Clinical and epidemiological study of acute lower respiratory tract infections caused by adenovirus in hospitalized children. Nineteen years of active epidemiological surveillance

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ABSTRACT

Introduction. Acute lower respiratory tract infection (ALRTI) caused by adenovirus is a major cause of morbidity and mortality in children.

Objectives. To describe the clinical and epidemiological pattern and associated factors in hospitalized children.

Methods. Cross-sectional study in children admitted due to ALRTI to Hospital de Niños "Ricardo Gutiérrez," in the Autonomous City of Buenos Aires, between 2000 and 2018. Viral diagnosis was done by indirect immunofluorescence in nasopharyngeal secretions. The clinical and epidemiological characteristics of adenovirus infection were compared to other respiratory viruses (respiratory syncytial virus, influenza, and parainfluenza). A multiple logistic regression was done to identify independent predictors of infection.

Results. Out of 16 018 patients with ALRTI, 13 545 were tested for respiratory viruses; 6047 (45 %) had a positive result. Adenovirus was the least common agent (4.4 % [265] of cases); it tended towards a reduction over the study period (peak in 2003) and circulated throughout the year (peak in July). In total, 63.8 % of patients were males; median age: 11 months (interquartile range: 6-20). The most common clinical presentation was pneumonia (63 %). Prior admissions due to respiratory conditions were seen in 50 %; 15.6 % were readmissions; 58.3 % had comorbidities. Ventilatory support was required by 19.2 % and complications were recorded in 44 %. The fatality rate was 7.7 %. Adenovirus infection was associated with age ≥ 12 months, male sex, clinical presentation of pneumonia, prior admissions due to respiratory conditions, and readmissions.

Conclusions. Adenoviruses were less common than other respiratory viruses, although their morbidity and mortality were important.

Key words: *acute lower respiratory tract infection, human adenovirus, pneumonia, pediatrics, epidemiology.*

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INTRODUCTION

Acute lower respiratory tract infections (ALRTIs) are the main cause of morbidity and mortality in children younger than 5 years, especially in low- and middle-income countries.[1,2] In Argentina, respiratory diseases are the third cause of mortality in the first 5 years of life, after perinatal conditions and congenital malformations.[3]

A report on ALRTI mortality by the Health Statistics and Information Department (*Dirección de Estadística e Información en Salud*, DEIS) for the 1980-2014 period showed that the highest number of deaths occurred in the first months of life: 68 % of cases were recorded in infants younger than 4 months. A high percentage of these cases corresponded to viral infections in healthy children and patients with underlying conditions.[4]

The most common viruses associated with ALRTI include respiratory syncytial virus (RSV), type A and type B influenza viruses (FluA and FluB viruses), parainfluenza virus 1, 2, and 3 (PIV 1-3), and adenovirus.[5,6] According to the 2018 report by the Laboratory-Based National Surveillance System (National Health Surveillance System [*Sistema Nacional de Vigilancia de la Salud de Argentina*, SNVS]/Laboratory Surveillance System [*Sistema de Vigilancia Laboratorial*, SIVILA]), adenovirus accounted for 7.5 % (2032/27 129) of all positive respiratory specimens collected. In the first epidemiological weeks (EWs) of the year, adenovirus circulation together with PIV was proportionally higher than that of RSV and Flu, and they re-emerged at

a higher rate once the RSV peak decreased.[7]

There are currently more than 85 types of adenovirus. Of them, 51 serotypes were identified by neutralization methods against surface antigens, whereas the most recent ones were identified by genetic analysis. Studies that date back to 1950 documented that species B (serotypes 3, 7, 14, 21, and 55), C (serotypes 1, 2, 5, and 6), and E (serotype 4) adenoviruses are associated with respiratory disease. Especially adenovirus B3 and adenovirus B7 are seen in children who require hospitalization.[8]

Adenovirus infections are distributed globally; they occur throughout the year[9,10] and may cause nosocomial infection outbreaks with a secondary attack rate of up to 55 %.[11,12] Adenoviruses that cause respiratory tract infections are spread through respiratory droplets or by contact with contaminated fomites. They may survive for long periods of time on environmental surfaces and cannot be deactivated by many disinfectants.[9,10]

Most adenovirus respiratory infections are mild to moderate, benign, and self-limited; however, sometimes they may cause severe clinical conditions and have pulmonary sequelae.[12-15] This study describes the clinical and epidemiological characteristics of patients hospitalized due to ALRTI caused by adenovirus at a children's hospital in order to establish infection-related factors and provide useful information for the development of future prevention or management strategies.

POPULATION AND METHODS

Study design

Prospective, analytical, and cross-sectional study on ALRTI cases in patients hospitalized at a children's hospital between 2000 and 2018.

Population

Analyzed data were obtained from the digital database of the ALRTI Epidemiological Surveillance Program of Hospital de Niños "Ricardo Gutiérrez" (HNRG), in the Autonomous City of Buenos Aires, which has been continually working since 2000. The database was completed prospectively through an active epidemiological surveillance. Data were collected from interviews, case histories, and medical records of patients hospitalized at the clinical hospitalization ward and the intermediate and intensive care units of HNRG, who received follow-up since their admission until their discharge.

Inclusion criteria

The data of all patients hospitalized at HNRG due to ALRTI caused by RSV, Flu, PIV or adenovirus between 2000 and 2018 were included.

Exclusion criteria

The data of patients hospitalized for a reason other than an ALRTI who developed an ALRTI with viral rescue 48 hours after admission were excluded.

CLINICAL CASE DEFINITIONS

An ALRTI[16] encompasses the following conditions:

1. Bronchiolitis: first wheezing episode associated with clinical evidence of viral infection in children younger than 2 years. It refers to an acute and diffuse lower airway inflammation of infectious origin, with small airway obstruction as the main clinical characteristic.
2. Pneumonia: acute infection of the lung parenchyma with clinical signs of invasion of the alveolar space.

Diagnostic method

Viral diagnosis was done by indirect immunofluorescence (IIF) with monoclonal antibodies (Light Diagnostics, Chemicon Int. Inc., USA) using nasopharyngeal secretions collected with a K-30 nasogastric tube[17] in the first 48 hours after admission in children younger than 5 years and sent immediately to the hospital's Laboratory of Virology for analysis.

Sample size and selection

Patients were included by consecutive sampling over the 19-year study period, and the data of the total study universe were collected. A sample size of at least 10 events for each outcome measure was considered enough to be included in a multiple model.

Data collection

The following data were collected in an epidemiological card: date of admission, demographic data (age, sex, place of origin), clinical presentation (bronchiolitis; focal or multifocal pneumonia, or pneumonia with effusion), prior hospitalizations related to a respiratory disease, readmission due to the same event, perinatal respiratory disease (with oxygen therapy requirement), prematurity (gestational age of less than 37 weeks), comorbidities, presence of household members or close contact

with a probably viral acute respiratory disease (rhinorrhea, cough and/or fever), complications during hospitalization and course (discharge, transfer to a different facility, death), treatment, and length of stay. The following conditions were considered comorbidities: chronic or recurrent respiratory disease, malnutrition (deficit in one or more anthropometric indicators below -2 standard deviations), congenital heart disease, genetic disorders, neurological disorders, and immunosuppression (hemato-oncological disease, immunosuppressive therapy, primary or acquired immunodeficiency).

The presence of any of the following conditions was recorded as chronic or recurrent respiratory disease: recurrent obstructive bronchitis (ROB) or asthma, gastroesophageal reflux, cystic fibrosis, bronchopulmonary dysplasia, recurrent pneumonia, and recurrent laryngitis. ROB was defined as the occurrence of two or more bronchial obstruction episodes in a year. The following conditions were recorded as complications: otitis, pneumothorax, persistent atelectasis, sepsis, and respiratory failure.

Statistical analysis

For data analysis, a general description was done in the first place by estimating the mean and standard deviation or the median and interquartile range (IQR) for numerical outcome measures, based on their distribution. The proportion and its corresponding 95 % confidence interval (CI) were estimated for categorical outcome measures.

Initially, a univariate analysis was performed to identify significant associations between the occurrence of ALRTI by adenovirus and the different potentially predictor outcome measures. The association and differences were assessed using the t test for continuous data and implementing the central limit theorem (considering that all outcome measures had a normal distribution) and the χ^2 test with Yates' correction for proportions and categorical outcome measures. The Wilcoxon test was done to compare median age. The odds ratio (OR) with a 95 % CI was used as a measure of association.

A univariate analysis was done for each outcome measure in relation to the main outcome using a simple logistic regression. A multiple logistic regression model was developed afterwards to identify predictor outcome measures of infection or fatality. Outcome measures significantly associated with the occurrence of ALRTI by adenovirus in the analysis of crude data ($p < 0.2$) and/or those considered clinically relevant were added one at a time; only those with a significant association with the studied event (Wald test) were maintained in the final model. The database was loaded into the Epi Info version 7 software, and the STATA/SE version 13 software was used for statistical analysis.

Ethical considerations

Patients' privacy rights were warranted in all cases based on the ethical principles for medical research involving human subjects established by the World Medical Association Declaration of Helsinki. The patient informed consent form was not applicable in this study because data were collected from a routine epidemiological surveillance activity in the setting of Argentine Law no. 15465/60. The study was approved by both the Ethics and Research Committees of HNRG. This study did not have any impact on human rights nor did it cause any harm to the environment, animals, or future generations.

RESULTS

General description of the population

In the 19-year study period, a total of 16 018 patients were hospitalized due to community acquired ALRTI; of them, 13 545 (85 %) were tested for respiratory viruses and 6047 (45 %) had a positive result (*Figure 1*). Adenovirus was the least frequently identified respiratory virus during the study period, accounting for 4.4 % (265/6047) of all positive cases (*Figure 2*).

Seasonality

Throughout our series, an annual tendency towards a reduction was observed in the number of ALRTI cases caused by adenovirus, with a maximum peak in 2003 (*Figure 2*). In relation to seasonality, adenovirus circulated throughout the year and its highest incidence peak was in July (*Figure 3*).

Description of cases and factors associated with adenovirus infection. Univariate analysis

Patients' median age was 11 months (IQR: 6-20 months), and 63.8 % were males. The most common clinical presentation was pneumonia (63 %). Also, 50 % of patients had been previously hospitalized due to respiratory conditions; 15.6 % corresponded to readmissions. Comorbidities were observed in 58.3 % of patients: recurrent

respiratory disease (80.5 %), chronic neurological disease (12.3 %), and congenital heart disease (9.7 %). In addition, 9.1 % had malnutrition, 18.1 %, a history of prematurity and 3.8 %, immunosuppression. During hospitalization, 19.2 % of patients required assisted mechanical ventilation (AMV). Complications occurred in 44 % of cases.

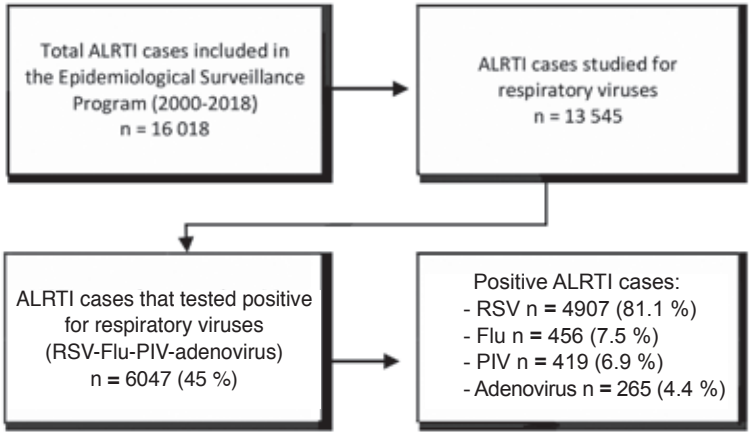
Table 1 describes the characteristics of ALRTI cases caused by adenovirus compared to other respiratory viruses.

The fatality rate was 7.7 % (20/260). The median age of deceased patients was 12 months (IQR: 6.5-22 months) and 11/20 (55 %) had a comorbidity. The adenovirus fatality rate was significantly higher than that of any of the other respiratory viruses (7.7 % versus 1.8 %; OR = 4.4; 95 % CI: 2.6-7.1; $p < 0.001$), and no significant differences were observed in the annual distribution of fatal cases (*Figure 4*).

Independent predictors of adenovirus infection. Multivariate analysis

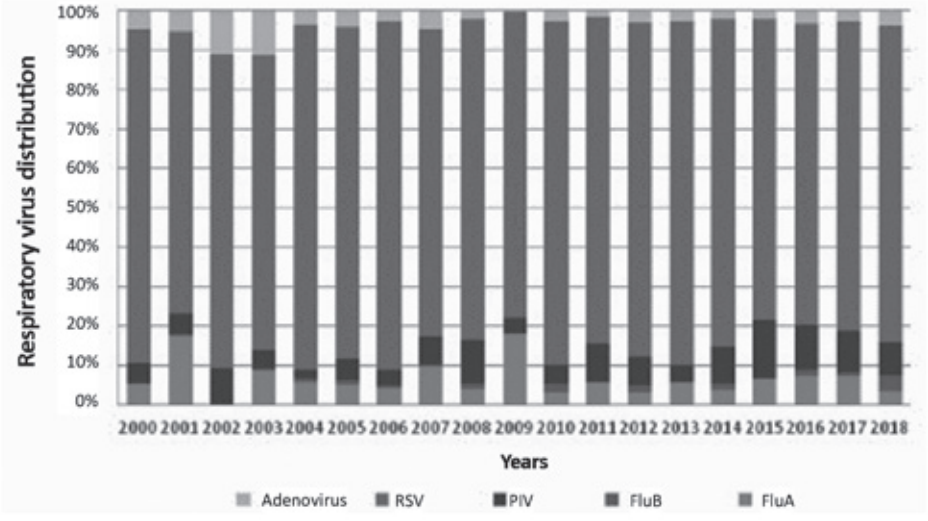
The following were independent predictors of adenovirus infection: male sex, age equal to or older than 12 months, readmission, prior

FIGURE 1. *Flow chart. General description of the population of acute lower respiratory tract infection cases*



ALRTI: acute lower respiratory tract infection; RSV: respiratory syncytial virus; Flu: influenza virus; PIV: parainfluenza virus.

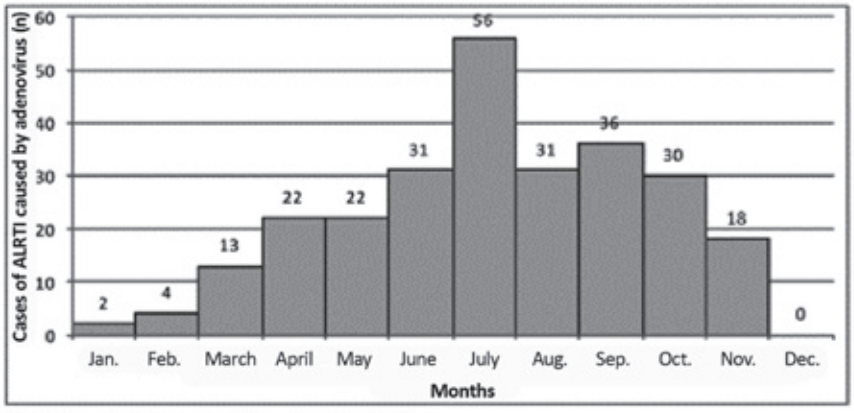
FIGURE 2. *Annual respiratory virus distribution, 2000-2018*



RSV: respiratory syncytial virus; Flu: influenza virus; PIV: parainfluenza virus.

hospitalizations due to respiratory causes, and clinical presentation of pneumonia (*Table 2*). The model showed an adequate calibration and was assessed using the Hosmer-Lemeshow test ($p = 0.16$). It also showed an acceptable discrimination as assessed by the receiver operating characteristic (ROC) curve, and the area under the curve was 0.70.

FIGURE 3. *Seasonal epidemic pattern of acute lower respiratory tract infection cases caused by adenovirus, 2000-2018*



ALRTI: acute lower respiratory tract infection.

TABLE 1. *Characteristics of acute lower respiratory tract infection cases caused by adenovirus compared to other viruses (respiratory syncytial virus, influenza, and parainfluenza)*

		Adenovirus + (n = 265)	Adenovirus – (n = 5782)	*p*
Sex (male)		63.8 %	56.2 %	0.014
Age (months)	Median (IQR)	11 (6-20)	7 (3-13)	<0.01
	<3 months old	3.8 %	18.2 %	<0.01
	<6 months old	18.1 %	40.2 %	<0.01
	<12 months old	50.6 %	70.8 %	<0.01
	<24 months old	83.1 %	89.9 %	<0.01
Prematurity		18.1 %	14.9 %	0.16
Perinatal respiratory disease		16.9 %	11.9 %	0.015
	Immunosuppression	3.8 %	2.3 %	0.12
	Malnutrition	9.1 %	5.2 %	0.06
	Readmission	15.6 %	4.2 %	<0.01
Prior hospitalization due to respiratory causes		50.0 %	30.3 %	<0.01
Pneumonia as admission diagnosis		63.0 %	39.9 %	<0.01
Comorbidities (58.3 %)				
n = 154	Chronic respiratory disease	80.5 %	75.8 %	0.18
	Chronic neurological disease	12.3 %	10.8 %	0.55
	Congenital heart disease	9.7 %	13.8 %	0.15
Assisted mechanical ventilation requirement		**19.2 %**	**8.4 %**	**<0.01**
Complications (44 %)				
n = 117	IARF	37.1 %	39.0 %	0.68
	Sepsis	17.2 %	16.3 %	0.81
Length of stay (median days; IQR)		9 (5-15)	7 (5-10)	<0.1
	Fatality rate	7.7 %	1.8 %	<0.01

IARF: impending acute respiratory failure; adenovirus +: ALRTI caused by adenovirus;
adenovirus -: ALRTI caused by respiratory syncytial virus, influenza or parainfluenza; IQR: interquartile range.

DISCUSSION

Active ALRTI epidemiological surveillance is critical to detect the seasonal increase in the number of cases in any season of the year in an early manner, identify affected population groups and their characteristics, and establish the frequency and distribution of involved etiologic agents.[16] IIF is the recommended respiratory virus diagnostic method (RSV, Flu, PIV, adenovirus) in ALRTI surveillance in the pediatric population. This is a simple, quick, low-cost technique with an adequate sensitivity and specificity; however, for adenovirus, they are lower than for other respiratory viruses.[18] In this regard, it is worth noting that more severe adenovirus infections secrete higher virus amounts, so IIF sensitivity in these cases goes up to 70-80 %.[19]

In our series, adenovirus was a low prevalence agent (4.3 %) among hospitalized children due to ALRTI, similar to what has been observed in other Argentine and Latin American studies that described a 2-8 % prevalence among ALRTIs with positive IIF.[5,6,20-24] However, in studies that used only molecular techniques, which were more sensitive for respiratory virus diagnosis, prevalence was higher.[23-29]

Adenovirus circulated throughout the year, as described in other studies,[6,9-11,21-24,26,28-32] with higher incidence peaks during the winter, which was consistent with the increase in the number of ALRTI cases,[20,30,32] unlike other studies that did not observe well defined seasonality patterns.[14,21-23,25-28] In 2003, a higher incidence of adenovirus infection was observed, with a subsequent tendency towards a reduction. Although it is important to consider the secular trend of this viral agent, flu and pneumococcal vaccine intervention programs may also account for such reduction. Several studies have demonstrated, in the pediatric population, a decreased incidence in pneumonia associated with viral infection after the introduction of the pneumococcal vaccine.[33,34]

FIGURE 4. *Annual case distribution and fatality rates of acute lower respiratory tract infection cases caused by adenovirus*

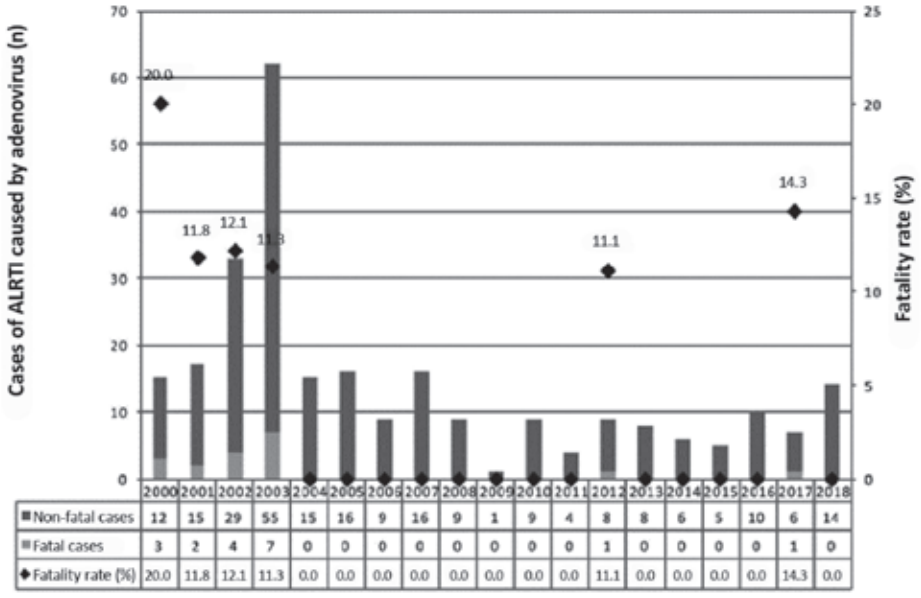


TABLE 2. *Independent predictors of adenovirus infection. Multivariate analysis*

Independent predictors	OR	95 % CI	*P*
Sex (male)	1.39	1.07-1.81	0.1013
Age ≥12 months	1.73	1.30-2.30	<0.001
Readmission due to the same event	3.36	2.29-4.93	<0.001
Prior hospitalization due to respiratory causes	1.44	1.05-1.96	0.020
Clinical presentation of pneumonia	2.04	1.55-2.67	<0.001

OR: odds ratio; CI: confidence interval.

Extensive bibliography describes the prevalence of respiratory adenovirus infection in infants.[14,20-22,25,27,30,32] In our series, half of patients were younger than 12 months, but the higher risk for infection in relation to other respiratory viruses was observed in children older than 12 months. Likewise, male patients and those with a history of hospitalizations due to respiratory causes or readmissions were significantly more affected, as described also by Pérez et al.[30]

A previous study conducted in our hospital on influenza infection predictors revealed that patients with prior hospitalization due to respiratory causes were more prone to be affected by seasonal flu. Likewise, readmission due to the same event was significantly associated with this infection.[31] In this study, such association was even stronger, i.e., readmission due to the same event was 3.4 times more likely to be related to an adenovirus infection. The percentage of prematurity was 18 %, similar to that observed in other studies done in this region,[25,32] and the high percentage of patients with comorbidities was also similar.[25,30,32] Adenovirus pneumonia in young children may have pulmonary sequelae, including bronchiectasis and obliterative bronchiolitis. A meta-analysis of pneumonia in children younger than 5 years found an association between adenovirus infection and a higher risk (55 %) for long-term sequelae compared to other causes of pneumonia.[15]

Although our study did not assess sequelae occurring after discharge, greater severity indicators of adenovirus infection were observed, similar to what has been described in the bibliography, such as a higher proportion of pneumonia as a clinical presentation,[12,14,20,25,27] AMV requirement,[21,25,30,32] length of stay,[21,30,32] and fatality.

The fatality rate for ALRTI caused by adenovirus varies among the different studies published in this region. It has been estimated to range between 3.4 % and 16.7 %,[14,25,30] depending, among other factors, on the serotype (higher for B7h). Our study did not analyze the serotype that would allow to identify if there was a more virulent genetic variant in any year.

A study carried out by Barrero et al., in the 1999-2010 period at HNRG described adenovirus serotypes B7 and B3 as the most prevalent ones. The diversity and pathogenicity of these serotypes are currently under study.[35] The fatality rate for adenovirus was almost 8 %, i.e., 4 times higher than that of other studied viruses; the median age of deceased patients was 12 months, and half of them had a comorbidity. Although the number of adenovirus cases decreased in recent years, no significant changes were observed in the fatality rate, unlike what has been observed by Machado et al., in Uruguay, who described a lower adenovirus severity compared to previous studies.[32]

The strengths of this study were its methodological design, an active, prospective surveillance based on solid epidemiological data, and a large enough sample that allowed to draw statistically significant conclusions. This model showed an adequate calibration and discrimination power in this population. A limitation was that the study was done in a single site, a tertiary care hospital, so the complexity of included patients makes it hard to extrapolate the results to the general population. The high proportion of comorbidities in these patients may have overestimated symptoms and severity when complications are analyzed.

CONCLUSION

Adenovirus infection showed an epidemic seasonal pattern with a higher incidence in the winter, a greater risk in children aged 12 months or older, males, patients with a history of prior hospitalizations due to respiratory causes, readmissions, and pneumonia as admission diagnosis. Clinicians should pay attention to these conditions when identifying ALRTI caused by adenovirus in hospitalized children.

It is worth noting that, in our series, although the number of adenovirus cases decreased in recent years, adenovirus evolutionary characteristics and severity have not changed. Its fatality rate was higher than for other studied viruses. It is important to maintain an ongoing surveillance that will allow to design better clinical and epidemiological management strategies for adenovirus infections. ■

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