not more than 91%)[10].

Clinical samples

Nasal swabs were collected the same day of identification of wheezing in children using sterile rayon-tipped applicators (Puritan Medical Products Co. LLC, Guilford, ME, USA) in accordance with World Health Organization guidelines[11]. The sample collected was maintained at 4°C in Leibovitz viral transport medium with 100 IU/ml penicillin, 0.01 mg/ml streptomycin, and 0.25 µg/ml amphotericin B (American Type Culture Collection, Manassas, VA, USA). The samples were processed and analyzed at the virology laboratory of the Instituto de Salud Pública (Public Health Institute) of the University of Veracruz (Veracruz, Mexico).

Virus detection

Viral genomes were extracted by using a PureLink™ Viral RNA/DNA Mini Kit (Invitrogen Corporation, Carlsbad, CA, USA). The detection of viruses (adenovirus, bocavirus, influenza type A, metapneumovirus, parainfluenza, respiratory syncytial virus, and rhinovirus) was carried out by using reverse transcription-polymerase chain reaction (RT-PCR) or PCR with previously described primers and methods[12].

Statistical analysis

The data analysis was performed by using SPSS v20.0 (IBM Corporation, Armonk, NY, USA). The quantitative variables are presented as mean and standard deviation, and qualitative variables as frequencies and proportions. To compare proportions, the chi-squared test or Fisher exact test was used as necessary. The prevalence of respiratory viral etiology in children with wheezing was estimated by dividing the frequency of viral genotype by the number of participants in the study; additionally, we estimated their respective 95% confidence intervals (CI). P values of not more than 0.05 were considered statistically significant.

Ethics

The study was approved by the Ethics Committee and the Committee on Hospital Research where the study was conducted, and written informed consent was obtained from parents or guardians of participating children.

Results

A total of 35 males and 20 females with wheezing were included, resulting in a male-to-female ratio of 1.8 to 1 (Table 1). About half of the children were less than a month old, and more than one third were over a year old. About 30.9% were born prematurely. The frequency of breastfeeding at the time of the study was nearly 50%, and the average age of onset of the process of weaning was 3.4 months. The average time of evolution of the disease was three days. For the current episode of respiratory disease, almost a third of the children were using some type of antibiotic. Pathogenic viruses were detected in 33 (60%; 95% CI: 46.8-71.9%) out of 55 children. The distribution of viral agents is presented in table 2. The most identified virus was hMPV (23.6%), followed by hBoV (14.5%), RSV and hRV (12.7% each), and to a lesser extent IF and PIF virus. Of these, five cases (9.1%; 95% CI: 3.5-19.9%) had a coinfection: RSV + IF (n = 1), RSV + hMPV (n = 1), RSV + hRV (n = 2), and lastly hMPV + PIF (n = 1).

Table 1. General characteristics of the population of children with wheezing

Male, n (%)	35 (63.6)
Age, months, n (%)	
< 1 month	27 (49.1)
1-11 months	9 (16.4)
12-24 months	19 (34.5)
Prematurity, n (%)	17 (30.9)
Breastfeeding, n (%)	
Yes	49 (89.1)
Current	25 (46.3)
Disease duration (days), mean ± SD	3.2 ± 1.0
Antibiotics use, n (%)	17 (30.9)

SD: standard deviation.

The clinical characteristics of children with a viral infection were similar to those of children without the presence of a virus (Table 3). In both groups, cough and rhinorrhea predominated (100%), and intercostal retractions were present in nearly 90% of the patients. Nearly 70% of children had a fever of at least 38°C. Diarrhea was present in < 15% of the cases in both groups. Of note, the SpO2 showed a statistically significant association with the presence of viral infection (p = 0.024).

Table 4 shows the frequency of the virus according the place where the children received medical care. In the outpatient group, rhinovirus (28.6%) prevailed; in the inpatient emergency room group, hMPV (41.2%) and hBoV (23.5%) prevailed, and in the inpatient inhalotherapy room group, hMPV (16.1%) prevailed. In slightly more than 70% of children, a virus was identified. Overall, there was no statistically significant difference between groups.

Discussion

This study provides new information related to the epidemiology of viral agents identified in Mexican children who suffered from wheezing and had no personal history of asthma, and hMPV and HBoV were the main viruses found in children < 2 years old.

The frequency of virus detection was 60%, and this places our population in an intermediate point because the frequency of virus detection in Japanese or Arab children has been reported to be > 80%[9,13]. In contrast, in two cities of Brazil, the frequency was < 40%[14]. Populations

Table 2. Prevalence of respiratory viruses in 55 children with wheezing

Virus	n	%	95% CI
Human metapneumovirus	13	23.6	14.2-36.5
Human bocavirus	8	14.5	7.3-26.4
Respiratory syncytial virus	7	12.7	6.0-24.3
Human rhinovirus	7	12.7	6.0-24.3
Human adenovirus	6	10.9	4.7-22.2
Influenza virus	3	5.5	1.3-15.4
Parainfluenza virus	3	5.5	1.3-15.4

Some children had coinfection with two viruses.

Table 3. Clinical features in 55 children with wheezing according to the viral identification

	Virus detection				
	Yes		No		
	(n = 33)	%	(n = 22)	%	P value
Cough	33	100	22	100	—
Rhinorrhea	33	100	22	100	—
Respiratory distress	31	93.9	21	95.5	0.999
Tearing eyes	31	93.9	21	95.5	0.999
Intercostal retractions	30	90.9	20	90.9	0.999
Fever ≥ 38ºC	22	66.7	14	63.6	0.817
Diarrhea	1	3.0	13	13.6	0.290
SpO2					0.024
≥ 96%	4	12.1	0	0	
95-92%	1	3.0	4	18.2	
≤ 91%	28	84.8	18	81.8	

*P value not calculated because it is a constant. SpO2, determined by pulse oximetry. P value obtained by Chi square test or Fisher exact test as required.

Table 4. Frequency of the virus according the place where the children received medical care

	Outpatient group (n = 7)	Inpatient group		
		Emergency room (n = 17)	Inhalotherapy room (n = 31)	P value
Human metapneumovirus	1 (14.3)	7 (41.2)	5 (16.1)	0.136
Human bocavirus	0 (0)	4 (23.5)	4 (12.9)	0.199
Respiratory syncytial virus	0 (0)	3 (17.6)	4 (12.9)	0.326
Human rhinovirus	2 (28.6)	1 (5.9)	4 (12.9)	0.349
Human adenovirus	0 (0)	3 (17.6)	3 (9.7)	0.309
Influenza virus	0 (0)	0 (0)	3 (9.7)	0.167
Parainfluenza virus	1 (14.3)	0 (0)	2 (6.5)	0.258
Any	4 (57.1)	12 (70.6)	17 (54.8)	0.552

of children with similar frequencies were found in South Korea and Africa[15,16]. Differences in techniques for identifying viruses, seasonal variation, and the severity of the disease appear to influence the prevalence of detecting viruses related to respiratory infections. Interestingly, the dominant viruses in children with acute wheezing were hMPV and HBoV. We consider this to be a novel situation, at least in our country, as previous reports had been consistent in identifying hRV or RSV as the agents most associated with wheezing in children < 2 years old[2,7,9,17,18]. hMPV is a relatively new pathogen described and has been studied only slightly in our country. Noyola, et al.[19] studied viruses in a group of children with upper and lower airway infection; in that study, hMPV was the second most common agent (6.1%), after RSV (34.6%). Additionally, they showed that the peak of hMPV was during the months of February and March in children whose median age was 10 months. Another study in Mexico showed that hMPV was the agent most frequently detected in children with influenza-like illness (20%)[20]; remarkably, this agent was more common in children older than 13-36 months; these cases predominated during the summer months. Worldwide we found that hMPV was present in 3.5% of Thai children with first-episode wheezing[21], and the months that prevailed were during the end of the rainy season, from August to November. In Virginia, in the USA, the frequency of hMPV in children with wheezing was 8.9% and this was most pronounced in the months of January to April[22]. Finally, in a group of Iranian children, hMPV was identified in 16.6% of cases and was more frequent during the months of October and November[23].

In our study, the second most common agent in the wheezing group was hBoV (14.5%). This virus belongs to the Parvoviridae family and, like hMPV, has been little studied in our country. In Finland, a group of children < 3 years old with a first episode of wheezing showed a frequency of hBoV infection very similar to ours (14.5%); however, a large proportion of these cases were coinfections; in an isolated manner, hBoV appeared in only 12 (5%) out of 259 cases[24].

In children who were < 1 year old and who had a lower respiratory tract infection, the rate of hBoV was 9.1%, and manifestations were cough and wheezing in > 80% of the recruited patients[25]. Currently, there is still controversy about the role of hBoV in the origin of wheezing. Our findings seem to favor a positive association because, in all of the infected children, hBoV was the only viral agent identified.

Adenoviruses belong to the genus Mastadenovirus; these viruses have also been linked to wheezing. In a study from China, the prevalence in children was 6.33%; slightly more than half were < 1 year old, and nearly 60% had wheezing as a manifestation of infection[26]. By comparison, our prevalence of hAD was much higher. An important facet of these viruses is the high risk that infected children have of being hospitalized, especially when respiratory distress, wheezing, or gastroenteritis is present[27]. Of note, influenza viruses were not among the main agents associated with wheezing children in our group and this is consistent with previous studies[2,7,17,19]. A first explanation for this may be found in the extensive vaccination campaigns for prevention of influenza virus spreading, implemented by medical health services in Mexico. A second possibility is the ability of viruses to induce infection frequently but with less severity[2]. Finally, differences related to extraction techniques of the viral genome may influence their lower detection. These last two explanations may also apply to the PIF virus. Coinfections were present in only five out of 55 children with wheezing, < 10% of cases. This differs significantly from that found in children in Argentina[7] and Finland[17], where coinfections had frequencies of 25 and 38%, respectively; our results are more like those in a population of Japanese children (12.2%)[9]. It has been reported that coinfections, rather than representing greater severity of the disease, suggest the possibility of contagion within the hospital[7]. If this is the case, what we are dealing with is nosocomial infection, which is beyond the scope of this study. However, our group has shown that an important determinant of the presence of coinfection is living in overcrowded conditions[12], a situation that is very common in Mexico; unfortunately this condition was not evaluated in this study. In five cases of coinfection, RSV was the most common viral agent identified. This is different from other studies, in which the predominant viruses have been hRV[7,9,17].

In an attempt to assess the need for hospitalization in the emergency department according to the viral agent, we categorized children by the area where they were receiving medical care. Thus, it was observed that those who were infected with hMPV or hBoV were more likely to be hospitalized. Further comparative studies with larger numbers of patients in each area will determine whether the viral agent is significantly associated with this factor. Choosing only children with no history of asthma allowed us to achieve a better understanding of the prevalence of the virus in children with acute wheezing. Although defining asthma in this age group is extremely difficult, wheezing episodes that warrant medical attention can hardly go unnoticed by parents. So it is possible that some of these children would be enrolled with their first episode of wheezing. However, we believe that some children may

actually be starting with asthma because the symptoms are similar. Also, it is possible that others already suffer from asthma and that the disease is exacerbated by viral infections[28].

Limitations

In interpreting these results, we recommend caution since the study was conducted only during the winter season. It is expected that the prevalence of different viruses would be modified if measurements had been made over an entire year. Nor should one underestimate the fact that some wheezing is associated with gastroesophageal reflux disease and that it is precisely in children < 2 years old where we can usually find this disorder. Finally, we must recognize that most children studied came to a pediatric emergency department, which shows the magnitude of perception of disease by parents. So, by reaching a greater number of outpatient children, we could offer a better understanding of the clinical spectrum of wheezing associated with viruses. It must also be considered that in those children in whom virus was not identified (40%), there is a possibility that a viral infection was involved with a viral etiology not present in the RNA/DNA kit used. Furthermore, by not investigating the presence of pathogenic bacteria of the respiratory tract, in addition to the detected virus, we cannot rule out the presence of bacterial agents such as *Mycoplasma pneumoniae*, which has been associated with nearly 20% of episodes of wheezing in children < 2 years old[29], or *Chlamydia pneumoniae*[30].

Conclusions

This study shows that two of the studied respiratory viruses, hMPV and hBoV, are the most commonly found agents in our population of children who are < 2 years old and suffer from wheezing. The clinical and epidemiological implications of these results are the reason for further study.

Declaration of interest

None of the authors has any conflict to declare. Similarly, there was no funding source.

References

1. Vidaurreta SM, Marcone DN, Ellis A, et al. Acute viral respiratory infection in children under 5 years: Epidemiological study in two centers in Buenos Aires, Argentina. Arch Argent Pediatr. 2011;109:296-304.
2. Bosis S, Esposito S, Niesters HG, et al. Role of respiratory pathogens in infants hospitalized for a first episode of wheezing and their impact on recurrences. Clin Microbiol Infect. 2008;14:677-84.
3. Moraes LS, Takano OA, Mallol J, Solé D. Prevalence and clinical characteristics of wheezing in children in the first year of life, living in Cuiabá, Mato Grosso, Brazil. Rev Paul Pediatr. 2014;32:313-9.
4. Mallol J, García-Marcos L, Solé D, Brand P; EISL Study Group. International prevalence of recurrent wheezing during the first year of life: variability, treatment patterns and use of health resources. Thorax. 2010;65:1004-9.
5. Bouzas ML, Solé D, Cardoso MR, et al. Wheezing in infants: frequency, clinical characteristics and treatment. J Pediatr (Rio J). 2012;88:361-5.
6. Margolis PA, Greenberg RA, Keyes LL, et al. Lower respiratory illness in infants and low socio economic status. Am J Public Health. 1992;82:1119-26.
7. Maffey AF, Venialgo CM, Barrero PR, et al. New respiratory viruses in children 2 months to 3 years old with recurrent wheeze. Arch Argent Pediatr. 2008;106:302-9.
8. López Pérez G, Morfín Maciel BM, Navarrete N, Aguirre A. Identification of influenza, parainfluenza, adenovirus and respiratory syncytial virus during rhinopharyngitis in a group of Mexican children with asthma and wheezing. Rev Alerg Mex. 2009;56:86-91.
9. Fujitsuka A, Tsukagoshi H, Arakawa M, et al. A molecular epidemiological study of respiratory viruses detected in Japanese children with acute wheezing illness. BMC Infect Dis. 2011;11:168.
10. Coarasa A, Giugno H, Cutri A, et al. Validation of a clinical prediction tool to evaluate severity in children with wheezing. Arch Argent Pediatr. 2010;108:116-23.
11. World Health Organization. Guidelines for the collection of human specimens for laboratory diagnosis of avian influenza infection. Available at: http://www.who.int/influenza/human_animal_interface/virology_laboratories_and_vaccines/guidelines_collection_h5n1_humans/en/index.html#
12. Díaz J, Morales-Romero J, Pérez-Gil G, et al. Viral coinfection in acute respiratory infection in Mexican children treated by the emergency service: A cross-sectional study. Ital J Pediatr. 2015;41:33.
13. Al-Ayed MS, Asaad AM, Qureshi MA, Ameen MS. Viral etiology of respiratory infections in children in south western Saudi Arabia using multiplex reverse-transcriptase polymerase chain reaction. Saudi Med J. 2014;35:1348-53.
14. Albuquerque MC, Varella RB, Santos N. Acute respiratory viral infections in children in Rio de Janeiro and Teresópolis, Brazil. Rev Inst Med Trop Sao Paulo. 2012;54:249-55.
15. Ahmed JA, Katz MA, Auko E, et al. Epidemiology of respiratory viral infections in two long-term refugee camps in Kenya, 2007-2010. BMC Infect Dis. 2012;12:7.
16. Kim JK, Jeon JS, Kim JW, Rheem I. Epidemiology of respiratory viral infection using multiplex rt-PCR in Cheonan, Korea (2006-2010). J Microbiol Biotechnol. 2013;23:267-73.
17. Turunen R, Koistinen A, Vuorinen T, et al. The first wheezing episode: respiratory virus etiology, atopic characteristics, and illness severity. Pediatr Allergy Immunol. 2014;25:796-803.
18. Smuts HE, Workman LJ, Zar HJ. Human rhinovirus infection in young African children with acute wheezing. BMC Infect Dis. 2011;11:65.
19. Noyola DE, Alpuche-Solís AG, Herrera-Díaz A, Soria-Guerra RE, Sánchez-Alvarado J, López-Revilla R. Human metapneumovirus infections in Mexico: epidemiological and clinical characteristics. J Med Microbiol. 2005;54:969-74.
20. Talavera GA, Mézquita NE. Human metapneumovirus in children with influenza-like illness in Yucatan, Mexico. Am J Trop Med Hyg. 2007;76:182-3.
21. Teeratakulpisarn J, Ekalaksananan T, Pientong C, Limwattananon C. Human metapneumovirus and respiratory syncytial virus detection in young children with acute bronchiolitis. Asian Pac J Allergy Immunol. 2007;25:139-45.
22. Williams JV, Tollefson SJ, Heymann PW, Carper HT, Patrie J, Crowe JE. Human metapneumovirus infection in children hospitalized for wheezing. J Allergy Clin Immunol. 2005;115:1311-2.
23. Moattari A, Aleyasin S, Arabpour M, Sadeghi S. Prevalence of human Metapneumovirus (hMPV) in children with wheezing in Shiraz-Iran. Iran J Allergy Asthma Immunol. 2010;9:250-4.
24. Allander T, Jartti T, Gupta S, et al. Human bocavirus and acute wheezing in children. Clin Infect Dis. 2007;44:904-10.
25. Al-Rousan HO, Meqdam MM, Alkhateeb A, Al-Shorman A, Qaisy LM, Al-Moqbel MS. Human bocavirus in Jordan: prevalence and clinical symptoms in hospitalised paediatric patients and molecular virus characterisation. Singapore Med J. 2011;52:365-9.
26. Gupta P, Goyal S, Tobias JD, et al. Risk factors associated with hospital admission among healthy children with adenovirus infection. Turk J Pediatr. 2011;53:597-603.
27. Jin Y, Zhang RF, Xie ZP, et al. Prevalence of adenovirus in children with acute respiratory tract infection in Lanzhou, China. Virol J. 2013;10:271.
28. Murray MG, Kanuga J, Yee E, Bahna SL. Milk-induced wheezing in children with asthma. Allergol Immunopathol (Madr). 2013;41:310-4.
29. Wang Y, Hao C, Ji W, Yan Y, Shao X, Xu J. Bronchiolitis associated with Mycoplasma pneumoniae in infants in Suzhou China between 2010 and 2012. Sci Rep. 2015;5:7846.
30. Zaitsu M. Does Chlamydia pneumoniae infection trigger to development of asthma in wheezy infants? J Asthma. 2009;46:967-8.