

The epidemiology and clinical characteristics of respiratory syncytial virus infection in children at a public pediatric referral hospital in Mexico

Juan Pablo Rodríguez-Auad^a, Margarita Nava-Frías^a, Jesús Casasola-Flores^a, Kyle M. Johnson^b, Alejandra Nava-Ruiz^a, Víctor Pérez-Robles^a, Miguela A. Caniza^{b,c,d,*}

^a Department of Pediatric Infectious Diseases, Hospital Infantil de México Federico Gómez, Mexico City, DF, Mexico

^b Department of Infectious Diseases, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis TN, 38105-3678, USA

^c International Outreach Program, St. Jude Children's Research Hospital, Memphis, Tennessee, USA

^d Department of Pediatrics, University of Tennessee Health Science Center, College of Medicine, Memphis, Tennessee, USA

ARTICLE INFO

Article history:

Received 9 March 2011

Received in revised form 24 February 2012

Accepted 5 March 2012

Corresponding Editor: Jane Zuckerman, London, UK

Keywords:

Respiratory syncytial virus

Respiratory infection

Children

High risk

Nosocomial

Mexico

Latin America

SUMMARY

Objectives: The aim of this study was to determine the epidemiological and clinical characteristics of children with respiratory syncytial virus (RSV) treated at a public referral children's hospital in Mexico. **Methods:** We reviewed RSV infection in patients aged 0–18 years who were treated at Hospital Infantil from January 2004 to December 2008.

Results: During the 5 years, 2797 samples were tested for respiratory viruses; 356 samples were positive for any virus, including 266 (74.7%) positive for RSV. Complete clinical information was available for 205 RSV patients. The mean age was 22 months, and 33.7% of the infections were nosocomially acquired. Hospitalization occurred in 187 children. Of 14 deaths, nine were directly attributed to RSV infection. During the study, RSV infections were seen throughout the year, predominating in the colder months. Of the 205 patients, 79.0% (162/205) had an underlying disease. Congenital heart disease was found in 30.2% (49/162), including three children (33.3%) who died of RSV. Thirty-three patients (16.1%) with RSV required mechanical ventilation. None of the children with RSV received palivizumab or ribavirin.

Conclusions: RSV caused high hospitalization rates and admission to intensive care units, especially among those with underlying illnesses and young infants. The data presented here will be useful for strategies to improve outcomes in children at risk of complications.

© 2012 International Society for Infectious Diseases. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Respiratory syncytial virus (RSV) is an important cause of viral lower respiratory tract infections in infants and children worldwide,^{1,2} and it is a significant pathogen in immune-compromised hosts and those with underlying cardiopulmonary diseases.^{3–5} Globally, the RSV burden is estimated at 64 million cases and 160 000 deaths annually;⁶ for those younger than 1 year old, the estimated RSV mortality rate was shown to be more than nine times that of influenza.⁷ A recent prospective study of Kenyan infants and children hospitalized with severe pneumonia showed that RSV was the predominant pathogen isolated,⁸ and other studies have shown similar findings.^{9,10}

RSV is transmitted by contact with infectious droplets. An incidence of nosocomial RSV infection of 6% (90 of 1568 documented RSV infections) was reported in a prospective multicenter surveillance study done in Germany covering six

consecutive seasons from 1999 to 2005.¹¹ Some investigators suggest that the true incidence of nosocomial RSV may be underestimated.¹² In a recent study in a general hospital in Mexico, investigators found that RSV was responsible for 26% of confirmed respiratory infections among those tested for RSV in children younger than 5 years old.¹³

To better understand the contribution of RSV infection to the morbidity and mortality of very high risk children, we analyzed the clinical characteristics and epidemiology of RSV in pediatric patients aged 0–18 years and their outcomes at Hospital Infantil de México Federico Gómez (Hospital Infantil) during 2004–2008.

2. Materials and methods

2.1. Setting

Hospital Infantil is a public, multi-specialty, teaching and referral hospital with 290 beds for children aged 0–18 years located in Mexico City. Patients admitted to Hospital Infantil are those with complex diseases who require highly specialized care and come from Mexico City, the surrounding communities, and

* Corresponding author. Tel.: +1 901 595 4194; fax: +1 901 595 2099.
E-mail address: miguela.caniza@stjude.org (M.A. Caniza).

other more distant cities. Mexico City has an elevation of 2240 meters (7350 feet) above sea level, and the cooler months are from November through February. Patients with RSV are allocated single-bed rooms if available, or are placed in rooms with other patients with RSV. Hospital Infantil is one of the three most important teaching pediatric centers in Mexico City, however other care centers for children who require hospitalization also exist in the city. During the study years, the average annual discharge was 6356 patients, and bed occupancy was 85.2%.

2.2. Study population and design

We conducted a retrospective, observational study that included all consecutive patients aged 0–18 years at Hospital Infantil with respiratory symptoms and a positive antigen test for RSV using an indirect immunofluorescence antibody assay (IFA) during the study period of January 1, 2004 through December 31, 2008. By using the microbiology laboratory registry, we constructed a list of patients with respiratory infections for whom respiratory virus testing was required. Patients who were positive for RSV and for whom complete demographic data and medical information were available were included in the study. Medical information required included underlying disease, date of onset of disease to determine whether community- or hospital-acquired, length of hospital stay, wards in which they were hospitalized, clinical presentation, laboratory information, development of complications, illness severity, and deaths related to RSV infection. Information was collected regarding initial hospital site of care where respiratory samples were obtained and signs and symptoms on presentation, such as cough, rhinorrhea, bronchospasm, respiratory distress, apnea, cyanosis, and fever ($\geq 38^\circ\text{C}$). The severity of the clinical status was determined on the basis of whether admission to the intensive care unit was required and whether mechanical ventilation was needed. The decision regarding tracheal intubation was determined by the patients' clinical status using the Silverman–Andersen score.¹⁴ RSV infection was considered nosocomial when the symptoms appeared on inpatient day 6 or later and if patients were readmitted with RSV less than 5 days after discharge and the first admission was for a non-RSV illness.^{15,16} The study was approved by the Institutional Research Ethics Committee of Hospital Infantil.

2.3. Sample collection and laboratory processing

All children with symptoms of viral upper or lower respiratory tract infection attending Hospital Infantil had nasal swabs taken for the study of the respiratory virus as part of the standard of care. Rayon-tipped, aluminum-shafted swabs (Copan Italia S.p.a., Brescia, Italy) were used to collect nasal secretion samples, and bronchial aspirate was collected from those who were intubated. To identify RSV antigen in the respiratory samples, an IFA was performed (Light Diagnostics Respiratory Panel I Viral Screening and Identification IFA, Millipore (UK) Ltd) for the detection of parainfluenza virus types 1, 2, and 3, adenovirus, influenza types A and B, and RSV. Metapneumovirus and rhinovirus were not tested for. The assay was conducted in accordance with the manufacturer's instructions. The samples were obtained at the point of patient care (i.e., the emergency department, intensive care units, or other inpatient wards).

2.4. Statistical methods

Frequencies and comparisons of variables in the information obtained were analyzed using SPSS version 16. Descriptive statistics such as means and proportions were used to report origin, month of diagnosis, age, hospitalization ward, length

Table 1

Viruses identified in respiratory infections at Hospital Infantil, 2004–2008

Virus	Year					Total
	2004	2005	2006	2007	2008	
RSV	49	57	23	89	48	266
Parainfluenza 3	2	1	4	18	4	29
Influenza A	1	3	0	21	0	25
Parainfluenza 2	2	1	0	3	7	13
Parainfluenza 1	7	0	1	0	3	11
Adenovirus	2	2	0	4	1	9
Influenza B	0	1	0	1	1	3
Total positive	63	65	28	136	64	356
Total negative	215	366	391	774	695	2441

RSV, respiratory syncytial virus.

of hospitalization, underlying illnesses, and severity of RSV infection.

3. Results

3.1. Study population

A total of 2797 respiratory secretion samples were collected from the same number of patients, and these samples were studied in the microbiology laboratory of Hospital Infantil. From 356 samples that were positive for any respiratory viral agent, RSV was the most frequently isolated virus (266, 74.7%; Table 1). For our study we selected 205 patients for whom complete clinical data were available. We had no clinical information on 61 patients (22.9%) with RSV infection, so they were excluded from further study. Occasionally, children who do not receive routine care at Hospital Infantil are tested in this hospital's laboratories. These children often do not have medical records at this hospital, and it is likely that the children in the group that we excluded for lack of clinical information were such children.

3.2. Demographic characteristics

The demographic and clinical characteristics of the 205 study subjects are shown in Table 2. The mean age of the patients was 22 months (range 0.6–180 months), and the median and the mode were 9 and 2 months, respectively. Eighty percent (164/205) of the patients infected with RSV were aged ≤ 24 months (Figure 1), and 50% were aged between 4 months (first quartile) and 21 months (third quartile). There were 105 girls and 100 boys. Of the 205 patients, 187 (91.2%) required hospitalization. Most of the patients (162/205, 79.0%) with RSV infections had an underlying disease, such as congenital heart disease (CHD; 49/162, 30.2%) and neoplastic diseases (28/162, 17.3%).

In most other reports, RSV has been seen in younger patients (i.e., those younger than 6 months);^{2,17} the mean age in our study was higher, but other measures of central tendencies (median and mode) were lower than the mean because of the asymmetric age distribution of our sample population (positively skewed). Thus, more than 60% were older than 6 months, in whom hospitalization was most likely due to underlying illnesses. Among patients with RSV infection, 12.8% were born at less than 34 weeks of gestation, 11.7% were born between 34 and 37 weeks of gestation, and 75.5% were full-term infants. Most of the patients (82.4%) originated from Mexico City and surrounding areas and the rest (17.6%) were from other regions of Mexico.

3.3. Epidemiology of RSV infections at Hospital Infantil

Most of the samples (112/205, 54.6%) were collected while the patients were in the emergency room; the rest were collected from

Table 2

Demographics and clinical characteristics of 205 patients with RSV infections at Hospital Infantil, 2004–2008

Demographics and characteristics	Result, % (n)
Mean age in months	22 (range 0.6–180)
Females	51.2% (105)
Underlying disease ^a	79.0% (162 patients with 175 diseases ^b)
Congenital heart disease	28% (49)
Neoplastic disease	16% (28)
Down syndrome	9.1% (16)
Bronchopulmonary dysplasia	5.7% (10)
Hepatopathy	5.7% (10)
Neurological diseases	5.7% (10)
Gastrointestinal disease	4.6% (8)
Congenital malformation – non-cardiac	4% (7)
Steroid use	4% (7)
HIV	3.4% (6)
Endocrine/metabolic	2.9% (5)
Infectious process – non-viral	2.9% (5)
Hematological – non-malignant	2.3% (4)
Pulmonary disease	2.3% (4)
Cystic fibrosis	1.1% (2)
Renal disease	1.1% (2)
Other ^c	1.1% (2)
Community-acquired RSV infection	66.3% (136)
Nosocomially-acquired RSV infection ^d	33.7% (69)
Point of care when diagnostic sample taken	
Emergency room	54.6% (112)
General ward	26.3% (54)
Surgery	7.3% (15)
Oncology	5.4% (11)
Intensive care unit	3.4% (7)
Neonatal intensive care unit	2.9% (6)
Diagnostic sample type	
Nasal swab	83.9% (172)
Bronchial aspirate	16.1% (33)
Respiratory symptoms	
Cough	80% (164)
Fever	55.6% (114)
Respiratory distress	47.8% (98)
Rhinorrhea	43.9% (90)
Apnea	3.9% (8)
<3 months	100% (8)
Diagnosis	
Pneumonia	65.3% (134)
Bronchiolitis	13.2% (27)
Pharyngitis	12.7% (26)
Other	8.8% (18)
Antibiotics upon admission	67.3% (138)

^a Some individuals had more than one underlying disease; total of 175 diseases.

^b Denominator for underlying diseases subgroup = 175 diseases.

^c Other diseases included a case of cervical lymphangioma and a case of craniosynostosis.

^d A nosocomial RSV infection in our study was defined by onset of symptoms on or after day 6 of hospitalization.

the general pediatric wards (54/205, 26.3%), surgical wards (15/205, 7.3%), oncology (11/205, 5.4%), intensive care unit (7/205, 3.4%), and neonatal intensive care unit (6/205, 2.9%). Most cases occurred in the fall (147/266, 55.3%), with 31.6% (84/266) in winter, 6.0% (16/266) in spring, and 7.1% (19/266) in summer. During the 5 years of the study, RSV infections were less common during the warmer months of the year (March to June), and peaked during the cooler months (August to March), changing year to year (Figure 2). Approximately a third (69/205, 33.7%) of the RSV infections were acquired in the hospital, and the rest were acquired in the community (136/205, 66.3%). The duration of hospitalization of patients with community-acquired infection ranged from 1 to 70 days (median 7 days). Of those inpatients, 49.3% (67/136) stayed less than 7 days, 27.9% (38/136) stayed 7–14 days, and 22.8% (31/136) stayed more than 14 days.

3.4. Clinical presentation and severity

At presentation, the patients had cough (164/205, 80%), fever (114/205, 55.6%), respiratory distress (98/205, 47.8%), and rhinorrhea (90/205, 43.9%). The most frequent findings by lung auscultation were crackles (98/205, 47.8%), rattles (117/205, 57.1%), and wheezing (55/205, 26.8%). Eight patients (3.9%) had apnea. The most frequent clinical diagnoses were pneumonia (134/205, 65.3%), bronchiolitis (27/205, 13.2%), and pharyngitis (26/205, 12.7%). Other less frequent diagnoses were atypical pneumonia (8/205, 3.9%), rhinitis (5/205, 2.4%), and otitis (3/205, 1.5%). Of the 111 patients with chest radiographs, 25.2% (28/111) had interstitial infiltrates, 23.4% (26/111) had perihilar infiltrates, and 18.0% (20/111) had lung overdistention. Other radiology findings were bilateral infiltrates, consolidation, infiltrates in both bases, and atelectasis. Most of the patients (138/205, 67.3%) received antibiotics upon admission to the hospital. The most frequently used antibiotics for suspected bacterial pneumonia were ampicillin (22.4%), cefuroxime (20.2%), and cefotaxime plus dicloxacillin (13.0%). Other antibiotics used were clarithromycin, cefepime plus amikacin, and amoxicillin/clavulanic acid.

In terms of the illness severity, 33/205 (16.1%) required mechanical ventilation and 14 of these children (42.4%) died. Nine deaths occurred at <30 days after testing positive for RSV and were possibly related to the RSV infection, giving a global mortality rate of 4.4% (9/205); the five other deaths occurred ≥30 days after the initial diagnosis of RSV and these deaths were not directly attributed to RSV. The mean age of the patients who died was 12 months. Five of the patients who died had a nosocomially-acquired RSV infection (Table 3). No prophylaxis with palivizumab or treatment with ribavirin was used in any of the patients in this study.

4. Discussion

RSV was the most frequent viral pathogen found in respiratory samples tested using IFA in Hospital Infantil during the 5-year study period from 2004 to 2008, accounting for 74.7% of all the respiratory viruses isolated from patients with respiratory tract infections. Most of the children with RSV required hospitalization, and more than three quarters were younger than 2 years old. In contrast to other published RSV epidemiologic studies,^{2,13,18} the patients we describe here were at high risk for RSV complications and were not receiving RSV prophylaxis. As a result, many of them were hospitalized. The most frequent underlying diseases among these hospitalized children were CHD, malignancies, and bronchopulmonary disease (BPD). Most of the patients had respiratory symptoms; some were severe and the patients required admission to the intensive care unit and assisted mechanical ventilation.

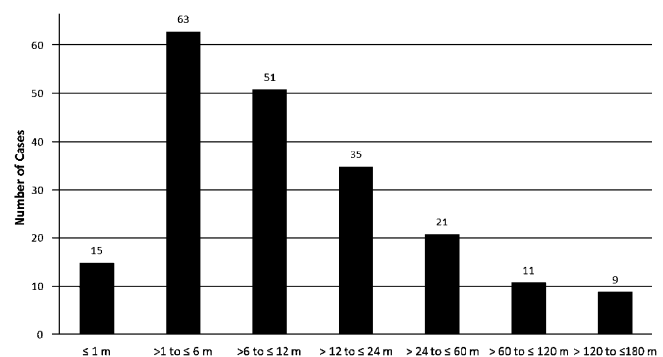


Figure 1. Age distribution of confirmed RSV infection cases at Hospital Infantil, 2004–2008 (n = 205).

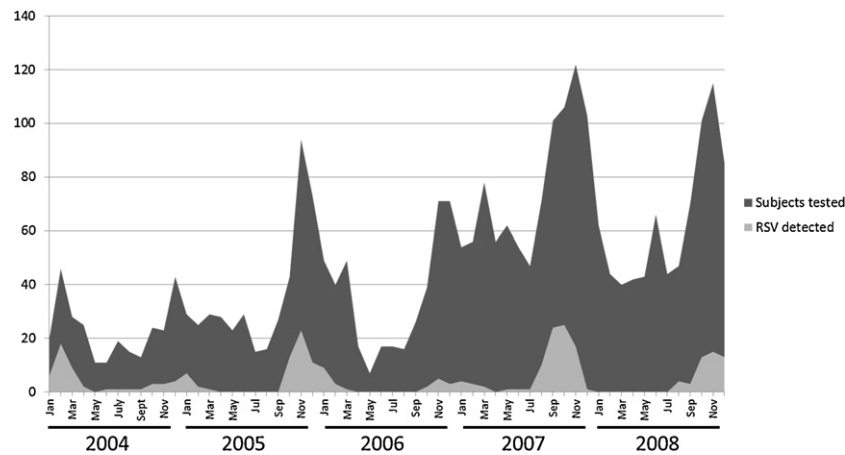


Figure 2. Seasonal and monthly distribution of subjects tested ($n = 2797$) for respiratory viruses and RSV detection ($n = 266$) from 2004 to 2008 in Hospital Infantil.

Table 3

Deaths in RSV-infected children at Hospital Infantil, 2004–2008

Patient ^a	Age (months)	Sex	Ward	Date of diagnosis	Source of RSV	Underlying diagnosis	Infectious syndrome	ICU admission
1	168	M	ICU	01/08/2004	Community	Down syndrome	Pneumonia	Yes
2	2	M	ICU	03/01/2004	Nosocomial	BPD	Pneumonia	Yes
3	4	F	IDU	12/15/2004	Nosocomial	BPD	Pneumonia	No
4	5	F	ER	02/01/2006	Community	CHD	Pneumonia	No
5	12	M	ICU	10/05/2006	Community	Previously healthy	Pneumonia	Yes
6	26	F	ER	03/15/2007	Community	CHD	Pneumonia	No
7	180	F	ER	09/17/2007	Community	SLE and high dose steroid use	Pneumonia	No
8	7	F	ICU	10/17/2007	Community	CHD	Pneumonia	Yes
9	21	F	ER	10/21/2008	Community	West syndrome	Pneumonia	No
10	5	M	ER	11/27/2008	Community	Neuropathy	Pneumonia	No
11	3	F	ER	08/29/2007	Community	CHD	Pneumonia	No
12	5	F	ICU	02/23/2004	Nosocomial	CHD	Pneumonia	Yes
13	4	M	ER	03/09/2004	Nosocomial	Previously healthy	Pneumonia	No
14	4	M	ER	11/15/2007	Nosocomial	Down syndrome	Pneumonia	No

RSV, respiratory syncytial virus; ICU, intensive care unit; ER, emergency room; IDU, infectious disease unit; M, male; F, female; BPD, bronchopulmonary dysplasia; CHD, congenital heart disease; SLE, systemic lupus erythematosus.

^a Patients 1–9 died within 30 days of the diagnosis of RSV infection; patients 10–14 died 30 days or more after the diagnosis of RSV infection.

Death was attributed directly to RSV infection in two thirds of the patients who died.

It is well established that most infants are infected with RSV by 2 years of age,¹⁹ and that the majority of these infections are symptomatic.²⁰ Lower respiratory tract infections occur in up to one third of symptomatic infections necessitating hospitalization.²⁰ The lower the age of these children, the higher the need for hospitalization.²¹ Mortality from RSV infection is low in healthy children, but this is increased in children with cardiac disease, chronic respiratory disease, or immune deficiencies.²² At Hospital Infantil, 80% ($n = 164$) of the participants were younger than 2 years of age. In this group, almost three quarters ($n = 121$, 73.8%) had an underlying disease. The mortality due to RSV was higher in this group of children with underlying diseases ($n = 8$, 6.6%) than in those without underlying diseases ($n = 1$, 2.3%).

In a study conducted by García et al.¹⁸ in Texas among children less than 2 years of age with bronchiolitis, it was found that 2840 children had RSV and that 770 (27.1%) of those children had risk factors such as prematurity, cardiopulmonary pathologies, congenital syndromes, immunodeficiencies, and neuromuscular disorders. Three children with RSV died (0.1%), and two of them (0.26%) had risk factors (one with congenital heart disease and the other had Moebius syndrome). The authors indicated that lower RSV infections in children with risk factors were most likely due to anti-RSV prophylaxis; however, the author pointed out that better prevention strategies are necessary.

Another study conducted by Noyola et al.¹³ studied respiratory infections among children less than 3 years of age in a public

general hospital in Mexico during a period of 24 months. RSV was detected in 153 of 616 subjects with respiratory infections. From this group, 120 (78.4%) infants with RSV infections were previously healthy and 33 (21.6%) had one or more underlying disorders. There were no deaths during the study period. Hospital Infantil is one of the few public and tertiary pediatric centers in Mexico, and children at high risk of RSV morbidity and mortality concentrate at this institution. Infected children often need frequent and/or prolonged hospitalization and access to intensive care units and mechanical ventilation, which increases the morbidity from RSV. In this hospital, as in most public hospitals in Mexico, high-risk children who qualify for seasonal RSV prophylaxis do not currently receive palivizumab, and if infected with RSV they do not receive specific antivirals for RSV. Some published studies have reported children with RSV at risk for complications separately from healthy children,^{3,4,11,18} and in others, the populations of healthy and at-risk children have been different to our study sample;^{8,12,13} therefore, our results are different due to the characteristics of the patients attending Hospital Infantil.

One third of the RSV cases were acquired in the hospital. Nosocomial RSV infection in immunocompromised patients and those with CHD places them at high risk for severe, often fatal, RSV pneumonia.^{3,7} In addition, the risk of death is higher among children who acquire an RSV infection nosocomially than among those who acquire RSV in the community.^{4,5} When implementing targeted interventions based on education of health care providers and adherence to infection prevention and control measures, the transmission rates decrease substantially.^{23,24} RSV can survive on

hard surfaces for up to 7 h and remains detectable on cloth, paper, and stethoscopes after 30 min.²⁴ Factors associated with nosocomial acquisition of RSV infection are young age, underlying or chronic disease, long hospitalization, crowding, suboptimal staff-to-patient ratio, and lack of good infection prevention practices such as isolation precautions, good hand hygiene, and visitation policies.^{6,23,24} We observed that most of these factors were present at Hospital Infantil during the study period. The most important measure for preventing infections is avoiding disease transmission and acquisition in the first place.²⁵ Infection prevention strategies are recommended to curb the transmission of respiratory viruses, including RSV. To lessen the rates of transmission during hospitalization, an institution-wide program must be established, preferably as part of an infection prevention and control program.^{24,26,27} Guidelines recommend rapid patient diagnosis, compliance with acceptable hand hygiene techniques, and cohorting of patients and staff.^{16,26} Emphasis on health care provider compliance with optimum prevention practices during epidemics must be the goal to decrease rates of nosocomial infection.²⁸

One fifth of the hospitalized children with RSV at Hospital Infantil acquired the infection in the community and required mechanical ventilation. The mortality was higher in those with underlying diseases. During the 5-year study period, none of the infants and children who qualified for prophylaxis received palivizumab. Reasons for not using this pharmacologic intervention were its cost and other competing needs at Hospital Infantil, which is a resource-limited public hospital. In children with risk factors for severe RSV, palivizumab, a humanized mouse antibody, is recommended during the RSV season.^{16,29} Like other immune-mediated factors, palivizumab functions by targeting the highly conserved RSV F glycoprotein, inhibiting viral entry into host cells.³⁰ Factors that lead to effective results in the use of palivizumab are safety and tolerability, ease of administration, and lack of interference with normal vaccinations. With the exception of a few reports^{29,31,32} in which therapy with palivizumab was successful in treatment, the primary indication in the use of this monoclonal antibody is for RSV prevention.^{30,33} Vaccination provides the best way to elicit a durable and effective immune response to an infection. Unfortunately, to date, no effective RSV vaccine has been developed. Until a good vaccine is available, measures to prevent infection during epidemics include the use of palivizumab and optimum infection prevention and control practices.³⁴

At Hospital Infantil, patients with RSV received hydration and nutritional and respiratory supportive care, including the use of bronchodilators and steroids, following current and official guidelines, such as those of the American Academy of Pediatrics.¹⁶ Treatment of RSV bronchiolitis, in addition to supportive care, must be individualized and provided early in the illness;³⁵ use of bronchodilators and steroids is common during the care of RSV bronchiolitis. According to some experts and based on the results of a meta-analysis of published studies, bronchodilators such as racemic epinephrine, salbutamol, and ipratropium bromide, despite transient relief of respiratory distress, have no beneficial effects on acute RSV bronchiolitis.^{36,37} More studies are needed for conclusive recommendations. Likewise, steroid use early in the course of the infection has demonstrated benefits,^{38,39} but support for conclusive recommendations are also needed. Systematic improvement in supportive measures, such as respiratory support therapy, hydration, and nutrition, can produce substantial results. Cost-effective actions such as these are amenable to hospitals like Hospital Infantil. These actions may positively affect survival among very young children and those with underlying diseases.

Hospital Infantil is one of three main hospitals in Mexico City for referral of highly complex pediatric disease cases, including

those children with CHD, other congenital malformations, prematurity, and immunodeficiency. Therefore, it was not surprising to find that the most frequent underlying diseases among children hospitalized for RSV infection at Hospital Infantil were CHD, malignancies, and BPD. Children with those pathologies have a more severe RSV course and often need hospital care for the complications of the underlying pathology and the RSV infection.^{3,7,22} Also, these patients often require prolonged hospitalization, thus increasing the chance of acquiring infections nosocomially, such as RSV infections during RSV epidemics.¹⁵ Our study provides a better understanding of the yearly RSV epidemics and their contribution to the burden of respiratory infections among our patients at Hospital Infantil. Data on the seasonality of RSV and institutional care and prevention guidelines are particularly useful to health care providers for the management of patients at high risk of morbidity and mortality and to administrators for planning and implementing cost-effective policies to satisfy the needs of such patients, especially during epidemics. These guidelines work better when adapted to the available resources and unique needs at each site; implementation and compliance with these guidelines during the RSV season has been shown to make a difference in outcomes.⁴⁰ Our findings, which were shared with the leaders of Hospital Infantil, initiated improvements in planning and implementing infection prevention and control strategies, especially for high-risk patients. As a direct result of our study, we are currently working on best care and prevention practice guidelines for respiratory infections at Hospital Infantil.

Limitations of our study include its retrospective nature, the fact that we obtained a relatively low number of positive RSV results, and that complete information was not available for almost 25% of patients with RSV infections. Weaknesses of retrospective studies are that they rely on existing medical records that were collected for reasons other than research, and when specific information is absent, this is difficult to resolve. Also, it is difficult to control biases and confounders in this type of study. However, retrospective studies are inexpensive, use existing records, and more importantly can generate hypotheses that can be tested prospectively.⁴¹ Our study had a relatively small number of positive respiratory virus results, including RSV, and we speculate on several possible reasons. First, we included the reports of all respiratory samples regardless of when in the duration of illness the sample was collected. The threshold for obtaining a respiratory sample in our patients was low, because most of them had serious risk factors for complications of RSV infection. In other studies^{8,13} a case definition was used for the collection of respiratory samples. Second, we used only one laboratory method (IFA) for testing viral pathogens. The sensitivity of IFA is less than other methods such as PCR and serology, which have been used in other studies.^{42,43} And finally, obtaining more than one sample improves the success of getting a positive result. Improving the stated limitations in the study design, sample collection, and laboratory methods will increase the success in ascertaining positive laboratory results. Reviewing the work flow at Hospital Infantil, it was estimated that most of the patients we lacked information for were not admitted to the hospital, and we concluded that their clinical course must have been mild. Even when including patients with incomplete information into our calculations, the hospitalization rate was still high (187 of 266 children with positive RSV tests). The participants discussed in this report consist of patients who had a confirmed RSV infection and most of them were admitted to Hospital Infantil. As such, almost 80% of the patients had an underlying disease and therefore a much higher risk of complications. Also, because Hospital Infantil is a referral center for patients with complex diseases, the epidemiology and outcomes may be different in a hospital treating children with less complex diseases.⁴⁴ However,

we think that since the conditions at Hospital Infantil may mirror other hospitals of similar socioeconomic background and referral patterns, the information presented here will be useful in guiding the formulation of local policies for the treatment and prevention of RSV and, most importantly, for allocating institutional resources, including personnel, for best care and prevention of RSV during epidemic seasons.

Acknowledgements

We thank the staff of Hospital Infantil de México for the excellent care of the children reported in this manuscript and David Galloway for excellent editorial advice. This study was supported by the Department of Pediatric Infectious Diseases of Hospital Infantil de México Federico Gómez and the American Lebanese Syrian Associated Charities (ALSAC).

Funding: This study was supported by the Department of Pediatric Infectious Diseases of Hospital Infantil de México and the American Lebanese Syrian Associated Charities (ALSAC).

Ethical approval: The study was approved by the Institutional Research Ethics Committee of Hospital Infantil.

Conflict of interest: None of the authors of this report have any conflicts of interest.

References

- Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet* 2010;**375**:1545–55.
- Stensballe LG. An epidemiological study of respiratory syncytial virus associated hospitalizations in Denmark. *Respir Res* 2002;**3**(Suppl 1):S34–9.
- Pezzotti P, Mantovani J, Benincori N, Mucchino E, Di Lallo D. Incidence and risk factors of hospitalization for bronchiolitis in preterm children: a retrospective longitudinal study in Italy. *BMC Pediatr* 2009;**9**:56.
- Blanchard SS, Gerrek M, Siegel C, Czinn SJ. Significant morbidity associated with RSV infection in immunosuppressed children following liver transplantation: case report and discussion regarding need of routine prophylaxis. *Pediatr Transplant* 2006;**10**:826–9.
- Ebbert JO, Limper AH. Respiratory syncytial virus pneumonitis in immunocompromised adults: clinical features and outcome. *Respiration* 2005;**72**:263–9.
- World Health Organization. *Respiratory syncytial virus and parainfluenza viruses*. Geneva: WHO; 2009. Available at: http://www.who.int/vaccine_research/diseases/ari/en/index2.html (accessed September 24, 2010).
- Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003;**289**:179–86.
- Berkley JA, Munywoki P, Ngama M, Kazungu S, Abwao J, Bett A, et al. Viral etiology of severe pneumonia among Kenyan infants and children. *JAMA* 2010;**303**:2051–7.
- Noyola DE, Rodriguez-Moreno G, Sanchez-Alvarado J, Martinez-Wagner R, Ochoa-Zavala R. Viral etiology of lower respiratory tract infections in hospitalized children in Mexico. *Pediatr Infect Dis J* 2004;**23**:118–23.
- Light M, Bauman J, Mavunda K, Malinoski F, Eggleston M. Correlation between respiratory syncytial virus (RSV) test data and hospitalization of children with lower respiratory tract illness in Florida. *Pediatr Infect Dis J* 2008;**27**:512–8.
- Simon A, Muller A, Khurana K, Engelhart S, Exner M, Schildgen O, et al. Nosocomial infection: a risk factor for a complicated course in children with respiratory syncytial virus infection—results from a prospective multicenter German surveillance study. *Int J Hyg Environ Health* 2008;**211**:241–50.
- Diez DJ, Ridao LM, Ubeda SI, Ballester SA. [Incidence and cost of hospitalizations for bronchiolitis and respiratory syncytial virus infections in the autonomous community of Valencia in Spain (2001 and 2002)]. *An Pediatr (Barc)* 2006;**65**:325–30.
- Noyola DE, Zuviri-Gonzalez A, Castro-García JA, Ochoa-Zavala JR. Impact of respiratory syncytial virus on hospital admissions in children younger than 3 years of age. *J Infect* 2007;**54**:180–4.
- Silverman WA, Andersen DH. A controlled clinical trial of effects of water mist on obstructive respiratory signs, death rate and necropsy findings among premature infants. *Pediatrics* 1956;**17**:1–10.
- Hall CB. The nosocomial spread of respiratory syncytial viral infections. *Amu Rev Med* 1983;**34**:311–9.
- American Academy of Pediatrics. Respiratory syncytial virus. In: Pickering LK, Baker C, Kimberlin DW, Long SS, editors. Red book: 2009 report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics; 2009. p. 560–9.
- Wahab AA, Dawod ST, Raman HM. Clinical characteristics of respiratory syncytial virus infection in hospitalized healthy infants and young children in Qatar. *J Trop Pediatr* 2001;**47**:363–6.
- García CG, Bhoore R, Soriano-Fallas A, Trost M, Chason R, Ramilo O, et al. Risk factors in children hospitalized with RSV bronchiolitis versus non-RSV bronchiolitis. *Pediatrics* 2010;**126**:e1453–60.
- Simoes EA. Respiratory syncytial virus. *Lancet* 1999;**354**:847–52.
- Tristram DA, Welliver RC. Respiratory syncytial virus. In: Long SS, Pickering LK, Prober CG, editors. *Principles and practices of pediatric infectious diseases*. 2nd ed., Philadelphia, PA: Churchill Livingstone; 2003. p. 1140–8.
- Boyce TG, Mellen BG, Mitchell EF, Wright PF, Griffin MR. Rates of hospitalization for respiratory syncytial virus infection among children in Medicaid. *J Pediatr* 2000;**137**:865–70.
- Thorburn K. Pre-existing disease is associated with a significantly higher risk of death in severe respiratory syncytial virus infection. *Arch Dis Child* 2009;**94**:99–103.
- Macartney KK, Gorelick MH, Manning ML, Hodinka RL, Bell LM. Nosocomial respiratory syncytial virus infections: the cost-effectiveness and cost-benefit of infection control. *Pediatrics* 2000;**106**:520–6.
- Lavergne V, Ghannoum M, Weiss K, Roy J, Beliveau C. Successful prevention of respiratory syncytial virus nosocomial transmission following an enhanced seasonal infection control program. *Bone Marrow Transplant* 2011;**46**:137–42.
- Hall CB. Nosocomial respiratory syncytial virus infections: the “Cold War” has not ended. *Clin Infect Dis* 2000;**31**:590–6.
- Groothuis J, Bauman J, Malinoski F, Eggleston M. Strategies for prevention of RSV nosocomial infection. *J Perinatol* 2008;**28**:319–23.
- Simon A, Khurana K, Wilkesmann A, Muller A, Engelhart S, Exner M, et al. Nosocomial respiratory syncytial virus infection: impact of prospective surveillance and targeted infection control. *Int J Hyg Environ Health* 2006;**209**:317–24.
- Bont L. Nosocomial RSV infection control and outbreak management. *Paediatr Respir Rev* 2009;**10**(Suppl 1):16–7.
- Tsitsikas DA, Oakervee H, Cavenagh JD, Gribben J, Agrawal SG, Mattes FM. Treatment of respiratory syncytial virus infection in haematopoietic stem cell transplant recipients with aerosolized ribavirin and the humanized monoclonal antibody palivizumab: a single centre experience. *Br J Haematol* 2009;**146**:574–6.
- Empey KM, Peebles Jr RS, Kolls JK. Pharmacologic advances in the treatment and prevention of respiratory syncytial virus. *Clin Infect Dis* 2010;**50**:1258–67.
- Boeckh M, Berrey MM, Bowden RA, Crawford SW, Balsley J, Corey L. Phase I evaluation of the respiratory syncytial virus-specific monoclonal antibody palivizumab in recipients of hematopoietic stem cell transplants. *J Infect Dis* 2001;**184**:350–4.
- Ghosh S, Champlin RE, Englund J, Giralt SA, Rolston K, Raad I, et al. Respiratory syncytial virus upper respiratory tract illnesses in adult blood and marrow transplant recipients: combination therapy with aerosolized ribavirin and intravenous immunoglobulin. *Bone Marrow Transplant* 2000;**25**:751–5.
- Kimpen JL. Prevention and treatment of respiratory syncytial virus bronchiolitis and postbronchiolitic wheezing. *Respir Res* 2002;**3**(Suppl 1):S40–5.
- Fretzayas A, Moustaki M. The challenges of RSV vaccines. Where do we stand? *Recent Pat Antiinfect Drug Discov* 2010;**5**:99–107.
- Checchia P. Identification and management of severe respiratory syncytial virus. *Am J Health Syst Pharm* 2008;**65**(Suppl 8):S7–12.
- Langley JM, Smith MB, LeBlanc JC, Joudrey H, Ojah CR, Pianosi P. Racemic epinephrine compared to salbutamol in hospitalized young children with bronchiolitis; a randomized controlled clinical trial [ISRCTN46561076]. *BMC Pediatr* 2005;**5**:7.
- Flores G, Horwitz RI. Efficacy of beta2-agonists in bronchiolitis: a reappraisal and meta-analysis. *Pediatrics* 1997;**100**:233–9.
- Schuh S, Coates AL, Binnie R, Allin T, Goia C, Corey M, et al. Efficacy of oral dexamethasone in outpatients with acute bronchiolitis. *J Pediatr* 2002;**140**:27–32.
- Bentur L, Shoseyov D, Feigenbaum D, Gorichovsky Y, Bibi H. Dexamethasone inhalations in RSV bronchiolitis: a double-blind, placebo-controlled study. *Acta Paediatr* 2005;**94**:866–71.
- McCarthy CA, Hall CB. Respiratory syncytial virus: concerns and control. *Pediatr Rev* 2003;**24**:301–9.
- Hess DR. Retrospective studies and chart reviews. *Respir Care* 2004;**49**:1171–4.
- Bezerra PG, Britto MC, Correia JB, Duarte Mdo C, Fonseca AM, Rose K, et al. Viral and atypical bacterial detection in acute respiratory infection in children under five years. *PLoS One* 2011;**6**:e18928.
- Stensballe LG, Kofoed PE, Nante EJ, Sambo M, Jensen IP, Aaby P. Duration of secretory IgM and IgA antibodies to respiratory syncytial virus in a community study in Guinea-Bissau. *Acta Paediatr* 2000;**89**:421–6.
- Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med* 2009;**360**:588–98.