Journal of Pediatric Infectious Diseases 5 (2010) 77–81
DOI 10.3233/JPI-2010-0222
IOS Press

RSV infection – Risk factors, complications and treatment in two Portuguese hospitals

Vanda Bento[a,*], Rita Machado[b], Marta Ferreira[a], Marta Conde[a], Helena Carreiro[a], Gonçalo Cordeiro Ferreira[b] and Maria João Rocha Brito[b]
[a]*Department of Pediatrics, Hospital Fernando Fonseca, Amadora, Portugal*
[b]*Department of Pediatrics, Hospital Dona Estefânia, Lisbon, Portugal*

Received 18 December 2008
Revised 20 March 2009
Accepted 12 May 2009

Abstract. The aim of this study was to characterize the infection by respiratory syncytial virus (RSV), identify risk factors, complications and compare treatment strategies in children admitted to two Portuguese hospitals. It was a retrospective study performed between January 2005 and December 2006. Demographic and socioeconomic data, risk factors, treatment, complications and medical follow-up were analyzed. A total of 328 children were studied (135 from Hospital Dona Estefânia and 193 from Hospital Fernando Fonseca), about half (52.7%) being male, with a mean age of 5 months. 41% of the patients were from a poor socioeconomic context, 55.8% had older siblings, 32.2% had smoking parents and 11.3% had reactive airway disease. Complications occurred in 76.1% of the patients, namely, hypoxemia (63.5%), secondary bacterial infection (26.5%), atelectasis (11.5%), respiratory failure (10%) and apnea (2.4%). Most of the patients (92.3%) were treated with bronchodilators, 69% had oxygen supplementation, 45% were on antibiotics and 31% were treated with systemic corticosteroids. Ten percent needed mechanical ventilation. Twenty-seven (8.2%) children developed reactive airway disease. Having older siblings (63.1% vs. 49.3% $P = 0.05$) and being newborn (32.7% vs. 16.5% $P = 0.006$) resulted as risk factors for complications, while the risk factors identified for bacterial infection were having older siblings (71.4% vs. 55.7%; $P = 0.013$) and being from a poor socioeconomic context (64.7% vs. 47.6%; $P = 0.017$). The treatment strategies differed in the two hospitals (Hospital Fernando Fonseca vs. Hospital Dona Estefânia) regarding the use of systemic corticosteroids (1.6% vs. 73.3%, $P = 0.000$) and antibiotics (39.4% vs. 52.6%; $P = 0.011$). RSV infections can result in serious complications. According to the current knowledge, most of the therapeutic measures carried out in this study were probably unnecessary. It is important to establish clear national guidelines for the treatment of RSV infection.

Keywords: Respiratory syncytial virus, risk factors, hospitalization, complications

1. Introduction

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infections in the first two years of life and is responsible for an important number of hospital admissions (of young children). This pathogen is ubiquitous throughout the world and causes seasonal outbreaks. In temperate climates, late fall and wintertime epidemics of bronchiolitis are usually associated to RSV infections. Severe disease is characterized by progressive respiratory effort, apnea, need for intravenous hydration, supplemental oxygen or mechanical ventilation. Risk factors for severe RSV disease are congenital heart disease, chronic lung conditions, prematurity and age less than 6 weeks. These factors in association with apnea during the acute phase, pulmonary consolidation on chest x-ray and hypoxemia

*Correspondence: Dr. Vanda Bento, Department of Pediatrics, Hospital Fernando Fonseca, IC 19 2700 Amadora, Portugal. Tel.: +351 214348401; Fax: +351 21 434 55 66; E-mail: vandaabento@gmail.com.

Table 1
Risk factors for respiratory syncytial virus infection in our population

Parameters	Hospital Fernando Fonseca n (%)	Hospital Dona Estefânia n (%)	Total n (%)
Prematurity	18 (9.3)	17 (12,6)	35 (10.6)
Daycare	21 (10.8)	25 (18.5)	46 (14)
Smoking parents	63 (32.6)	41 (30.7)	104 (32.2)
Older brothers	123 (63.7)	60 (44.4)	183 (55.8)
Asthma in family	34 (17.6)	46 (34)	80 (24.3)
Poor economic status	75 (38.8)	60 (44.4)	135 (41)
Congenital cardiopathy	3 (1.5)	6 (4.4)	9 (2.7)
Chronic pulmonary disease	2 (1)	1 (0.7)	3 (0.9)
Reactive airway disease	25 (12.9)	12 (8.8)	37 (11.3)
Immunodeficiency	0 (0)	2 (1.5)	2 (0.6)

on admission, are independently associated with length of hospitalization for RSV [1,2]. Despite the common occurrence of RSV lower respiratory tract infections, there is a great deal of uncertainty regarding its management. At the present time, there appears to be no evidence supporting any therapy for acute bronchiolitis other than supportive measures such as oxygen supplementation or intravenous feeding. In fact, the use of bronchodilators, corticosteroids and ribavirin are not supported by any of the systematic reviews published [3–8].

The aim of this study was to characterize the infection by RSV, identify risk factors, complications and compare treatment strategies in children admitted to a pediatric hospital in the central area of Lisbon, Hospital Dona Estefânia, (HDE) and to a pediatric hospital in a suburban area in the outskirts of Lisbon, Amadora-Sintra, Hospital Fernando Fonseca (HFF).

2. Materials and methods

A retrospective study of children, under 36 months of age, admitted with RSV infection between January 2005 and December 2006. Laboratory testing for RSV was performed using an indirect immunofluorescence test (Bartels VRK®) and a rapid chromatography test of nasopharyngeal secretions (RSV Respi-Strip®). Less than 1.5% of cases were diagnosed using serology (Euroimmun Elisa incubation: Anti-RSV enzyme-linked immunosorbent assay (immunoglobulin G) and anti-RSV enzyme-linked immunosorbent assay (immunoglobulin M®).

Demographic and socioeconomic data, risk factors, treatment, complications, length of hospitalization, medical treatment since discharge, medical follow-up and hospitalization costs were analyzed. Hypoxemia was defined as oxygen saturation below 94%. Bacterial superinfection was considered when abnormal white blood cell count ($\geqslant 15.000$ or $\leqslant 5000/\text{mm}^3$), C-reactive protein above 5 mg/dL, lobar consolidation on the chest X-ray or acute otitis media were present. Recurrent wheezing was defined as three or more episodes of cough and shortness of breath with expiratory rhonchi documented by a physician in the files. Immunodeficiency, chronic neonatal lung disease, congenital heart disease and recurrent wheezing were considered chronic diseases. Statistical analysis was performed using SPSS® 11.0 for windows. Chi-square and Fisher's exact test were used to compare frequencies between groups. Student's t-test and Mann-Whitney U rank sum test were used to compare means or medians between groups. $P < 0.05$ was considered significant.

3. Results

A total of 328 patients were included (135 from HDE and 193 from HFF) with a mean age at admission of 5 months and median of 3 months (patients age ranged from 9 days to 36 months). About half (52.7%) were male and 72.3 % were white. 183 (55.8%) patients had older siblings, 135 (41%) were from a poor socioeconomic context, 104 (32.2%) had smoking parents, and 46 (14%) attended daycare. Eighty (24.3%) children had a family history of asthma and 37 (11.3%) had reactive airway disease. Amongst the 50 (15.2%) children with chronic disease, three had chronic lung disease, nine had congenital heart disease, two were immunocompromised and 37 patients had recurrent wheezing. Thirty-five (10.6%) patients were born prematurely and three had received palivizumab. (Table 1) There was no statistically significant difference between hospitals in respect to patients with chronic diseases. On admission the diagnosis was bronchiolitis in 285 (86.9%), pneumonia in 34 (10.3%), laryngitis in five (1.5%) and upper respiratory infection in four cases (1.2%).

Complications occurred in 249 cases (76.1%): hypoxemia (63.5%), bacterial infection (26.5%), atelecta-

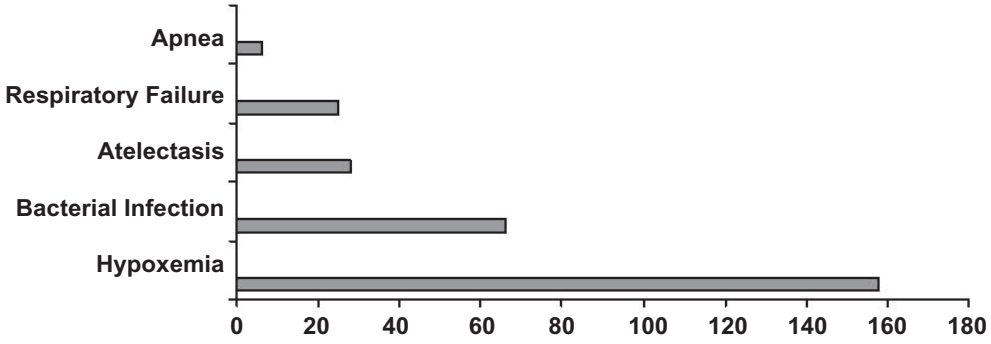

Fig. 1. Complications observed during hospitalization.

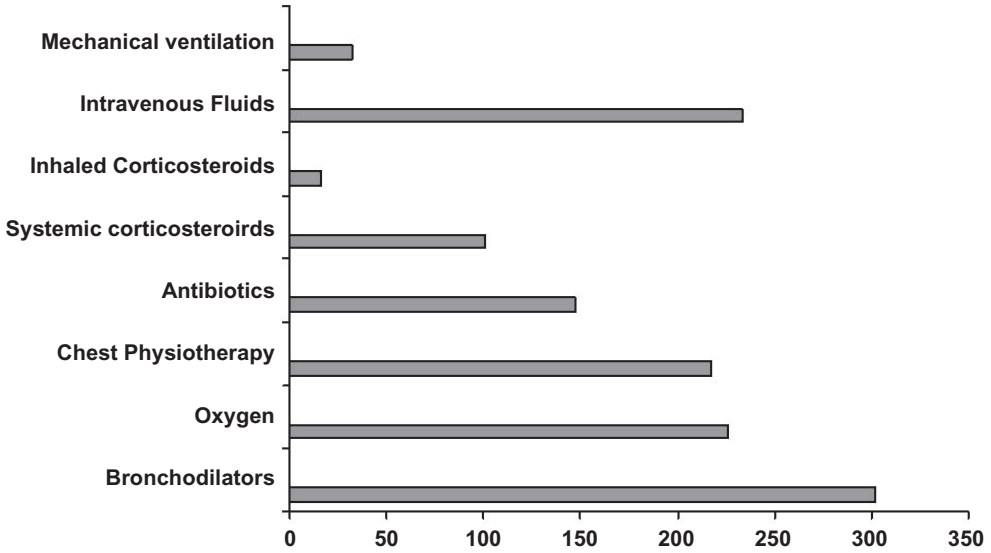

Fig. 2. Treatment options used in children admitted with respiratory syncytial virus infection.

sis (11.5%) respiratory failure (10%) and apnea (2.4%). The mortality rate was 0.9% (three children) and was related to respiratory insufficiency (Fig. 1). Two children were younger than 1-month-old. Risk factors for complications were being newborn (32.7% vs. 16.5%, $P = 0.006$), white race (84.8 % vs. 72.6%, $P = 0.024$) and having older siblings (63.1% vs. 49.3%, $P = 0.05$). Risk factors identified for developing bacterial superinfection was having older siblings (71.4% vs. 55.7%, $P = 0.013$) and being from a poor socioeconomic context (64.7% vs. 47.6%, $P = 0.017$).

Therapeutics administered included bronchodilators in 92.3%, oxygen in 69%, chest physiotherapy in 66.1%, antibiotics in 45%, systemic corticosteroids in 31%, and inhaled corticosteroids in 4.8%. Seventy-one percent of children needed intravenous fluids and 10% mechanical ventilation (Fig. 2). The newborn group (87.9% vs. 22, 1%, $P < 0.001$, Odds ratio-25.542) and the group of children under 6 months of age (97% vs. 62.6%, $P < 0.001$, Odds ratio-19.13) were at a higher risk for needing mechanical ventilation. None was medicated with ribavirin.

The treatment strategies differed in the two hospitals (HFF vs. HDE) regarding the use of systemic corticosteroids (1.6% vs. 73.3%, $P = 0.000$) and antibiotics (39.4% vs. 52.6%; $P = 0.011$) (Table 2).

The mean length of hospital stay was 8.8 days (median of 8 days, with a minimum stay of 1 and a maximum of 78 days). There was no statistically significant difference between hospitals with respect to length of stay. Sixty-three patients (19%) needed intensive care treatment.

After discharge, 169 (51.2%) children were prescribed bronchodilators, 69 (21%) were on antibiotics, 48 (14.6%) had chest physiotherapy, 32 (9.7%) were on systemic corticosteroids, and three (0.9%) needed

Table 2
Comparison of treatment strategies between the two hospitals Hospital Fernando Fonseca and Hospital Dona Estefânia

Parameters	Hospital Fernando Fonseca n (%)	Hospital Dona Estefânia n (%)	P
Inhaled corticosteroids	10 (5.2)	6 (4.4)	0.679
Chest physiotherapy	135 (74.4)	82 (60.7)	0.007
Mechanical ventilation	21 (10.9)	12 (8.9)	0.587
Oxygen	127 (65.8)	99 (73.3)	0.319
Antibiotics	76 (39.4)	71 (52.6)	0.011
Systemic corticosteroids	3 (1.6)	99 (73.3)	< 0.001
Bronchodilators	172 (90.1)	131 (97.8)	0.006

oxygen. Twenty-seven children (8.2%) developed recurrent wheezing. There was no statistically significant difference between the two hospitals.

The cost of the hospitalization of the 328 children was 573,370 Euro. The average cost per child was different in the two hospitals but not statistically significant (2022 vs. 1546 Euro, $P = 0.115$).

4. Discussion

Our study provides an insight into the management of acute RSV infection in two Lisbon hospitals. The considerable differences between the management of this disease in the two hospitals are comparable to those observed between hospitals in other countries [1,3,9, 10]. A recent survey revealed that management of acute bronchiolitis varies considerably between and within countries and continents [1]. Those differences have been found in the use of ventilation, intensive care, and drugs such as bronchodilators, steroids, ribavirin and antibiotics. Actually, studies performed in the United States, Canada and Netherlands demonstrated that this variation is related to hospital and individual preferences, rather than with patient severity or impact on outcome [9,11]. In a small country such as ours, these differences are quite striking. A statistically significant difference in the characteristics of our population with respect to chronic diseases was not found, so the most likely explanation for this phenomenon is the lack of a national consensus on the management of RSV infection. In 2006, the American Academy of Pediatrics published evidence-based guidelines for the Diagnosis and Management of Bronchiolitis. These guidelines address the diagnosis of bronchiolitis as well as various therapeutic interventions including bronchodilators, corticosteroids, antibiotics, hydration, chest physiotherapy, and oxygen. Recommendations are made also for RSV infection [11]. These guidelines recommend that bronchodilators, corticosteroids, chest physiotherapy and antibiotics should not be used routinely in the management of bronchiolitis. Our study shows that practices in use at our hospitals differ from the current guidelines. We think that new prospective multicentric studies are needed to study the impact of theses guidelines on the management and outcome of children hospitalized for RSV infection.

We found that newborns, white children and children having older siblings had a higher risk of developing complications. Except for newborns, these weren't traditional risk factors identified in other studies of RSV infections [1,3,9,12–16], perhaps because they were considered only factors of increased risk of acquiring RSV disease.

We found a 26.5% rate of bacterial superinfection, including children with the diagnosis of acute otitis media. Several retrospective studies identified lower rates of serious bacterial infections (3.7%) [17–19], and others reported about 53% of bacterial acute otitis media in RSV infected children [20]. None reported the global incidence of bacterial superinfection. Leukocytosis, increased C-reactive protein levels and lobar consolidation on the chest X-ray are found in up to 30% of infants with viral bronchiolitis and do not allow for adequate identification of patients with bacterial infection [9]. According to this, the incidence of secondary bacterial infection may be overestimated in the present study. Forty-five percent of our population was treated with antibiotics and only 26.5% had supposed bacterial infection. Concomitant serious bacterial infections are rare in infants and children hospitalized with RSV lower respiratory tract infections. The empiric use of broad-spectrum intravenous antibiotics is unnecessary in children with typical signs and symptoms of RSV lower respiratory tract infection [21].

Our data identified that having older siblings and coming from a poor socioeconomic context are risk factors for developing bacterial infection in the course of the disease. Nevertheless, prospective studies are needed, to support measures of prevention and the management of these situations.

Consistent with data published in previous studies [1, 9] the mortality rate was below 1% and occurred in children less than 3 months of age.

The average days of hospital stay was eight in our population, similar to data published on Canadian RSV patients [9] and in studies among Continental Europe [1]. In the US, Australia and UK the average days of hospitalization was four. These differences are probably related to different discharge criteria and not to a higher proportion of severely ill cases, as suggested by other studies [1].

References

[1] C.E. Behrendt, M.D. Decker, D.J. Burch and P.H. Watson, International variation in the management of infants hospitalized with respiratory syncytial virus. International RSV Study Group, *Eur J Pediatr* **15** (1998), 215–220.

[2] S. Unger and S. Cunningham, Effect of oxygen supplementation on length of stay for infants hospitalized with acute viral bronchiolitis, *Pediatrics* **121** (2008), 470–475.

[3] P.L. Brand and A.A. Vaessen-Verberne, Differences in management of ronchiolitis between hospitals in The Netherlands. Dutch Paediatric Respiratory Society, *Eur J Pediatr* **159** (2000), 343–347.

[4] M.M. Garrison, D.A. Christakis, E. Harvey, P. Cummings and R.L. Davis, Systemic corticosteroids in infant bronchiolitis: A meta-analysis, *Pediatrics* **105** (2000), E44.

[5] W.C. Bordley, M. Viswanathan, V.J. King et al., Diagnosis and testing in bronchiolitis: a systematic review, *Arch Pediatr Adolesc Med* **158** (2004), 119–126.

[6] H. Patel, R.W. Platt, G.S. Pekeles and F.M. Ducharme, A randomized, controlled trial of the effectiveness of nebulized therapy with epinephrine compared with albuterol and saline in infants hospitalized for acute viral bronchiolitis, *J Pediatr* **141** (2002), 818–824.

[7] L. Hartling, N. Wiebe, K. Russell, H. Patel and T.P. Klassen, Epinephrine for bronchiolitis, *Cochrane Database Syst Rev* **1** (2004), CD003123.

[8] H. Patel, R. Platt, J.M. Lozano and E.E. Wang, Glucocorticoids for acute viral bronchiolitis in infants and young children, *Cochrane Database Syst Rev* **3** (2004), CD004878.

[9] E.E. Wang, B.J. Law, F.D. Boucher et al., Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study of admission and management variation in patients hospitalized with respiratory syncytial viral lower respiratory tract infectionm, *J Pediatr* **129** (1996), 390–395.

[10] D.A. Christakis, C.A. Cowan, M.M. Garrison, R. Molteni, E. Marcuse and D.M. Zerr, Variation in inpatient diagnostic testing and management of bronchiolitis, **Pediatrics 115** (2005), 878–884.

[11] Diagnosis and management of bronchiolitis. American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis, *Pediatrics* **118** (2006), 1774–1793.

[12] K.N. Carroll, T. Gebretsadik, M.R. Griffin et al., Increasing burden and risk factors for bronchiolitis-related medical visits in infants enrolled in a state health care insurance plan, *Pediatrics* **122** (2008), 58–64.

[13] G. Corsello, P. Di Carlo, L. Salsa et al., Respiratory syncytial virus infection in a Sicilian pediatric population: risk factors, epidemiology, and severity, *Allergy Asthma Proc* **29** (2008), 205–210.

[14] C.B. Hall, G.A. Weinberg, M.K. Iwane et al., The burden of respiratory syncytial virus infection in young children, *N Engl J Med* **360** (2009), 588–598.

[15] M. Lanari, M. Giovannini, L. Giuffré et al., Prevalence of respiratory syncytial virus infection in Italian infants hospitalized for acute lower respiratory tract infections, and association between respiratory syncytial virus infection risk factors and disease severity, *Pediatr Pulmonol* **33** (2002), 458–465.

[16] G.A. Rossi, M.C. Medici, M.C. Arcangeletti et al., Risk factors for severe RSV-induced lower respiratory tract infection over four consecutive epidemics, *Eur J Pediatr* **166** (2007), 1267–1272.

[17] S. Leader and K. Kohlhase, Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000, *J Pediatr* **143** (2003), 127–132.

[18] K. Purcell and J. Fergie, Lack of usefulness of an abnormal white blood cell count for predicting a concurrent serious bacterial infection in infants and young children hospitalized with respiratory syncytial virus lower respiratory tract infection, *Pediatr Infect Dis J* **26** (2007), 311–315.

[19] B. Resch, W. Gusenleitner and W.D. Mueller, Risk of concurrent bacterial infection in preterm infants hospitalized due to respiratory syncytial virus infection, *Acta Paediatr* **96** (2007), 495–498.

[20] G. Shazberg, S. Revel-Vilk, D. Shoseyov, A. Ben-Ami, A. Klar and H. Hurvitz, The clinical course of bronchiolitis associated with acute otitis media, *Arch Dis Child* **83** (2000), 317–319.

[21] K. Purcell and J. Fergie, Concurrent serious bacterial infections in 2396 infants and children hospitalized with respiratory syncytial virus lower respiratory tract infections, *Arch Pediatr Adolesc Med* **156** (2002), 322–324.