Viral causes of acute respiratory infection among Egyptian children hospitalized with severe acute asthma exacerbation

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Background
Viral respiratory infections are associated with nearly 80% of asthma exacerbation episodes. These can have severe adverse outcomes in patients with established asthma.

Aim
The aim of the study was to identify the viral causes of acute respiratory infection that precipitate acute asthma exacerbation in Egyptian asthmatic children.

Patients and methods
The current prospective study was conducted in Cairo University Children's Hospitals from December 2010 to December 2011. All asthmatic children ($n=130$) aged 2–12 years admitted with asthma exacerbation due to severe lower respiratory tract infection were included. All cases were subjected to nasopharyngeal or throat swabs that were analyzed for common respiratory viruses, including respiratory syncytial virus (RSV), human metapneumovirus (hMPV), influenza B (Flu B), human parainfluenza virus (hPIV), influenza A (H1N1), and adenovirus (ADV) using the real-time PCR technique. All patients were followed up to record the outcome.

Results
PCR analysis was positive for one respiratory virus in 54 asthmatic patients (41.5%) and was negative in 76 patients (58.5%), with a high predominance of RSV (51.9%) and hMPV (25.9%) especially in winter and early spring months. Hypoxia was detected in all patients with RSV infection; of these patients, 21.4% were admitted to the ICU, 14.3% required mechanical ventilation, and 14.3% died. In contrast, among those with hMPV infection, hypoxia was detected in 71.4%; none required ICU admission or mechanical ventilation.

Conclusion and recommendations
Viral etiology of lower respiratory tract infections constitutes an important cause of acute asthma exacerbation in asthmatic children admitted to children's hospitals in Cairo, supporting the need for large-scale multicentric studies on asthmatic patients over multiple years using a wider-panel PCR for detection of respiratory viruses.

Keywords:
asthma exacerbation, children, Egypt, PCR, viruses

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Introduction

Bronchial asthma prevalence has increased considerably in recent decades such that it is now one of the most common chronic disorders in the world [1]. A previous study conducted in Cairo, Egypt, to ascertain the prevalence of asthma among children revealed that the overall prevalence of ever wheezing, wheezing during the last year, and physician-diagnosed asthma was 26.5, 14.7, and 9.4%, respectively [2].

Asthma exacerbation is a cause of strong concern among children and parents, and it represents a challenge for pediatric healthcare providers [3]. Upper respiratory viral infections are associated with nearly 80% of asthma exacerbation episodes. Further, viral respiratory infections can have severe adverse outcomes in patients with established asthma [4].

Respiratory viruses that have been detected in patients with asthma exacerbation include the respiratory syncytial virus (RSV), influenza viruses, human metapneumoviruses (hMPV), human parainfluenza viruses (hPIV), and corona viruses. In a recent epidemiological study, rhinoviruses were found to be significantly associated with asthma exacerbation [5].

However, the prevalence of viral respiratory infections varies greatly across different regions; for example, influenza is associated with more number of hospitalization cases among children in Hong Kong compared with temperate regions [6].

With the development of PCR technology, a larger number of respiratory viruses can be detected, and this technology has a high degree of sensitivity and specificity [7].

The aim of this study was to identify the viral causes of acute respiratory infection that precipitate severe acute asthma exacerbation, necessitating hospitalization of Egyptian children.

Patients and methods

The present study was conducted in the specialized Children Hospital and El Monira Children Hospital of Cairo University as a part of the Surveillance for Severe Acute Respiratory Illness (SARI Surveillance), which was conducted through collaboration between the US Novel researches unite No.3 and Cairo University hospitals from 1 January 2011 to 31 December 2011. All asthmatic children who were hospitalized with severe acute lower respiratory tract infections causing acute asthma exacerbation that necessitated hospitalization were included in this study. A total of 130 asthmatic children fulfilling the criteria of case definition were enrolled. Patients' ages ranged from 2 to 12 years. Verbal informed consent was obtained from the children's parents.

A case of severe acute lower respiratory infection was defined by the presence of fever at the onset of the disease and/or current fever or hypothermia, together with at least one of the following symptoms: cough, tachypnea, sputum, hemoptysis, chest pain, sore throat, and shortness of breath. The presence of working ala nasi, intercostal retraction, grunting, inability to drink or breastfeed, persistent vomiting, lethargy, or convulsion was taken as evidence of severe acute lower respiratory tract infection. Asthmatic children were diagnosed clinically on the basis of a history of repeated episodes of wheezing, with rapid response to bronchodilator therapy and/or on long-term controller therapy for asthma.

The following specific groups were excluded: children with chronic nonasthmatic lung diseases, neonates, children with infantile wheezing, and patients who were unwilling to participate in this study. All patients were subjected to detailed history taking for classification of asthma severity according to the international guidelines NAEPP 1997 (National Asthma Education and Prevention Program) [8], as well as to detailed history taking of SARI, complete blood analysis, chest radiograph, and oropharyngeal or nasopharyngeal swabs. Follow-up of all enrolled patients was carried out to record the outcome for each patient. The obtained swabs were transported to be prepared in the clinical microbiology laboratory of Cairo University Specialized Children Hospital, where real-time PCR analysis was performed for the following respiratory viruses, influenza A (H1N1), RSV, hMPV, hPIV, and adenovirus (ADV), according to standardized protocols of the USA CDC in Atlanta, Georgia [9].

Statistical analysis

Data were analyzed using SPSS win statistical package, version 15 (SPSS Inc., Chicago, Illinois, USA). Frequency distributions, percentages, mean ± SD, χ^2-tests, and Fisher's exact tests were used for data presentation and analysis. P values less than 0.05 were considered significant.

Ethical considerations

The protocol was approved by the Cairo University Hospital Research Ethical Committee (REC).

Results

This study included 130 asthmatic children hospitalized with acute asthma exacerbation as a result of severe acute lower respiratory tract infection during the period from 1 January 2011 to 31 December 2011. Patients' ages ranged from 2 to 12 years with a mean age of 2.95 ± 2.46 years; 90 patients were male and 40 were female. PCR analysis of respiratory specimens was positive for viruses in 54 patients (41.5%) and negative in 76 patients (58.5%). The demographic and clinical characteristics of the study participants are presented in Table 1. There was no significant difference between virus positive and virus negative PCR patient groups as regards age, sex, and clinical characteristics. The male-to-female ratio was 1.3 : 1 for virus positive PCR patients and 3.2 : 1 for virus negative PCR patients. Most of the patients developed hypoxia (92.6% of patients with virus positive PCR and 84.3% with virus negative PCR) and the duration of oxygen therapy was 4.1 ± 2.4 days for virus positive PCR patients and 5.2 ± 5.5 days for virus negative PCR patients. There was no significant difference between the two groups with respect to complications and outcome. Clinical characteristics of the study population are shown in Table 1.

The laboratory and radiological findings are given in Table 2. The lymphocytic count and direct platelet count were significantly higher for virus negative PCR patients compared with virus positive PCR patients ($P = 0.030$ and 0.029, respectively). There was no significant difference between the two groups with regard to the total leukocyte count and radiological findings.

The PCR analysis of the respiratory specimens of asthmatic patients with acute exacerbation of asthma associated with lower respiratory tract infections was positive for one respiratory virus in 54 asthmatic patients (41.5%) and was negative in 76 patients (58.5%). Mixed virus infection was not detected in any of our patients. Among the virus positive patients, 22 had mild persistent asthma, 16 had moderate persistent asthma, and 16 had severe persistent asthma. Details of the results of PCR testing in different grades of asthma severity are presented in Table 3.

Details of the seasonal distribution of viruses among viral PCR-positive patients are presented in Fig. 1. It was noticed that RSV infections occurred nearly throughout

Table 1. Demographic and clinical characteristics of asthmatic children with acute asthma exacerbation

Patients characteristics	Virus positive PCR patients ($N=54$)	Virus negative PCR patients ($N=76$)	P value[a]
Age (years)			
2–5	24 (44.4)	42 (55.3)	0.286
6–12	30 (55.6)	34 (44.7)	
Sex			
Female	24 (44.4)	18 (23.7)	0.014*
Male	30 (55.6)	58 (76.3)	
Manifestations of severe acute lower respiratory tract infections			
Nasal flaring	44 (88.0)	62 (83.8)	1.000
Chest indrawing	44 (88.0)	56 (73.7)	0.399
Grunting	28 (58.3)	34 (45.9)	0.478
Unable to drink or breastfeed	16 (33.3)	14 (18.9)	0.205
Lethargy/unconscious	10 (20.8)	6 (8.1)	0.103
Convulsions	6 (12.5)	2 (2.7)	0.066
Asthma severity classification			
Mild persistent (total 86)	22 (40.7)	64 (84.2)	0.000*
Moderate persistent (total 26)	16 (29.6)	10 (13.2)	0.026*
Severe persistent (total 18)	16 (29.6)	2 (2.6)	0.000*
Complications and outcomes			
Hypoxia	50 (92.6)	64 (84.2)	0.392
Duration of oxygen therapy (mean ± SD)	4.1 ± 2.4	5.2 ± 5.5	0.583
ICU admission	12 (22.2)	22 (28.9)	0.425
Mechanical ventilation	10 (18.5)	16 (21.1)	0.825
Death	6 (11.1)	10 (13.2)	0.792

Values are presented as number (%).
[a]Analysis using Fisher's exact test.
*$P<0.05$, significant.

Table 2. Laboratory and radiological findings of asthmatic children with acute asthma exacerbation

Investigations	Virus positive PCR patients	Virus negative PCR patients	P value*
Complete blood count (mean ± SD)			
White blood cells	8226.1 ± 3739.1	10380.7 ± 3854.1	0.05[a]
Lymphocytic count	26.4 ± 21.6	35.4 ± 15.6	0.03[a]
Platelets count	323.6 ± 179.7	406.1 ± 177.3	0.02[a]
Chest radiograph findings [N (%)]			
Consolidation	22 (40.7)	30 (39.4)	1.000[b]
Infiltrations	32 (59.3)	46 (60.6)	1.000[b]

[a]Analysis using Fisher's exact test.
[b]Analysis using Mann–Whitney test.
*$P<0.05$, significant.

the year with the highest overall activity during September through December.

Most children (92%) developed hypoxia. Patients with ADV and pH1N1 were more likely to be admitted to the ICU (50 and 100%, respectively) and to need mechanical ventilation (50 and 100%, respectively) than were other patients. Death occurred more frequently among RSV cases (four cases, 14.3%) and hPIV3 cases (two cases, 33.3%). Adenovirus was associated with prolonged hospital stay (median = 15, range = 7–23) compared with RSV (median = 8, range = 2–36), hMPV (median = 7, range = 4–18), and hPIV3 (median = 8, range = 7–19). Details of complications encountered through the course of infection with different viruses are presented in Table 4.

Discussion

In the present study 41.5% of our enrolled patients were PCR positive for viral agents associated with acute asthma exacerbation that necessitated hospitalization in asthmatic children, compared with 58.5% of patients who were PCR negative for these viruses. These low results can be attributed to our selected population: we studied asthmatic children hospitalized with lower respiratory tract infection and exacerbation of asthma symptoms, whereas most studies have investigated asthma exacerbation following upper respiratory tract infections. Prospective epidemiologic studies report that up to 80% of childhood exacerbations are associated with viral upper respiratory tract infections [10].

In this study, viral etiologies of severe asthma exacerbation in children have comparable clinical (Table 1), laboratory, and radiological (Table 2) findings to nonviral ones, which underscores the importance of definitive laboratory investigations to identify the exact etiology, whether it is viral, bacterial, or otherwise. The complete blood profile may be of help in differentiating between the viral and nonviral etiology of acute severe exacerbation of asthma as the lymphocytic and platelet counts were significantly higher in PCR-negative patients compared with PCR-positive ones. Although the total leukocytic count was higher in PCR-negative patients compared with PCR-positive ones, it was of no significance. This raises the concern about making the decision to prescribe parenteral antibiotics for these children based solely on CBC and clinical and radiological signs and show the importance of bacterial culture and virology screening workup in such patients.

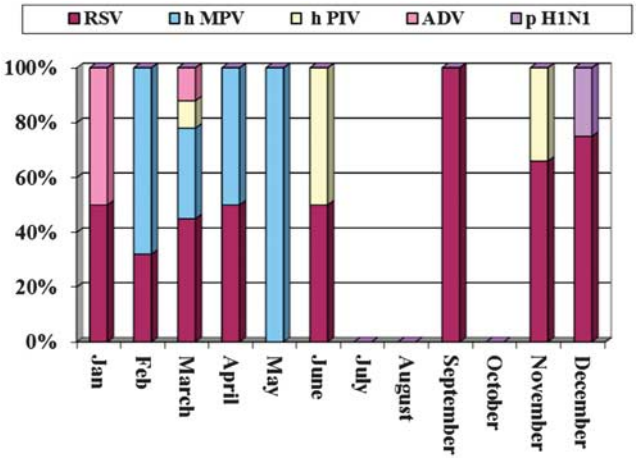
Although not statistically significant, it is worth mentioning that our study reveals that PCR-positive viral infections are associated with more severe clinical respiratory signs in asthmatics (e.g. grunting in 58% compared with 45% and chest indrawing in 88% compared with 73% of PCR-positive and PCR-negative

Table 3. Asthma severity among virus positive patients with acute asthma exacerbation

	Viruses				
Severity	RSV ($n=28$)	hMPV ($n=14$)	hPIV3 ($n=6$)	ADV ($n=4$)	pH1N1 ($n=2$)
Mild persistent	12 (42.8)	8 (57.1)	2 (33.3)	0 (0)	0 (0)
Moderate persistent	8 (28.6)	6 (42.9)	2 (33.3)	0 (0)	0 (0)
Severe persistent	8 (28.6)	0 (0)	2 (33.3)	4 (100)	2 (100)

Values are presented as number (%).
ADV, adenovirus; hMPV, human metapneumovirus; pH1N1, pandemic influenza A; hPIV, human parainfluenza virus; RSV, respiratory syncytial virus.

Figure 1.



Seasonal distribution of respiratory viruses among asthmatic children with acute asthma exacerbation. ADV, adenovirus; Flu B, influenza B; hMPV, human metapneumovirus; pH1N1, pandemic influenza A; hPIV, human parainfluenza virus; RSV, respiratory syncytial virus.

patients, respectively) (Table 1). The effects of an infection may vary according to genetic background, the current immune status of the host, and parallel environmental stimuli, in addition to the particular infectious agent itself. Moreover, childhood is a very special period because of the continuous growth processes taking place, such as neural, immune, and respiratory maturation [11].

In this study, viral PCR-negative patients were more likely to experience ICU admission and mechanical ventilation and deaths compared with viral PCR positive ones. This can be explained either by the presence of other respiratory viruses that were not included in this PCR panel, for example, rhinovirus, or when the exacerbation is due to bacterial infections.

Although some studies reported the occurrence of multiple viral isolates [12–13], only single viral isolates were detected in our study. The most frequently isolated virus in this study was RSV in 51.9% of all asthmatic patients hospitalized with acute asthma exacerbation associated with acute lower respiratory tract infection; this was followed by hMPV in 25.9% of these children (Table 4). As in the previous literature, RSV is always the leading pathogen of acute lower respiratory tract infection; the isolation rate varies with different study designs and geographical areas [14].

Also, RSV infections were present throughout the year with a high predominance in autumn months (Fig. 1); it is the only virus isolated in September. In contrast, hMPV is isolated only during late winter through spring months and it is the only virus isolated in May. This was in accordance with the fact that hMPV strains vary with location and time [15].

hMPV isolation has been reported around the world since 2001 [16–17]. In hospitalized children, hMPV infection shows varied prevalence from 1.5 to 17.5% and it is as serious as RSV infection and therefore deserves the same attention [18].

ADV infection was detected mainly in winter months and was associated with more prolonged hospital stay compared with other viruses. It was isolated in four patients with severe persistent asthma, and two of them needed mechanical ventilation. Similarly, it does not appear that pH1N1 was a main contributor to asthma exacerbation necessitating hospitalization in asthmatic children in this study; it was isolated only in two patients with severe persistent asthma, and both required mechanical ventilation.

Although other studies have suggested that other respiratory viruses might play a significant role in exacerbation of asthma [3–5], in the present study we found an association between asthma exacerbation and lower respiratory tract infection with RSV and hMPV. The seasonal, year to year, and geographical variability in activity levels of these respiratory viruses, differences in patient populations, specimen collection, or test methodologies, or both might have contributed to the differences between our findings and those of other studies.

Unlike many other studies on respiratory viruses in acute asthma exacerbation, we collected respiratory secretions by using combined nasopharyngeal and throat swabs rather than nasal lavage specimens. Although it is possible that the use of swab instead of lavage may decrease the detection rates for some respiratory viruses, the potential loss in sensitivity was likely compensated by the use of very sensitive PCR assays.

Limiting the present study is the small spectrum of respiratory viruses with the absence of rhinoviruses detection, which have been proven to be strongly associated with acute asthma exacerbation in children [3,5]. One other limitation is the modest sample size and the corresponding limited ability to look more

Table 4. Frequency and outcome of respiratory viruses among asthmatic children with acute asthma exacerbation ($n=54$)

Viruses	Frequency	Days of hospital stay [median (range)]	Hypoxia	ICU admission	Mechanical ventilation	Death
RSV	28 (51.9)	8 (2–36)	28 (100)	6 (21.4)	4 (14.3)	4 (14.3)
hMPV	14 (25.9)	7 (4–18)	10 (71.4)	0 (0.0)	0 (0.0)	0 (0.0)
hPIV3	6 (11.1)	8 (7–19)	6 (100)	2 (33.3)	2 (33.3)	2 (33.3)
ADV	4 (7.4)	15 (7–23)	4 (100)	2 (50)	2 (50)	0 (0.0)
pH1N1	2 (3.7)	10 (9–11)	2 (100.0)	2 (100)	2 (100)	0 (0.0)
Total	54 (100)	–	50 (92.6)	12(22.2)	10 (18.5)	6 (11.1)

Values are presented as number (%).
ADV, adenovirus; hMPV, human metapneumovirus; pH1N1, pandemic influenza A; hPIV, human parainfluenza virus; RSV, respiratory syncytial virus.

carefully at the different grades of asthma severity that might have clarified or identified new findings.

Conclusion and recommendations

The viral etiology of lower respiratory tract infections constitutes an important cause of acute exacerbation in asthmatic children, with a high predominance of RSV and hMPV viruses, especially in winter and early spring months.

Large-scale multicentric studies on asthmatic patients conducted over multiple years using a wider-panel PCR for respiratory virus detection taking into consideration rhinoviruses are needed to fully understand the role of all respiratory viruses in acute asthma exacerbation in children.

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Conflicts of interest

There are no conflicts of interest.

References

1 Anandan C, Nurmatov U, Van Schayck OCP, Sheikh A. Is the prevalence of asthma declining? Systematic review of epidemiological studies. Allergy 2010; 65:152–167.

2 Georgy V, Fahim HI, El Gaafary M, Walters S. Prevalence and socioeconomic associations of asthma and allergic rhinitis in nothern Africa. Eur Respir J 2006; 28:756–762.

3 Busse WW, Lemanske RF Jr, Gern JE. The role of viral respiratory infections in asthma and asthma exacerbations. Lancet 2010; 376:826–834.

4 Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, *et al*. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. BMJ 1995; 310:1225–1229.

5 Khetsuriani N, Kazerouni NN, Erdman DD, Lu X, Redd SC, Anderson LJ, Teaque WG. Prevalence of viral respiratory tract infections in children with asthma. J Allergy Clin Immunol 2007; 119:314–321.

6 Chiu SS, Lau YL, Chan KH, Wong WH, Peiris JS. Influenza-related hospitalizations among children in Hong Kong. N Engl J Med 2002; 347: 2097–2103.

7 Erdman DD, Weinberg GA, Edward KM, Walker FJ, Anderson BC, Winter J, *et al*. GenScan reverse transcriptase-PCR assay for detection of six common respiratory viruses in young children hospitalized with acute respiratory illness. J Clin Microbiol 2003; 41:4298–4303.

8 Expert Panel Report-2, National Asthma Education and Prevention Program (NAEPP): Guidelines for diagnosis and management of asthma, National Heart, Lung and Blood Institute, National Institute of Health Publication No 91-3042, Bethesda National Institute of Health, 1997.

9 The Centers for Disease Control and Prevention Technologies Brochure; 2011. Available at *http://www.cdc.gov/osels/laboratory_science/tech_tran/doc/June_2011_Brochure.pdf* [Accessed 16 January 2013].

10 Ozcan C, Toyran M, Civelek E, Erkocoglu M, Altas AB, Albayrak N, *et al*. Evaluation of respiratory viral pathogens in acute asthma exacerbations during childhood. J Asthma 2011; 48:888–893.

11 Xepapadaki P, Papadopoulos NG. Childhood asthma and infection: virus-induced exacerbations as determinants and modifiers. Eur Respir J 2010; 36:438–445.

12 Niang MN, Diop OM, Sarr FD, Goudiaby D, Malou-Sompy H, Ndiaye K, *et al*. Viral etiology of respiratory infections in children under 5 years old living in tropical rural areas of Senegal: The EVIRA project. J Med Virol 2010; 82:866–872.

13 Zhang HY, Li ZM, Zhang GL, Diao TT, Cao CX, Sun HQ. Respiratory viruses in hospitalized children with acute lower respiratory tract infections in Harbin, China. Jpn J Infect Dis 2009; 62:458–460.

14 Mlinaric-Galinovic G, Vilibic-Cavlek T, Ljubin-Sternak S, Drazenovic V, Galinovic I, Tomic V, *et al*. Eleven consecutive years of respiratory syncytial virus outbreaks in Croatia. Pediatr Int 2009; 51:237–240.

15 Al-Sonboli N, Hart CH, Al-Aghbari N, Al-Ansi A, Ashoor O, Cuevas LE. Human metapneumovirus and respiratory syncytial virus disease in children, Yemen. Emerg Infect Dis 2006; 12:1437–1439.

16 Williams JV, Harris PA, Tollefson SJ, Halburnt-Rush LL, Pingsterhau JM, Edwards KM, *et al*. Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. N Engl J Med 2004; 350:443–450.

17 Do Carmo Debur M, Bordignon J, Duarte dos Santos CN, Vidal LR, Nogueira MB, de Almeida SM, *et al*. Acute respiratory infection by human metapneumovirus in children in southern Brazil. J Clin Virol 2007; 39:59–62.

18 Wilkesmann A, Schildgen O, Eis-Hubinger AM, Geikowski T, Glatzel T, Lentze MJ, *et al*. Human metapneumovirus infections cause similar symptoms and clinical severity as respiratory syncytial virus infections. Eur J Pediatr 2006; 165:467–475.