

Research article

## Adenovirus type 7 associated with severe and fatal acute lower respiratory infections in Argentine children

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### Abstract

**Background:** Adenoviruses are the second most prevalent cause of acute lower respiratory infection of viral origin in children under four years of age in Buenos Aires, Argentina. The purpose of this study was to analyze the clinical features and outcome of acute lower respiratory infection associated with different adenovirus genotypes in children.

**Methods:** Twenty-four cases of acute lower respiratory infection and adenovirus diagnosis reported in a pediatric unit during a two-year period were retrospectively reviewed. Adenovirus was detected by antigen detection and isolation in HEp-2 cells. Adenovirus DNA from 17 isolates was studied by restriction enzyme analysis with Bam HI and Sma I.

**Results:** Subgenus b was found in 82.3% of the cases, and subgenus c in 17.7%. Within subgenus b, only genotype 7 was detected, with genomic variant 7h in 85.7% (12/14) and genomic variant 7i in 14.3% (2/14).

Mean age was  $8.8 \pm 6$  months, and male to female ratio was 3.8: 1. At admission, pneumonia was observed in 71% of the cases and bronchiolitis in 29%. Malnutrition occurred in 37% of the cases; tachypnea in 79%; chest indrawing in 66%; wheezing in 58%; apneas in 16%; and conjunctivitis in 29%. Blood cultures for bacteria and antigen detection of other respiratory viruses were negative.

During hospitalization, fatality rate was 16.7% (4 /24). Of the patients who died, three had Ad 7h and one Ad 7i. Thus, fatality rate for adenovirus type 7 reached 28.6% (4/14).

**Conclusions:** These results show the predominance of adenovirus 7 and high lethality associated with the genomic variants 7h and 7i in children hospitalized with acute lower respiratory infection.

### Background

Acute respiratory infection of the lower tract is a serious

cause of morbidity and mortality in young children, particularly in developing countries, where the risk of death

is 30 times higher than in the northern hemisphere [1]. In Argentina, acute lower respiratory infection is the third cause of death in children under one year of age [Miceli, I., Ministerio de Salud Pública y Acción Social, personal communication].

In the northern hemisphere, viruses are the agents most frequently associated with acute lower respiratory infections in children under 5 years of age. Adenoviruses (Ad) are the third viral agent (3%) after Respiratory Syncytial virus (RSV) (32–36%) and Parainfluenza viruses (17%) [2,3]. In Sweden, Ad are responsible for 5% of acute lower respiratory infection in hospitalized children [4]. Respiratory diseases are usually caused by Ad from subgenus b (serotypes 3 and 7), subgenus c (serotypes 1, 2 and 5), and subgenus e (serotype 4) [4].

In Buenos Aires, Argentina, viruses are also the first cause of acute lower respiratory infection in children under 5 years of age [5]. In this population, Ad proved to be the second viral agent after RSV, with detection rates of 2.7%

(27 Ad cases/1,003 patients) [5] and 2.5% (31 Ad cases/1,234 patients) [6] in inpatients under 5 years of age. However, higher Ad frequencies were observed in specialized hospitals, where rates reached 14.3% [7] and 34% [Mistchenko, A, 1996, personal communication].

Restriction enzyme analysis of viral DNA provides an essential tool for epidemiological studies, allowing the typing of Ad to subgenus level and the differentiation of genomic variants within a given serotype [4]. In the Southern Cone countries, molecular studies of Ad isolated from children with lower respiratory infection have shown the predominance of the genome type 7h. This variant was repeatedly associated with severe and frequently fatal outcome of necrotizing bronchiolitis or pneumonia [8–12].

The objective of this study was to analyze the clinical features and outcome of acute lower respiratory infection associated with different adenovirus genotypes in hospitalized children.

**Table 1: Clinical features at admission of children with acute lower respiratory infection with and without adenovirus infection**

Features	With Adenovirus infection n = 24		Without Adenovirus infection* n = 75		
	n	%	n	%	
<b>Age (months)</b>					
0–11	18	(75)	63	(84)	
12–24	6	(25)	12	(16)	
Mean age ± SE months		8.8 ± 6		6.8 ± 6.7 **	ns
<b>Sex</b>					
Male/female ratio		3.8:1		2.7:1 ***	ns
<b>Diagnosis at admission</b>					
Pneumonia	17	(71)	36	(48) ***	ns, p < 0.051
Bronchiolitis	7	(29)	39	(52)	
<b>Nutritional Status</b>					
Malnutrition	9	(37.5)	25	(33.8)	
Breast feeding	14	(58.3)	43	(57.5)	
<b>Signs and Symptoms</b>					
Fever (>38°C)	20	(83)	49	(65)	
Rhinorrhea	17	(70.8)	51	(67.5)	
Tachypnea	19	(79.2)	59	(78.8)	
Respiratory rate/min		40.0 ± 28.0		39.0 ± 31.0	
Cough	18	(75)	55	(73.8)	
Chest indrawing	16	(66.6)	52	(68.8)	
Wheezing	14	(58.3)	29	(38.8)	
Roncus	12	(50)	29	(38.8)	
Rales	18	(75)	57	(76.3)	
Apneas	4	(16.6)	7	(8.8) ***	ns
Conjunctivitis	7	(29)	17	(22.5)	

\* Children admitted to this hospital with ALRI, in whom RSV and Adenovirus diagnosis were excluded. \*\* "t" Student test ; \*\*\* X<sup>2</sup> test; ns: not significant

**Methods**

**Population**

Children included in this study were selected from a group of 168 patients with ALRI, admitted to a unit of the " P de Elizalde" Hospital in Buenos Aires, between May 1991 and December 1992 [7]. Clinical records from 24 children with Ad infection, (24/168) (14,3%), were retrospectively reviewed. Data from 75 children with neither RSV nor Ad infection were also analyzed.

Ad diagnosis was made by both indirect immunofluorescence and culture isolation. Children eligible for the study were those under 2 years of age, with clinical diagnosis of pneumonia or bronchiolitis, and less than 7 days of evolution at admission. Children with a history of asthma, HIV diagnosis, cystic fibrosis, measles or nosocomial infections were excluded.

Clinical diagnoses of pneumonia or bronchiolitis were made by both physical examination and chest X-ray, following the WHO guidelines [13]. Nasopharyngeal aspirate and blood culture for bacteria were obtained at admission. An informed consent signed by parents was obtained in all cases.

**Virological Methods**

*Ad detection*

Nasopharyngeal aspirates were processed at CEMIC Virology Laboratory. Antigen detection was performed by indirect immunofluorescence with a monoclonal antibody

(Chemicon, USA) and isolation was made in HEp-2 cells as described in the literature [7,13]. Genomic analyses were performed 2 years later. Ad isolates, kept at -70°C, were amplified in HEp-2 cells; viral DNA was extracted and studied by restriction enzyme analysis with Bam HI and Sma I endonucleases as previously described [10,14].

*Bacteriologic methods*

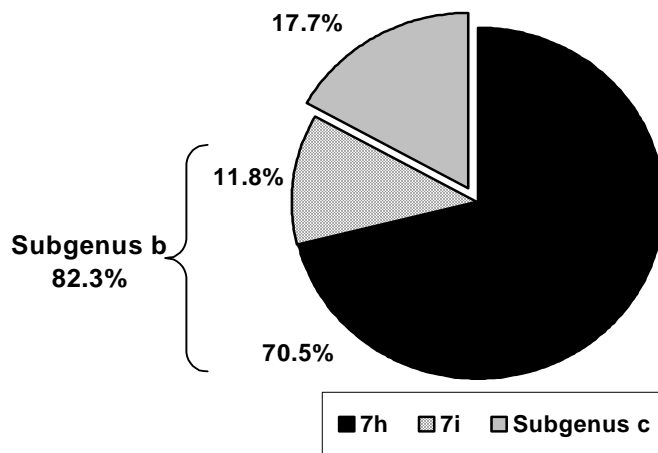
Blood cultures obtained at admission and stools from children who developed diarrheawere studied by standard methods at "P. de Elizalde" Hospital.

**Results**

**Clinical features at admission (Table I)**

Mean age was 8.8 ± 6 months, and 75% of the patients were between 6 and 24 months old. Male to female ratio was 3.8: 1. Clinical diagnoses were pneumonia (71%) and bronchiolitis (29%). Malnutrition was detected in 37.5 % of the cases, and 58% were breast fed.

The severity of the disease may be inferred from the high rates of tachypnea (79.2%), rales (75%), chest indrawing (66.6%), wheezing (58.3%), and apneas (16.6%). In addition to respiratory signs, 29% of the patients presented conjunctivitis. Although no statistically significant differences in signs and symptoms were observed between children with Ad and those without RSV or Ad infection, pneumonia was more frequently found in children with Ad.



**Figure 1**

Genome analysis of 17 adenovirus isolated from children with acute lower respiratory infection.

**Table 2: Clinical features, outcome and adenovirus genotypes in 17 children with acute lower respiratory infection**

Case #	Admission	Sex	Age months	Diagnosis	Underlying condition	Genotype	Outcome
<b>1991</b>							
1	Sept	M	2	Multifocal Pneumonia	Malnutrition Grade I	2D7	NF
2	Oct	M	24	Bilateral Pneumonia	None	7h	Dead* Sepsis, pneumonia
3	Nov	M	3	Multifocal Pneumonia	Malnutrition Grade II, Diarrhea	7h	Dead** Reye Syndrome, pneumonia
4	Nov	M	8	Bronchiolitis	Preterm Previous lung Sequelae, Preterm	7h	NF
<b>1992</b>							
5	Feb	M	3	Bronchiolitis	Preterm	1D1	Discharged
6	Feb	M	6	Bronchiolitis, Conjunctivitis	None	1D1	Discharged
7	Mar	F	7	Pneumonia	Congenital heart disease	7h	NF
8	July	M	12	Pneumonia	Previous ALRI	7h	NF
9	July	M	2	Bronchiolitis	None	7h	NF
10	July	M	15	Pneumonia, Otitis	Anemia	7h	Discharged
11	Aug	M	8	Pneumonia, Otitis	None	7h	Dead, pneumonia
12	Aug	F	2	Pneumonia	Congenital heart disease Malnutrition Grade II	7i	Dead***, empyema
13	Aug	M	9	Pneumonia	Macrocephaly	7i	NF
14	Sept	M	8	Bifocal Pneumonia	Hydrocephalus	7h	Discharged
15	Oct	M	8	Bifocal Pneumonia, Conjunctivitis	None	7h	NF
16	Nov	M	2	Pneumonia	None	7h	NF
17	Nov	M	6	Pneumonia, Conjunctivitis	Hypogammaglobulinemia	7h	Discharged

In all cases, blood cultures for bacteria were negative at admission. During diarrhea, the following bacteria were recovered from stools: \* *Klebsiella*; \*\* *Pseudomonas*; \*\*\* *Salmonella*. NF: not followed. Six patients were not followed because their parents took them from our hospital after the acute stage of the disease. Therefore, the outcome is not available.

### Frequency of Ad genotypes (Figure 1)

The 24 Ad cases found by antigen detection on nasopharyngeal aspirates were also isolated in culture. Ad strains were kept at -70°C until genomic analysis was performed 2 years later. Only 17 strains were recovered in culture, since the rest failed to be appropriately amplified. Molecular restriction analysis with Bam HI and Sma I was performed in the amplified strains, and showed subgenus b in 82.3 % (14 strains) and subgenus c in 17.7% (3 strains). Within subgenus b, the genome type most frequently detected was Ad 7h (85.7 %) (12 strains), while Ad 7i was found in 14.2 % (2 strains). Within the subgenus c strains, genome types Ad 2D7 were detected in 1 case, and Ad 1D1 in another 2 cases.

### Clinical features and outcome of 17 patients and Ad genotypes (Table 2)

At admission, all blood cultures were negative for bacteria, and no other respiratory viruses were detected in nasopharyngeal aspirates.

Out of the 12 patients with Ad 7h, 3 died, 3 recovered 1–2 weeks after hospitalization, and 6 were lost to follow up because their parents took them to another hospital. Regarding the 3 fatal cases with Ad 7h, bacterial etiology could not be clearly associated with death. In case # 11, all bacterial cultures were negative. A *Klebsiella* was detected in the stools of case # 2, and a *Pseudomonas* in the stools of case # 3.

The fatal case associated with Ad 7i was a 2-month-old female with congenital heart disease and malnutrition

grade II (case # 12). This patient died with empyema 10 days after hospitalization and mechanical ventilation, and a non-typhi Salmonella was recovered from her stools.

Regarding the patients who recovered from Ad 7h infection and were discharged, 3 presented underlying conditions: case # 10 anemia, case #14 hydrocephalus, and case # 17 hypogammaglobulinemia.

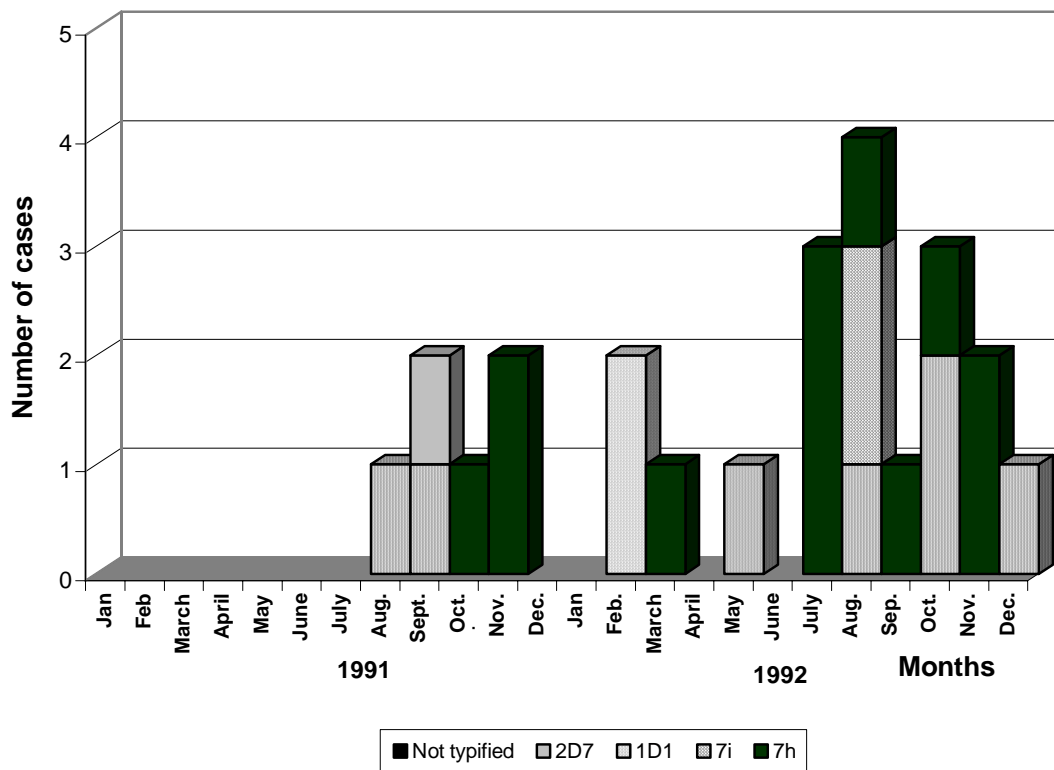
**Fatality rate (Table 3)**

The overall case fatality rate in hospitalized children with acute lower respiratory infection and associated Ad infection was 16.7 % (4/24). Considering only Ad 7 cases, case lethality reached 28.6%. Ad 7h was found in the respiratory samples of three patients, and Ad 7i in one.

Of the 3 patients who died with Ad 7h, 2 presented no underlying conditions, while 1 (case # 3) was a preterm male with malnutrition grade II. No fatal cases were recorded among the 75 children who presented neither RSV nor Ad infection.

**Table 3: Fatality rate during hospitalization associated with adenovirus genome type 7 in children with acute respiratory infection of the lower tract**

Case Fatality Rate	Fatalities/patients with Ad	(%)
Ad Genome type 7	4/14	(28.6)
Genomic variant Ad 7h	3/12	(25)
Genomic variant Ad 7i	1/2	(50)
Total (all variants)	4/24	(16.7)



**Figure 2**  
Monthly distribution of 24 adenovirus cases in children under 2 years of age hospitalized with acute lower respiratory infection.

**Seasonal distribution of Adenovirus genotypes (Figure 2)**

Ad cases were detected throughout the 2-year study period. Different patterns were observed in 1991 and 1992. In 1991, Ad cases were not found in winter but in spring. In 1992, the first Ad cases, Ad 1D1, occurred in February. The first Ad 7h was recorded in March. In winter, 3 cases were detected in July and 1 in August. Another 4 Ad 7h cases were recorded in spring. The 2 Ad 7i were detected in August, 1992.

**Discussion**

Children included in this study were selected from a group of 168 patients with acute lower respiratory infection studied in a pediatric hospital for two consecutive years. RSV was the most frequently detected virus (36.3%) (61/168), followed by Ad (14.3%) (24/168) ( $p < 0.0001$ ) [7]. The clinical features and outcomes of 24 children with Ad diagnosis were analyzed according to different Ad genotypes.

The frequency of community acquired Ad infection detected in this hospital in the studied period (14.3%) was higher than that reported for primary care centers in Buenos Aires city (2.5 %) [5,6,14]. The diagnostic methods used in those studies were immunofluorescence and/or culture. Probably, the use of more sensitive procedures such as PCR, currently available, would have increased these frequencies. [15–18]

Patients attending this hospital lived under low socio-economic conditions in poor areas of the city. Ad were highly associated with pneumonia (71%) rather than with bronchiolitis (21%), (Table 1) and were more frequently observed in males and in children older than 6 months. In 1991, Ad were detected in spring and at the end of winter, and in 1992, in spring (Figure 2). In contrast, RSV was mainly associated with bronchiolitis in younger children, and the outbreak showed a clear peak during the winter of the two years studied [7].

A predominance of Ad subgenus b (82.3 %) was observed, with genome type 7h being the most frequently detected (85.7%) (Figure 1).

The long lasting predominance of a few genomic types of Ad in a certain region has been reported for other countries [19], as shown in a study of 212 Ad strains isolated in the Southern Cone countries from 1984 to 1990. Between 1984 and 1985, Ad 7c was the predominant strain, while a switch to Ad 7h was observed in 1986. Thereafter, the circulation of Ad 7h has been documented in children with community acquired necrotizing bronchiolitis or severe pneumonia in Buenos Aires [6,8–11,20,21]. Furthermore, certain hospitals have reported nosocomial outbreaks in crowded conditions, which are associated

with high case lethality and development of lung sequelae [9].

In the present study, the overall fatality rate during hospitalization of patients with Ad 7 reached 28.6%. Of these patients, 3 had Ad 7h, and 1 Ad 7i. These severe cases could be strongly associated with Ad 7, since antigen detection of other respiratory viruses and blood cultures for bacteria were negative. Bacteria isolated from stools of the 3 children who developed diarrhea cannot be the main cause of death. Furthermore, among fatal cases with Ad 7h, no underlying conditions were observed in patients # 2 and # 11, while case # 3 was a preterm child with malnutrition grade II.

The fatal case with Ad 7i was a 2-month-old female with a congenital heart disease and malnutrition (# 12). When studied with 8 different restriction enzymes, Ad 7i proved to be closely related to Ad 7h, only differing in the restriction patterns with Bam HI and Cfo [8,11,22,23].

Murtagh et al. [9] reported a case lethality of 34.5 % (10 fatalities /29 patients) in pediatric acute lower respiratory disease associated with Ad 7h at Garrahan Hospital in Buenos Aires. In this series, 52% of the children recovered, but 14% developed severe lung sequelae. Pathogenic mechanisms involved in Ad infection of the respiratory tract are unclear. Therefore, neither specific treatment nor vaccines for civilian population are available. The role of maternal antibodies has not yet been studied.

Different sequences in the early region E3 or in the fiber have been suggested to result in diverse degrees of virulence or tropism by encoding proteins that may modulate the immune response and play a role in pathogenesis [24,25]. Although host risk factors such as immunodeficiencies, malnutrition or previous viral infections have been suggested to have an effect on the development of severe Ad infection, higher pathogenicity of some genome types is clearly associated with a fatal outcome [26]. This is the case of Ad 7h in Argentina, as shown once more in this paper.

Ad 7h has been recently isolated from children with upper respiratory infection in Japan. The authors reported that these strains are closely related to the Argentine Ad 7h, and suggested the spread of this emerging virus from South America to Japan, since Ad 7 was absent from this country for several decades [27].

In Argentina, lack of a national surveillance program for Ad infection, scarcity of autopsies, and difficulties in the follow up of patients for detection of lung sequelae restrict our knowledge of the general impact of Ad infection. Fur-

ther studies should be performed to elucidate the epidemiology of Ad in pediatric respiratory infections.

### Conclusions

The results herein obtained show predominance of adenovirus 7 (82 %) and high lethality associated with the genomic variants 7 h and 7 i (28.6%) in children hospitalized with acute lower respiratory infection.

### Competing interests

None declared.

### Authors' contributions

GC designed the study and wrote the paper. CV carried out the virologic study and participated in writing the paper. AM was in charge of patients' examination. PVR performed the statistical analysis. MCA was in charge of patients' examination.

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