The Differences Between RSV and no RSV Acute Bronchiolitis in Hospitalized Infants: A Cross-Sectional Study

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Abstract
To identify the differences between the RSV and non-RSV bronchiolitis in hospitalized infants in a Greek tertiary pediatric unit and the possible risk factors related to severe forms of the illness. We performed a retrospective cross-sectional data analysis by reviewing medical records of patients that were hospitalized for acute bronchiolitis from 2012 to 2019. The patients with RSV bronchiolitis were found to require antibiotic treatment, IV fluids, adrenaline, and hypertonic saline inhalations more frequently than the non-RSV patients. They also required prolonged hospitalization, especially those that were admitted to PICU, and received oxygen therapy for longer periods. We searched risk factors for severe forms of the disease according to the need for admission to PICU, the supplemental oxygen and the extended length of hospital stay, concurrently. The patients with RSV bronchiolitis developed more severe illness in comparison with patients with bronchiolitis due to other respiratory viruses.

Keywords
acute bronchiolitis, infants, respiratory infection, respiratory syncytial virus

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Introduction
In the first year of life, acute bronchiolitis (AB) is the most common viral infection of the lower respiratory tract, causing increased morbidity, hospitalization, and possible long-term complications in infants.1 The RSV virus, as the most common cause of this illness, is estimated to be responsible for 3.4 million hospital admissions and 199,000 deaths per year, mainly in the developing world.2

Although it is a relatively old disease, there are many unanswered questions about it. Neither the disease’s pathophysiological mechanism nor the elements that play an important role in the body’s immune response have been fully clarified. Therefore, effective methods of prevention and treatment need to be designed and established in clinical practice.3

The exact epidemiological features of the disease need to be determined, especially in hospitalized patients who will contribute to the design of new and more expensive treatments. As for now, the treatment remains supportive but several treatment options—mainly new antiviral agents—are in the process of testing for safety and efficacy.4 Furthermore, there are few studies that focus on different characteristics of the illness depending either on the pathogen that causes it or disagreements about the disease’s severity reliant on the country or cities.5,6 So far, it has not yet been possible to detect patients who are going to be critically ill, resulting in closer monitoring, individualized treatment, and possibly better prognosis.

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In this study, an epidemiologically recording of AB in hospitalized infants in a tertiary Greek pediatric center was attempted. Also, the differences between the RSV group and the group infected with other respiratory viruses were recorded. Finally, possible risk factors leading to the development of a serious disease were noted.

Methods

Ethical Approval and Informed Consent

We designed a retrospective cross-sectional analysis which was conducted in the First Pediatric Department of Children’s General Hospital “Panagiotis & Aglaia Kyriakou” in Athens with approval of the Institutional Ethics Committee of the hospital (Ref. A-1329/F). The diagnosis of AB was based solely on the clinical picture of the patients.

Inclusion Criteria

We reviewed the medical records of patients diagnosed from the year 2012 to 2019 with acute RSV bronchiolitis, AB due to other defined viruses, and acute unspecified bronchiolitis. Only infants up to 1 year of age who presented with the first episode of AB were included. The diagnosis was made in those infants who initially showed symptoms of upper respiratory tract infection and later signs of respiratory distress while other possible diagnoses were ruled out.

Patients above 1 year of age or with multiple episodes of AB or with medical records lacking important information, or those who developed AB during their hospital stay (but the initial cause of admission was different) were excluded.

A nasopharyngeal swab was obtained from each patient. RSV antigen was detected in respiratory cells by direct immunofluorescence, according to the manufacturer’s instructions.

Data selection

All demographic characteristics were fully collected from patients’ medical records (birthweight, gestational age, sex, age, and weight at admission). Any chronic health conditions or possible bacterial infections on the ground of AB (such as acute otitis media, urinary tract infection, sepsis, pneumonia, and meningitis) were recorded. Furthermore, the number of patients transferred to PICU, the type of respiratory support needed, blood test results (full blood count, biochemistry, and blood cultures), findings on cardiac examination, chest X-ray, lumbar puncture results, and type and duration of the treatment (oxygen therapy, bronchodilators, and corticosteroids) were noted. At last, fever’s characteristics (height and duration), the length of hospitalization, respiration rate and oxygen saturation upon patients’ admission to the hospital, and the need for intravenous hydration were also collected.

The onset of severe disease was assessed by the extended duration of hospitalization (≥7 days), the need for oxygen supplementation, and transfer to the PICU.

Statistical Analysis

Statistical analysis was performed via the SAS for Windows 9.4 software platform (SAS Institute Inc., NC, USA). Descriptive values were expressed as mean ± standard deviation (SD) for the continuous variables or frequency and percentages for the categorical. Comparisons between groups for the qualitative parameters were made using the chi-square test and if required Fisher exact, odds ratios (OR) were calculated and reported along with the relevant 95% confidence interval (CI). The continuous parameters’ normality was tested using the Kolmogorov-Smirnov test. Statistical tests were t-test or Kruskal-Wallis (if normality was not ensured). The significance level (P-value) was set to .05 and all tests were 2 sided.

Results

Study Population

Based on the study’s inclusion criteria, 519 medical records were reviewed in total. Twenty-eight patients were excluded from the study. About 13 due to being older than 1 year of age, 7 due to insufficient data from medical records, 7 due to multiple episodes of AB, and 1 due to multimorbidity. The 491 patients were divided into 2 groups. The first one was with RSV AB, including 295 patients and the second one with non-RSV AB counting 196 patients (Figure 1).

Demographic Characteristics

The differences between the 2 groups in terms of demographic characteristics are presented in Table 1. Weight in admission was statistically significant lower in the group with RSV AB (5.5 kg ± 1.8 kg vs 6.1 kg ± 2.0 kg [mean ± SD], P < .0005) as well as patients’ age (3.2 months ± 2.6 months vs 4.39 months ± 2.9 months [mean ± SD], P < .0001). The male sex prevailed in both groups without recording a statistically significant difference between the 2 groups.
Seasonal Distribution

Hospitalizations for the RSV infection group began to increase in November and were peaked between December and February. On the other hand, for the non-RSV group, the hospitalizations showed a double peak, 1 in October and 1 in March. Figure 2 shows the seasonal distribution of cases per group.

Laboratory Results

White blood cell count, neutrophil count, CRP, and sodium levels were recorded. A statistically significant difference between the 2 groups was observed only in the absolute number of white blood cells. Specifically, the RSV group had a lower number than the non-RSV group (11302/mm³ ± 4493/mm³, 14033/mm³ ± 5209/mm³ [mean ± SD], \( P < .0001 \)).

Management Modalities

Patients with RSV infection were more likely to receive nebulized epinephrine (43.2% vs 32.7%, \( P = .019 \)) and hypertonic saline (15.7% vs 6.7%, \( P = .0028 \)). On the other hand, patients with non-RSV infection were more likely to receive nebulized corticosteroids (27% vs 16.7%, \( P = .005 \)) and ipratropium bromide (16.8% vs 7.8%, \( P = .0021 \)).

Radiological Findings

Chest X-ray was performed at a rate of 67.5%. No statistically significant differences were found between the 2 groups. A 19.5% showed normal chest X-ray. More frequently findings were peribronchial thickening, hyperinflation, and atelectasis.

Table 1. Demographic Characteristics of Hospitalized Patients With Acute Bronchiolitis (RSV Group, No-RSV Group).

| Characteristic                  | RSV group (N = 295) | Non RSV group (N = 196) | \( P \) value |
|--------------------------------|---------------------|-------------------------|--------------|
| Age (months) [mean ± SD] (N = 491) | 3.2 ± 2.6           | 4.39 ± 2.9              | <.0001       |
| Birth weight (kg) [mean ± SD] (N = 434) | 3.1 ± 0.6           | 2.9 ± 0.8               | .0845        |
| Gestational age (weeks) [mean ± SD] (N = 433) | 37.9 ± 2.3          | 37.2 ± 3.3              | .2731        |
| Admission weight (kg) [mean ± SD] (N = 483) | 5.5 ± 1.8           | 6.1 ± 2.0               | .0005        |
| Gender (male) [N,%] (N = 491) | 183, 37.3%          | 129, 41.4%              | .3938        |
Bacterial Infections

The most common bacterial infection was acute otitis media (14.6%), followed by pneumonia (11.8%), urinary tract infection (2.24%), sepsis (1%), and meningitis (0.6%). No statistically significant difference was recorded between the 2 groups. An important parameter is that the group with RSV infection received antibiotic treatment more frequently because of possible severe bacterial infection than the other group ($P = .005$).

Severe Forms of the Disease

No death was recorded in either group. However, the group with RSV infection had an increased length of hospital stay (5 days vs 4 days, $P = .0001$), increased length of PICU stay (4 days vs 2.5 days, $P = .01$), lower SpO2 levels (96.5% vs 97%, $P = .03$), and showed febrile illness more frequently (48.3% vs 32.6%, $P = .0008$) than the other.

The severity of the disease was assessed by the patients’ need for oxygen, the prolonged duration of hospitalization (more than 7 days), and the patient’s transfer to PICU. We did not find potential risk factors that affected adversely all 3 variables simultaneously (Table 2). Table 3 summarizes all the statistically significant differences between the 2 groups.

Discussion

AB remains one of the main causes of morbidity and hospitalization in infants with viral infections. Herein we analyzed patients’ profiles and differences according to their pathogen. In Greece, there are few epidemiological records of this disease, especially in hospitalized patients.7

In our study, it was once more confirmed that the main pathogen of AB is RSV and, as it was shown in studies from Western countries it ranges from 50% to 90%.8,9 In this study, RSV accounts for 60% of cases.

The seasonal distribution of RSV AB in the Northern Hemisphere occurs from December to March with a peak in February,10 in contrast to tropical countries, where the peak occurs during the rainy season. This is a significant difference with the non-RSV group which seems to have a more even distribution of cases per month with 2 smaller peaks, 1 in October and 1 in March. The latter distribution is in concordance with the seasonal distribution of other respiratory viruses causing acute bronchiolitis (rhinovirus, influenza, bocavirus, parainfluenza, and human metapneumovirus).11

At hospital admission, the group with RSV infection was weighed less. In both groups, the male sex predominated as expected12 due to the lung immaturity in male infants versus females.13
Table 2. Risk Factors Associated With Disease Severity in Hospitalized Patients With Acute Bronchiolitis (RSV Group, No-RSV Group).

| Severity indicator | Oxygen need (treat in hood) | ICU need | Hospitalization ≥7 days |
|--------------------|-----------------------------|----------|-------------------------|
|                    | RSV | Non RSV | RSV | Non RSV | RSV | Non RSV |
| Characteristic     | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | P |
| Age                | 0.74 (0.62-0.88) | .007 | 0.72 (0.55-0.95) | .0203 | 0.8 (0.4-1.57) | .5100 | 0.46 (<0.001-<0.999) | .9548 |
| Admission weight (kg) | 0.94 (0.58-1.52) | 0.811 | 1.34 (0.89-2.02) | .1639 | 0.497 (0.297-0.834) | .0081 | 0.033 (<0.001<0.999) | .8879 |
| Apneas (reference: No) | 1.34 (1.38-128.67) | .0251 | 188 (20.92-1689.87) | <.0001 | 9.52 (0.93-97.95) | .0582 | 2.86 (0.32-25.8) | .3485 |
| Congenital heart disease (reference: No) | 1.55 (0.18-13.32) | .688 | 1.09 (0.14-8.54) | .9329 | 8.5 (4.61-44.97) | .0225 |
| Intravenous fluids (reference: No) | 5.69 (2.34-13.84) | .596 | 5.69 (2.06-15.75) | .0008 | 3.19 (0.37-27.85) | .4080 | 5.26 (1.41-11.37) | .0428 |
| Fever (>38°C) (reference: No) | 2.04 (0.5-5.00) | .1357 | 0.58 (0.21-1.63) | .3056 | 7.51 (1.37-41.17) | .0202 | 0.4 (0.05-3.52) | .4978 |
| CRP (mg/dl) (reference: No) | 1.02 (0.99-1.05) | 0.1599 | 1.04 (0.98-1.1) | .2028 | 1.02 (1.1-1.05) | .0909 | 0.55 (0.12-2.48) | .4359 |
| Chronic disease (reference: No) | 0.44 (0.13-1.53) | 0.1954 | 1.21 (0.31-4.76) | .7808 | 1.37 (0.43-4.42) | .9591 | 0.59 (0.51-13.24) | .4084 |
| Prematurity (reference: No) | 2.89 (0.47-17.6) | 0.2507 | 3.15 (0.4-24.56) | .2745 | 2.09 (0.56-7.78) | .9557 | 1.26 (0.14-11.27) | .5311 |

*All patients with apneas were treated in hood.

*All patients admitted in ICU were treated with IV fluid.
Despite the recommendations, the percentage of patients who had a chest X-ray was high (67.5%). There was no difference in the X-ray’s findings between the 2 groups of patients. The consolidations that were observed in a considerable number of patients (17.4%) led quite often to unnecessary administration of antibiotics. This fairly common clinical practice can be partly explained by the absence of an accurate diagnostic tool for distinguishing viral from bacterial lower respiratory tract infections. Therefore, imaging tests should be reserved only for patients with a complicated and atypical course of the disease.14

An increased number of patients underwent general blood tests (96%) as well as blood cultures (51%) contrary to the recommendations. In the RSV group, the blood cultures were taken more often probably due to the smaller age and the presence of fever.

In the literature, AB has been associated with hyponatremia and other electrolyte imbalance due to dehydration15,16 but in our study, we found normal sodium levels in both groups. CRP was slightly above normal in both groups. Absolute white cell counts were higher in the RSV group but since this finding was not accompanied by a shift to the left it is of no real clinical significance.

The risk of bacterial coinfection in patients with AB is low.17 From the 495 patients, severe bacterial infections such as sepsis occurred only in 1% and meningitis in 0.6% (all observed in infants <3 months). The most common bacterial infection was acute otitis media (14.6%), which is consistent with what has already been reported.18 Only 2.4% of cases developed urinary tract infections. Therefore, diagnostic testing for urinary tract infections needs to be limited only in high-risk patients in view of possible side effects from bladder catheterization or suprapubic aspiration.

So far there is no effective drug treatment that reduces disease’s duration, protects against deterioration, and decreases the chances of hospitalization.19,20 Herein, those who were treated with inhaled bronchodilators, corticosteroids, or hypertonic saline had a longer hospital stay than those who had not received any. In addition, systemic corticosteroids did not appear to improve patients’ outcomes. Very mindful use of the above treatments is required, especially in severely ill infants. The development of new targeted individualized pharmaceutical agents is crucial.

In this study, severe forms of the disease were determined by the extended duration of hospitalization

### Table 3. Differences in Hospitalized Patients With Acute Bronchiolitis (RSV Group, No-RSV Group).

| Characteristic                              | RSV group (N = 295) | Non RSV group (N = 196) | P  | OR (96%CI) |
|--------------------------------------------|---------------------|-------------------------|----|------------|
| Age (months), median [Q1-Q3 range]         | 2 (1-4)             | 3 (2-6)                 | <.0001 | na         |
| Admission weight (kg), median [Q1-Q3 range] | 5.3 (4.3-6.5)       | 6 (4.7-7.3)             | .0005 | na         |
| Possible serious bacterial infection, N (%) | 30 (10.2%)          | 8 (4.08%)               | .0151 | 2.7 (1.2-6) |
| Chronic disease, N (%)                     | 57 (19.79%)         | 54 (28.57%)             | .0350 | .6 (4.0-9)  |
| Blood culture, N (%)                       | 162 (55.1%)         | 88 (44.9%)              | .0338 | 1.5 (1-2.2) |
| Lumbar puncture, N (%)                     | 31 (10.54%)         | 4 (2.04%)               | .0002 | 5.7 (2-16.3) |
| WBC/mm³, median [Q1-Q3 range]              | 10 600 (8300-13 900)| 13 300 (9900-17 200)    | <.0001 | na         |
| spO₂, median [Q1-Q3 range]                 | 96.5 (94.98)        | 97 (95-98)              | .0348 | na         |
| Fever (>38°C), N (%)                       | 142 (48.3%)         | 64 (32.65%)             | .0008 | 1.9 (1.3-2.8) |
| Inhaled ipratropium bromide, N (%)         | 23 (7.82%)          | 33 (16.84%)             | .0034 | 0.4 (0.2-0.7) |
| Duration of inhaled ipratropium bromide (days), median [Q1-Q3 range] | 4 (1-6)             | 2 (1-3)                 | .0274 | na         |
| Inhaled epinephrine, N (%)                 | 127 (43.2%)         | 64 (32.65%)             | .0232 | 1.6 (1.1-2.3) |
| Duration of inhaled epinephrine (days), median [Q1-Q3 range] | 4 (2-5)             | 3 (2-4)                 | .0086 | na         |
| Inhaled steroids, N (%)                    | 49 (16.67%)         | 53 (27.04%)             | .0064 | 0.5 (0.3-0.8) |
| Intravenous fluids, N (%)                  | 219 (74.74%)        | 121 (61.74%)            | .0026 | 1.8 (1.2-2.7) |
| Duration of intravenous fluids (days), median [Q1-Q3 range] | 2 (2-4)             | 2 (1-4)                 | .0035 | na         |
| Inhaled hypertonic saline, N (%)           | 46 (15.65%)         | 13 (6.67%)              | .0028 | 2.6 (1.4-4.9) |
| Hospitalization (days), median [Q1-Q3 range] | 5 (3-6)             | 4 (2-5)                 | <.0001 | na         |
| ICU hospitalization (days), median [Q1-Q3 range] | 4 (2.5-6.5)        | 2.5 (1-3)               | .0150 | na         |
(≥7 days), patients’ transfer to the PICU, and the need for supportive oxygen therapy. No variable was found that affected all 3 parameters concurrently. The small age at hospital admission and the presence of congenital heart disease, play a negative prognostic role in patients’ outcomes as mentioned in previous studies. Also in this study, the RSV group showed less oxygen saturation on admission, needed a longer hospital and PICU stay, developed more frequent fever, and received more frequent and longer intravenous fluids and oxygen. The above suggests that RSV disease is more severe and responsible for prolonged hospitalizations and are in agreement with the literature.

Limitations
First of all, the retrospective nature of this study imposes limitations on the review of all necessary patients’ data, including family and perinatal history. Also, the inability to detect pathogens other than RSV, did not allow us to study the distinct epidemiological features and how coinfections affect the severity of the disease. Third, the sample did not include patients from other tertiary pediatric centers in Greece, which creates obvious limitations in drawing conclusions.

Conclusion
AB still remains a disease with high morbidity in infancy, burdening the healthcare systems and creating stress to parents. It is also associated with long-term complications of the respiratory system in children.

RSV causes more serious illness than other viruses. It is necessary to design reliable risk scores for the detection of patients who are at high risk of developing serious illness and to develop optimal treatments that will improve the outcome of infants with bronchiolitis. Compliance with international and local guidelines for disease’s diagnosis and management is essential.

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