Burden of Respiratory Syncytial Virus Disease and Mortality Risk Factors in Argentina:

18 Years Active Surveillance in a Children´s Hospital

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Abstract

Background: Respiratory Syncytial Virus (RSV) is the leading cause of acute lower respiratory infection (ALRI) in children. We aimed to describe the clinical-epidemiological pattern and risk factors for mortality associated with RSV infection.

Methods: A prospective, cross-sectional study of ALRI in children admitted to the Children's Hospital among 2000-2017. Viral diagnosis was made by fluorescent antibody techniques or real time-PCR. We compared clinical-epidemiological characteristics of RSV infection in non-fatal versus fatal cases. Multiple logistic regression was used to identify independent predictors of mortality.

Results: Of a total 15,451 patients with ALRI, 13,033 were tested for respiratory viruses and 5831 (45%) were positive: RSV 81.3% (4738), influenza 7.6% (440), parainfluenza 6.9% (402) and adenovirus 4.3% (251). RSV had a seasonal epidemic pattern coinciding with months of lowest average temperature. RSV cases show a case fatality rate of 1.7% (82/4687). Fatal cases had a higher proportion of: prematurity (p<0.01), perinatal respiratory history (p<0.01), malnourishment (p<0.01), congenital heart disease (p<0.01), chronic neurological disease (p<0.01) and pneumonia at clinical presentation (p=0.014). No significant difference between genders was observed. Most deaths occurred among children who had complications: respiratory distress (80.5%), nosocomial infections (45.7%), sepsis (31.7%) and atelectasis (13.4%). Independent predictors of RSV mortality were: moderate to severe malnourishment, OR 3.69 (95% CI 1.98-6.87) p< 0.0001, chronic neurological disease, OR 4.14 (95% CI 2.12-8.08) p< 0.0001, congenital heart disease, OR 4.18 (95% CI 2.39-7.32) p< 0.0001 and the age less than 6 months, OR 1.99 (95%CI 1.24-3.18) p=0.004.

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Conclusion: RSV showed an epidemic pattern affecting mostly young children. Malnourishment, chronic neurological disease, congenital heart disease and the age less than 6 months were the independent risk factors for RSV mortality.

Key Words: Respiratory syncytial virus, case fatality rate, bronchiolitis, pediatrics, epidemiology.

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Introduction

Acute lower respiratory infection (ALRI) is the most common reason for outpatient visits, school absenteeism and hospitalizations among children [1,2]. In Argentina, it is an important cause of mortality as well as hospital admissions during the winter months in all age groups, particularly in children younger than 5 and adults older than 65 years of age. Most of these infections are viral in origin generating significant morbidity and mortality in individuals with risk factors [3]. Respiratory syncytial virus (RSV) is the main cause of bronchiolitis and pneumonia in infants and young children worldwide [4]. Primary infection usually occurs in young children 6 weeks to 2 years of age [2,5-9], and is a leading cause of death in infants less than 6 months. Mortality rates are higher in developing countries than in developed countries, particularly in children less than age of 5 years[10].

RSV is spread through direct or indirect contact with nasal and oral secretions of infected individuals. Children are primarily responsible for transmission because they have higher viral loads than adults [11]. Reinfections can occur in any stage of life and are usually mild or asymptomatic in adults, but can cause severe disease in the elderly [12]. RSV is also an important pathogen in other risk groups such as preterm infants and children with bronchopulmonary dysplasia or hemodynamically unstable congenital heart disease [13]. Worldwide, this virus is responsible for 30 million episodes of ALRI and for more than 50,000 deaths per year in children younger than 5 years [14]. A recent publication on global RSV mortality, which included data from our hospital, estimated that the virus causes one third of all deaths in children less than one year of age [15]. In Argentina, based on information provided by the National Laboratory-based Surveillance System (SNVS-SIVILA), out of a total of 30,949 positive respiratory samples

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collected in 2017 between epidemiologic weeks 1 and 44, RSV was the main pathogen found in 61.4% (n=18,738) of samples, followed by influenza viruses (IF) 20.8% (n=6349) [16].

Given the global burden of RSV disease in children, the aim of this study was to describe the clinical and epidemiologic characteristics of RSV-ALRI and estimate case fatality risk factors in patients admitted to our hospital.

Methods

We conducted a prospective, cross-sectional study. Patients with ALRI acquired in the community admitted to the Ricardo Gutierrez Children's Hospital, Buenos Aires, between 2000 and 2017 were identified through an active surveillance program.

Population

All children less than 18 years of age hospitalized for ALRI acquired in the community, namely those presenting bronchiolitis or pneumonia were included. Both definitions met WHO criteria for ALRI[17].

Exclusion criteria

Patients admitted for other causes who developed ALRI during hospitalization.

Data collection

Data was collected using a specific case-report form and included: date of admission, demographics (age, sex, city of residence), clinical presentation (bronchiolitis, pneumonia), previous hospitalizations for respiratory diseases, readmission within the same episode, co-morbidities, history of close contact with individuals presenting acute respiratory symptoms of probable viral origin (runny nose, cough, and/or fever), perinatal respiratory disorders, complications during hospitalization, treatment, length of stay and outcome (discharged home, transferred to another hospital or died). Co-morbidities included chronic or recurrent respiratory

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disease, moderate to severe malnourishment, congenital heart disease, genetic or neurologic diseases and immunodeficiency.

Chronic or recurrent respiratory disease, were also reported, namely, recurrent obstructive bronchitis or asthma (two or more episodes of bronchial-obstruction), gastroesophageal reflux disease, cystic fibrosis, bronchopulmonary dysplasia, recurrent laryngitis and pneumonia; as were in-hospital complications such as nosocomial infections, sepsis, persistent atelectasis, pneumothorax, pleural effusion, pulmonary bullae, lung abscesses, ear infections, diarrhea, seizures, and meningitis.

Nosocomial infection was defined as exacerbation of respiratory symptoms not present at admission (even if incubation was a possibility), diagnosed in patients hospitalized for ≥48 hours, presenting fever, increased oxygen requirement or changes in radiologic pattern.

Diagnostic methods

World Health Organization guidelines were used for clinical and radiologic diagnosis of bronchiolitis and pneumonia [17]. Viral diagnosis was performed in all cases by indirect fluorescent antibody (IFA) testing on nasopharyngeal specimens. After real-time polymerase chain reaction (RT-PCR) assay became available in 2009, it has been used together with IFA test to detect RSV, IF A and B, parainfluenza (PIF) and adenovirus (AV). Commercially available kits were used in all cases.

Statistical analysis

Categorical variables were analyzed using the χ2 test with Yates correction. We used the Wilcoxon test for median age comparison. Odds ratio (OR) with 95% confidence interval (CI) was used for association analysis; a bivariate analysis was performed initially to identify significant associations and multivariate logistic regression was subsequently carried out to

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establish independent predictors of case fatality. P values < 0.05 were considered statistically significant. STATA / SE version 13 was used for the analysis.

Multivariate analysis

A logistic regression model was constructed to identify the predictors of mortality by RSV. The variables with significant association with death in the crude analysis and / or those considered clinically relevant, were added one at a time in the multivariate model and only those significantly associated with the outcome in the multivariable context (Wald test) were retained in the final model. We checked the changes on the coefficients in order to find confounding variables.

Calibration and discrimination

The calibration and discrimination of the model were evaluated with the Hosmer-Lemeshow goodness-of-fit test and the area under the ROC curve.

Seasonality

RSV season onset and offset were calculated as described by Panozzo et al. in 2007 [18].

Ethical considerations

Privacy rights of patients were observed in all cases in accordance with the World Medical Association Declaration of Helsinki International Code of Ethics for experiments involving humans. Patient's informed consent is not applicable in this study because data were obtained from a routine epidemiologic surveillance activity included in the framework of Argentinean Law 15465/60. The study was approved by the Ethics and Research Committees of the Ricardo Gutierrez Children's Hospital. This study will not affect human rights, nor will it cause damage to the environment, animals and/or future generations.

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Results

A total of 15,451 patients were admitted for ALRI acquired in the community over a period of 18 years, from them 13,033 (84%) children were tested for respiratory viruses and 5,831 (45%) had positive results (see Figure, Supplemental Digital Content 1, http://links.lww.com/INF/D397). RSV predominated throughout the entire study period (4738, 81.3%), followed by IF (440, 7.6%), PIF (402, 6.9%) and AV (251, 4.3%).

RSV had a seasonal epidemic pattern (viral activity onset and offset 18 and 33 epidemiologic weeks respectively) coinciding with months of lowest median temperature and highest relative humidity (May-July). (Figure 1)

In our study population there was a slight predominance of boys (56.5%), and the median age was 7 months (IQR 2-12); almost two thirds were infants less than 12 months and 42% less than 6 months of age.

The distribution of the different clinical and epidemiologic characteristics of patients with RSV disease and their relationship with the outcome (death) is expressed in Table 1, comparing non-fatal and fatal cases.

RSV case fatality rate was 1.7% (82/4687).

The annual mortality rate distribution was not stable over the study period with the highest mortality in the year 2002. (Figure 2)

In fatal cases, the most frequent complications were respiratory distress (80.5%), nosocomial infections (45.7%), sepsis (31.7%) and atelectasis (13.4%) (Table 2).

Independent predictors of RSV mortality were: moderate to severe malnourishment, chronic neurologic disease, congenital heart disease and age less than 6 months. (Table 3)

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The final model achieved good calibration (p=0.85) and discrimination with an area under the ROC curve of 0.712.

Discussion

In this study, we evaluated the characteristics and outcome of patients with RSV-ALRI based on active surveillance and systematic data collection over a period of 18 years. Active surveillance of ALRI is crucial for rapid detection of increase in number of cases, identification of high risk groups and to determine the frequency, distribution and characteristics of disease-causing agents [19,20].

RSV was the most frequent pathogen found in positive samples from the patients included in our center (81.3%) and that incidence was highest in infants less than one year of age (74% of cases). These results are similar to those of other epidemiologic studies carried out in the region [21-23]. RSV circulation showed a seasonal epidemic pattern as seen in temperate climate regions. Onset and offset of viral activity were registered during epidemiologic weeks 18 and 33 respectively, coinciding with months of lowest median temperature and highest relative humidity in Argentina (May-July) [23]. Kamigaki et al. found that mean temperature and specific humidity were also positively associated with influenza and RSV at Philippine sites[24]. In addition, Meerhoff et al., reported that the combination of both (temperature and humidity) contribute more to RSV activity than each factor independently [25]. Furthermore, Walton et al. showed that real time weather forecasts have the potential to predict RSV outbreaks [26]. Although we found a similar epidemic seasonal pattern, a proper time-series analysis is needed to draw robust conclusions as the mentioned authors

Around the world, 1-3% of healthy children are hospitalized as result of RSV respiratory infections during the first year of life.[2,3,6,27] In our study, although most patients were healthy

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children younger than one year of age, patients with underlying conditions such as prematurity, congenital heart disease, malnutrition and chronic neurologic disease showed higher rates of mortality [28-29]. In a meta-analysis on incidence and mortality of RSV infections in children, Stein et al. concluded that the virus was an important cause of hospitalization and mortality, and that gestational age was a critical determinant of disease severity in the first year of life [30]. Unfortunately as we have not recorded gestational age data in the whole series we could not include this variable in the analysis.

Although being a boy was found to be a risk factor in some studies [31], we did not observe significant gender differences in our population. Regarding congenital heart disease (CHD) a 20 years systematic review was undertaken across studies reporting data for hospital visits/admissions for RSV infection among children with CHD, concluding that young children with CHD have a significant risk for RSV mortality [32]. This risk is specially for severe disease and hospitalization and, in some instances, may require admission to the intensive care unit (ICU), supplemental oxygen therapy and prolonged mechanical ventilation[33,34].

In a study based on national data sets, Byington et al. also found children with complex chronic conditions accounted for most RSV associated deaths [35]. Scheltema et al. also found that more than half of all children included in the RSV Gold RSV associated study had a weight for age of less than -2 SDs[15]. García et al. describe several factors that independently correlated with the severity of illness as trisomy 21, lower weights on admission, neuromuscular disorders [28]. Death from RSV infection was more common in patients requiring mechanical ventilation, longer hospital length of stay, presenting sepsis and atelectasis, in line with other regional studies[36,37]. Most deaths were associated with complex chronic conditions or acute disorders

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such as sepsis or respiratory failure. Moreover many children have more than one complication during hospitalization.

Case fatality rate was 1.7% (82/4687) similar to values reported by Nair et al. who found rates of 0.3 and 2.1% in children under 5 years and 0.7 and 2.1% in infants (<1 year of age) for industrialized and developing countries, respectively [38].

One of the strengths of this study lies in its methodologic design, a prospective active surveillance based on robust epidemiologic data, a sample large enough that allows statistical robust conclusions and individual data of each patient. The model showed good calibration and discriminative capacity in the studied population.

In addition indirect immunofluorescence test is recommended for rapid detection and diagnosis of respiratory viruses. This method is widely used because it is a simple, quick, low-cost test with high specificity and sensitivity detecting viruses that usually cause ALRI, namely RSV, IF, PIF and AV [38-41].

As a limitation, this study was conducted in a single tertiary hospital, so the complexity of our patients makes it difficult to extrapolate results to the general population. The high proportion of comorbidities in our patients perhaps overestimates the more severe RSV symptoms when we analyzed complications. Moreover, hospital case-fatality ratios cannot be translated to population-based mortality.

Around 60 different strategies to prevent RSV infection are being developed involving candidate vaccines and human monoclonal antibodies, of which 16 are currently undergoing phase I-III studies [42]. The data afforded by this epidemiologic study and other similar investigations will be

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crucial to assess the effectiveness and impact of new RSV vaccines, as well as for establishing

age-specific immunization strategies and harmonizing health care policies [43].

In conclusion, multiple independent characteristics have been identified that significantly

increase the risk of death in the population studied.

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Table 1: Characteristics of patients with RSV disease comparing non-fatal and fatal cases.

Variables		Total RSV cases n=4738	Non-fatal RSV cases n= 4605	Fatal RSV cases n= 82	*p*
Age n (%)	Median (months); IQR	7; 3-12	5; 2-11	7; 3-12	0.1
	< 6 months	2022 (42.7)	1961 (42.6)	42 (51.2)	0.15
	< 12 months	3505 (74)	3379 (73.5)	63 (76.8)	0.58
Sex (boys) n (%)		2679 (56.5)	2578 (56.6)	41 (50)	0.27
Prematurity n (%)		655 (13.85)	629 (13.7)	20 (24.4)	0.008
Neonatal respiratory history n (%)		527 (11.15)	500 (10.9)	21 (25.6)	<0.01
Immunosuppression n (%)		87 (1.84)	83 (1.8)	2 (2.4)	0.99
Malnourishment n (%)		218 (4.62)	197 (4.3)	17 (20.7)	<0.01
Previous hospitalizations for respiratory causes n (%)		1246 (26.4)	1193 (26)	36 (43.9)	<0.01
Re-admission for same episode n (%)		153 (3.24)	141 (3.1)	7 (8.5)	0.012
Pneumonia as clinical presentation n (%)		1832 (38.7)	1772 (38.5)	43 (52.4)	0.014
Comorbidities n (%)	Total	1947 (41.1)	1872 (40.7)	54 (65.8)	<0.01
	Recurrent obstructive bronchitis	1339 (28.27)	1306 (28.4)	21 (25.6)	0.67
	Congenital heart disease	282 (5.85)	263 (5.7)	19 (23.2)	<0.01
	Chronic neurologic disease	198 (4.18)	180 (3.9)	13 (15.8)	<0.01

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Table 2: Complications in patients with RSV-ALRI

Complications	Total RSV cases n= 4687	Non-fatal cases n=4605	Fatal cases n=82	p
Total n (%)	5121*	981 (21.3)	77 (93.9)	<0.01
Respiratory distress	380 (8)	312 (6.8)	66 (80.5)	<0.01
Atelectasia	179 (3.8)	168 (3.6)	11 (13.4)	<0.01
Sepsis	149 (3.18)	120 (2.6)	26 (31.7)	<0.01
Nosocomial Infection	288 (6.3)	251 (5.6)	37 (45.7)	<0.01
Length of hospital stay median (days); IQR	7 (5-10)	7 (5-10)	17 (8-31)	<0.01

* Many children have more than one complication during hospitalization.

Table 3: Results of the final model of Multiple Logistic Regression: independent predictors

for RSV mortality

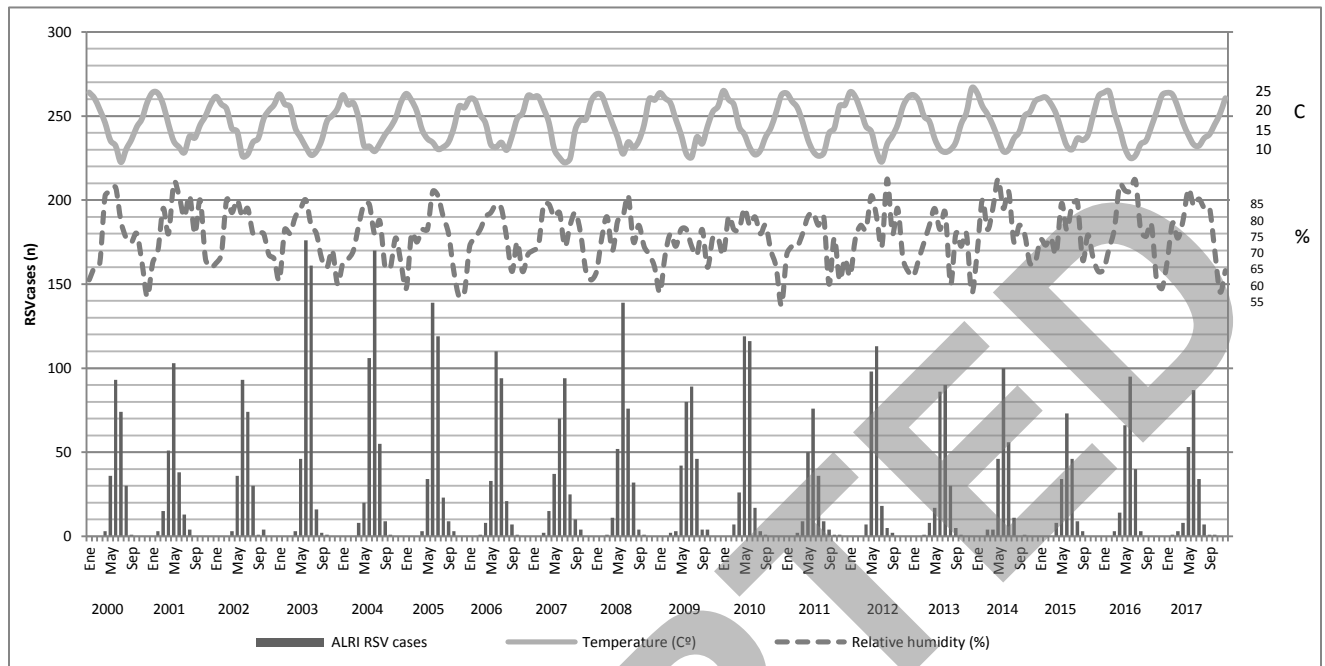| Variables	OR	95% CI	*p*
Malnourishment	3.69	1.98-6.87	< 0.0001
Chronic neurologic disease	4.14	2.12-8.08	< 0.0001
Congenital heart disease	4.18	2.39-7.32	< 0.0001
Age less than 6 months	1.99	1.24-3.18	0.004

Figure 1: RSV Seasonal Pattern. 2000-2017

Figure 2: Annual RSV cases and mortality rate distribution. 2000-2017.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Fatal cases (n)	6	7	13	11	10	5	1	4	5	0	0	5	5	2	4	2	1	1
Mortality rate (%)	2.2	3.1	5.4	2.7	2.7	1.5	0.4	1.7	1.6	0	0	2.7	2.1	0.9	1.8	1.2	0.5	0.5