Epidemiology of patients hospitalised due to bronchiolitis in the south of Europe: Analysis of the epidemics, 2010–2015

José Miguel Ramos-Fernández, Eva Pedrero-Segura, Mario Gutiérrez-Bedmar, Beatriz Delgado-Martín, Ana María Cordón-Martínez, David Moreno-Pérez, Antonio Urda-Cardona

Introduction: The renewal of clinical practice guidelines on acute bronchiolitis (AB) requires the re-assessment of the consequences of their implementation. An update is presented on the main clinical and epidemiological variables in patients hospitalised due to AB in Southern Europe and an analysis is made of the causes associated with longer hospital stay.

Patients and method: A retrospective study was conducted on patients admitted to hospital due to AB during 5 epidemics (2010–2015), with an analysis of the major clinical and epidemiological variables. A logistic regression analysis was performed on the factors associated with a longer hospital stay.

Results: The beginning of the epidemic occurred between the 4th week of September and the 3rd week of October. Of those children under 2 years (42,530), 15.21% (6,468 patients) attended paediatric emergency department due to having AB, and 2.36% (1,006 patients) were admitted.
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Of these, 18.5% were premature, 12.2% had a birth weight <2300 g, 21.1% were younger than 1 month, 10.8% consulted for associated apnoea, 31.1% had an intake <50%, and 13.1% had bacterial superinfection. These factors were independently associated with prolonged stay. The median length of stay was 5 days, and 8.5% of cases were admitted to a paediatric intensive care unit (PICU).

Conclusions: The beginning of the bronchiolitis epidemic showed a variability of up to 4 weeks in this region. Five years after implementing the new guidelines, the incidence of admissions was approximately 2.3%, and appeared stable compared to previous studies. The mean age of the patients decreased to 2.4 months, although with a similar proportion of PICU admissions of 8.5%.

Independent factors associated with prolonged stay were: low birth weight, age less than one month, apnoea prior-to-admission, intake of less than 50%, and severe bacterial superinfection. Respiratory bacterial infection exceeded the prevalence of urinary tract infection.

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Introduction

Despite the passage of time, no infectious illness—recognised from the dawn of European paediatrics1—has ever generated a greater health care burden than acute bronchiolitis (AB).2–6 Respiratory syncytial virus (RSV) is the causative agent in approximately 60%–75% of cases.5,7 As was the case in the early approaches to its management,1 there is no etiologic treatment for this disease once it is diagnosed, so it is based on symptomatic treatment and respiratory support of varying intensity, and has been revised in recent years in several clinical practice guidelines (CPGs).8–11

The possibility of vaccinating infants or pregnant women is drawing near,12 and the strategy to fight this disease requires adequate knowledge of its epidemiology based on
the geographical and environmental characteristics of each region in order to carry out interventions fitting specific circumstances. The results of epidemiological studies on AB published in Europe, most of which have been conducted in hospitalised patients, are somewhat inconsistent.\textsuperscript{2,3,13-16} Updates of CPGs for the management of AB and their implementation—as was the case in our hospital—since 2010\textsuperscript{11} warrant an evaluation of the results of their introduction and their impact on inpatient care delivery.

Our aim was to describe and compare key epidemiological and clinical variables in patients admitted to a tertiary referral hospital in a coastal town in southern Europe during 5 recent outbreaks of AB after an updated CPG had been firmly established following its introduction in 2010.\textsuperscript{11} We analysed the incidence of hospitalisation relative to emergency department visits and the need for care at the paediatric intensive care unit (PICU) level, as well as severity defined in terms of length of stay and associated factors. We also estimated the timing of the epidemic season onset and its inter-annual variability.

Patients and methods

We conducted a retrospective study in patients admitted to a tertiary referral hospital between October 1, 2010 and March 31, 2015 with a discharge diagnosis of AB defined, on the basis of the classical criteria of McConnochie, as the first episode of acute lower respiratory illness associated with a history of cold symptoms in children aged 24 months or younger.\textsuperscript{17} This women’s and children’s hospital is the main hospital for a health department with a catchment area of 1.2 million inhabitants including a catchment paediatric population of approximately 100,000 children, of who we estimated 42,530 were aged 24 months, and thus eligible for inclusion, at the beginning of the study. Its geographical location on the coast at 36°43′ North makes it the southernmost tertiary referral children’s hospital in Europe, with a Mediterranean climate.

The medical records of our patients had uniform documentation of the most important variables, as this is a frequent illness with a standardised management. The criteria for hospital admission were those established in the aforementioned CPG.\textsuperscript{11} In our hospital, all patients were evaluated for the presence of RSV at admission with a rapid antigen detection test on nasopharyngeal aspirate samples (RSV card letitest\textsuperscript{6}, Leti Diagnostics, Barcelona, Spain) to determine cohort membership.\textsuperscript{18} From the moment of admission, all patients underwent continuous pulse oximetry monitoring until they were completely stable in an inpatient unit specifically dedicated to infants with AB.

The researchers also reviewed the medical records of patients managed in the emergency department to determine the count and incidence of other cases with a diagnostic code of AB at discharge during the period under study. For hospitalised patients, we reviewed the electronic health records to collect demographic and clinical information. We collected data for the following variables in each patient: sex, age, month of admission, birth weight, gestational age, maternal age, postmenstrual age, multiple pregnancy, caesarean delivery, environmental and/or prenatal exposure to tobacco, breastfeeding, siblings aged less than 6 years and aged 6–14 years, history of atopy in first-degree relatives, chronic disease (personal history of heart disease, disabling neurologic disease or bronchopulmonary dysplasia), days elapsed from onset to admission, fever, degree of loss of appetite, underweight (<3rd percentile), severity at admission determined by means of a validated scale,\textsuperscript{19} presence of apnoea, length of stay (in days) in ward and in intensive care unit, and severe bacterial co-infection (confirmed or suspected). Cases of UTI and sepsis were confirmed by positive urine and/or blood culture results in association with compatible symptoms. When it came to suspected respiratory co-infection, its presence was determined based on previously described clinical and laboratory criteria.\textsuperscript{20-22} Including elevation of acute phase reactants, with a concentration of more than 70 mg/L for CRP and more than 0.5 ng/mL for procalcitonin.

We considered that an outbreak had started when the weekly incidence of AB in the emergency department exceeded the upper bound of the 95% confidence interval for the baseline incidence of cases outside the epidemic season (from April to September) for two consecutive weeks, applying the classical approach of Serfling.\textsuperscript{23}

We compared the behaviour of the study variables based on the presence of RSV, and analysed the risk factors for increased length of stay using the mean length of stay in days from previous studies as a reference.\textsuperscript{7} In the analysis of length of stay, we excluded patients with underlying diseases and focused on healthy patients, who constitute approximately 95% of the total in most case series.\textsuperscript{14,24,25} We performed the statistical analysis with the free software PSSP. We summarised qualitative variables as percentages and quantitative variables as mean and standard deviation. We used the chi square test to study the association between quantitative variables. We used logistic regression for the multivariate analysis of factors associated to increased length of stay, including in the final model those variables for which we have obtained a \( p \)-value of less than 0.25 in the bivariate analysis. We defined statistical significance as a \( p \)-value of less than 0.05 in any of the hypothesis tests, and calculated all confidence intervals for a 95% confidence level.

Results

In the period under study, 15.21% (6468 patients) of children aged less than 24 months sought care in our emergency department for AB, and 2.36% (1006 patients) were admitted to hospital. Table 1 summarises the characteristics of our sample. The baseline weekly incidence calculated for the April-to-October periods was of 5.17 cases (95% CI, 4.46–5.91). Table 2 shows the outbreak onset week for each season, determined based on the incidence rate. In our study, the differences in the timing of season onset spanned 4 weeks. Fig. 1 shows the incidence of hospitalisation by month of the year.

Respiratory syncytial virus was detected in the aspirate specimens of 77.9% of hospitalised patients. Table 3 shows the data for the different variables based on the presence or absence of RSV with their respective frequencies (n). The mean age was 2.46 months (95% CI, 2.34–2.59); 71.8% of the patients were aged less than 3 months, 93.6% less than
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Also, 66 weeks of gestation, 6 weeks postmenstrual age, 6 total length of stay, and 6 PICU length of stay were included in the study. The patients were admitted to the PICU, with a mean age of 6 months and a median of 6 months. Of all patients, 53.3% were male and 81.5% had a history of heart disease, neurologic disease, and bronchopulmonary dysplasia. Respiratory syncytial virus was detected in 9 patients who received doses of palivizumab. In 53.9% of cases, patients sought care in the day of onset of respiratory problems.

In our series, 37.3% of patients presented with fever and 28.8% with respiratory symptoms. Eight percent presented had weights below the third percentile. Based on the severity scale score at admission, we classified 62.6% of cases as moderate and 5.4% as severe. A history of apnoea prior to admission was reported in 10.8%, but only 4.9% of patients had episodes of apnoea in hospital. Nasogastric tube feeding was required in 13.9% of cases, and 8.5% required admission to the PICU. 53 cases: 53 required CPAP, 21 invasive mechanical ventilation, 4 high-frequency ventilation, 7 high-flow oxygen therapy. Only 11.4% did not require oxygen therapy. Severe bacterial infections were present in 15.5% (there were three detected types: UTI, respiratory superinfection and sepsis; Table 2), of which only 1.9% were classified as nosocomial. Readmission occurred in 2.1% of cases. Two patients died, which amounted to 0.19% of hospitalised patients.

There were no significant differences between epidemic seasons in mean length of stay. Table 4 shows the results of the comparison of patients with stays longer than the median stay, which was of 5 days, and the rest of the sample. The variables that were statistically significant in the final model were age, a history of apnoea prior to admission, bacterial co-infection and reduced oral intake of less than 50% at the time of admission (Table 5).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Quantitative variables in patients admitted with bronchiolitis included in the study (n = 1006).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Birth weight (g)</td>
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<tr>
<td>Weeks of gestation</td>
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<tr>
<td>Age (months)</td>
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<tr>
<td>Postmenstrual age</td>
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<td>Maternal age (years)</td>
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<td>Total length of stay</td>
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<tr>
<td>PICU length of stay</td>
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</table>

PICU, paediatric intensive care unit.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Mean cases per week of patients with bronchiolitis managed in the emergency department outside the epidemic season (April 1 through September 30), 95% confidence interval, and outbreak onset week.</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Mean cases/week</td>
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<tr>
<td>2010–2011</td>
<td>5.83</td>
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<td>2011–2012</td>
<td>5.73</td>
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<td>2012–2013</td>
<td>4.50</td>
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<td>2013–2014</td>
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<td>2014–2015</td>
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<tr>
<td>Total</td>
<td>5.17</td>
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</table>

Figure 1 Number of hospital admissions due to acute bronchiolitis by month of the year and presence or absence of respiratory syncytial virus (RSV) during 5 outbreaks in the 2010–2015 period.

had siblings aged less than 6 years and 24.2% siblings aged 6–14 years. There was a personal history of heart disease, neurologic disease and bronchopulmonary dysplasia in 2.9%, 1.3% and 1.7% of patients, respectively. Respiratory syncytial virus was detected in 9 patients that received doses of palivizumab. In 53.9% of cases, patients sought care in the day of onset of respiratory problems.
Table 3  Comparison of epidemiological and clinical variables in hospitalised patients with bronchiolitis based on the presence or absence of RSV using the chi square test.

<table>
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<tr>
<th></th>
<th>(n = 1006) n</th>
<th>%</th>
<th>RSV % (n = 778)</th>
<th>Non-RSV % (n = 228)</th>
<th>p</th>
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<td><strong>Age (months)</strong></td>
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<td>&lt;1</td>
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<td>21.1</td>
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<td>0.866</td>
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<td>50.4</td>
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<td><strong>Sex</strong></td>
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<tr>
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<td>53.3</td>
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<td>59.1</td>
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<tr>
<td>Female</td>
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<td><strong>Birth weight (g)</strong></td>
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<td>&lt;2300</td>
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<td>998</td>
<td>81.5</td>
<td>83.9</td>
<td>73.0</td>
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<td>32–36</td>
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<td>15.6</td>
<td>14.4</td>
<td>19.8</td>
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</tr>
<tr>
<td>&lt;32</td>
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<td>2.9</td>
<td>1.7</td>
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<td><strong>Multiple gestation</strong></td>
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<td>7.3</td>
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<td>C-section</td>
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<td>31.1</td>
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<td><strong>Maternal age (years)</strong></td>
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<td>23.0</td>
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<td>Prenatal tobacco exposure</td>
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<td>19.7</td>
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<td>Environmental smoke</td>
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<td>35.7</td>
<td>48.8</td>
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<td>Atopy in family</td>
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<td>22.6</td>
<td>21.6</td>
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<td>Siblings &lt;6 years</td>
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<td>63.4</td>
<td>61.8</td>
<td>68.8</td>
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<td>Siblings 6–14 years</td>
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<td><strong>Days since onset</strong></td>
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<td>1 day</td>
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<td>3 days</td>
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<td>&gt;3 days</td>
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<td><strong>Fever &gt;38 °C</strong></td>
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<td>SpO₂ &lt;92%</td>
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<td>30.7</td>
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<td>Oral intake &lt;50%</td>
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<td>32.2</td>
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<td>Nasogastric tube feeding</td>
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ABSS, acute bronchiolitis severity scale; PICU, paediatric intensive care unit; RSV, respiratory syncytial virus; SpO₂, oxygen saturation; UTI, urinary tract infection.

Significant p-values presented in boldface.
Table 4  Comparison of epidemiological and clinical variables in hospitalised patients with bronchiolitis based on length of stay using the chi square test.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total % (n = 950)</th>
<th>LOS ≤5 days % (n = 561)</th>
<th>LOS &gt;5 days % (n = 386)</th>
<th>p</th>
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</thead>
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<td><strong>Age (months)</strong></td>
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<td></td>
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<td>&lt;0.001</td>
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<td>21.1</td>
<td>15.5</td>
<td>28.2</td>
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<td>1–3</td>
<td>50.6</td>
<td>51.6</td>
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<td>&gt;3</td>
<td>28.3</td>
<td>32.9</td>
<td>22.5</td>
<td></td>
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<td><strong>Sex</strong></td>
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<td>Female</td>
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<td>46.5</td>
<td>57.0</td>
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<td><strong>Birth weight (g)</strong></td>
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<td></td>
<td>&lt;0.001</td>
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<td>&lt;2300</td>
<td>12.2</td>
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<td>16.4</td>
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<td>32–36</td>
<td>15.6</td>
<td>10.5</td>
<td>22.0</td>
<td></td>
</tr>
<tr>
<td>&lt;32</td>
<td>2.9</td>
<td>2.7</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td><strong>Multiple pregnancy</strong></td>
<td>7.6</td>
<td>5.2</td>
<td>10.8</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>C-section</strong></td>
<td>30.8</td>
<td>29.8</td>
<td>32.2</td>
<td>0.423</td>
</tr>
<tr>
<td><strong>Maternal age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.303</td>
</tr>
<tr>
<td>&lt;25</td>
<td>26.2</td>
<td>27.1</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>25–30</td>
<td>28.5</td>
<td>28.2</td>
<td>28.8</td>
<td></td>
</tr>
<tr>
<td>30–34</td>
<td>25.2</td>
<td>26.7</td>
<td>23.3</td>
<td></td>
</tr>
<tr>
<td>&gt;34</td>
<td>20.2</td>
<td>18.0</td>
<td>23.0</td>
<td></td>
</tr>
<tr>
<td><strong>Breastfeeding</strong></td>
<td>40.0</td>
<td>38.9</td>
<td>41.3</td>
<td>0.450</td>
</tr>
<tr>
<td><strong>Prenatal tobacco exposure</strong></td>
<td>17.6</td>
<td>17.8</td>
<td>17.3</td>
<td>0.843</td>
</tr>
<tr>
<td><strong>Exposure to smoke</strong></td>
<td>38.6</td>
<td>39.4</td>
<td>37.6</td>
<td>0.577</td>
</tr>
<tr>
<td><strong>Atopy in family</strong></td>
<td>22.6</td>
<td>23.8</td>
<td>20.9</td>
<td>0.280</td>
</tr>
<tr>
<td><strong>Siblings &lt;6 years</strong></td>
<td>63.4</td>
<td>60.5</td>
<td>66.8</td>
<td>0.054</td>
</tr>
<tr>
<td><strong>Siblings 6–14 years</strong></td>
<td>24.2</td>
<td>25.8</td>
<td>22.4</td>
<td>0.273</td>
</tr>
<tr>
<td><strong>Days from onset</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.032</td>
</tr>
<tr>
<td>1 day</td>
<td>54.0</td>
<td>49.8</td>
<td>59.3</td>
<td></td>
</tr>
<tr>
<td>2 days</td>
<td>22.0</td>
<td>24.2</td>
<td>19.3</td>
<td></td>
</tr>
<tr>
<td>3 days</td>
<td>12.3</td>
<td>13.7</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td>&gt;3 days</td>
<td>11.7</td>
<td>12.4</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td><strong>Fever &gt;38°C</strong></td>
<td>37.3</td>
<td>36.7</td>
<td>39.6</td>
<td>0.208</td>
</tr>
<tr>
<td><strong>SpO2 &lt;92%</strong></td>
<td>28.8</td>
<td>25.4</td>
<td>37.2</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Oral intake &lt;50%</strong></td>
<td>31.1</td>
<td>28.5</td>
<td>34.3</td>
<td>0.102</td>
</tr>
<tr>
<td><strong>Weight percentile &lt;3rd percentile</strong></td>
<td>8.0</td>
<td>5.4</td>
<td>11.4</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>ABSS</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.028</td>
</tr>
<tr>
<td>Mild</td>
<td>33.0</td>
<td>35.7</td>
<td>26.4</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>62.6</td>
<td>59.9</td>
<td>66.1</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>5.4</td>
<td>4.4</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td><strong>Apnoea prior to admission</strong></td>
<td>10.8</td>
<td>6.1</td>
<td>16.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Apnoea during stay</strong></td>
<td>4.9</td>
<td>0.5</td>
<td>10.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Nasogastric tube feeding</strong></td>
<td>13.9</td>
<td>2.7</td>
<td>27.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PICU admission</strong></td>
<td>8.5</td>
<td>0.5</td>
<td>18.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Severe bacterial infection</strong></td>
<td>15.5</td>
<td>4.2</td>
<td>29.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>84.5</td>
<td>95.8</td>
<td>70.7</td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td>3.0</td>
<td>1.1</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>10.9</td>
<td>2.8</td>
<td>20.9</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>1.6</td>
<td>0.4</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td><strong>Readmission</strong></td>
<td>2.1</td>
<td>1.1</td>
<td>3.5</td>
<td>0.009</td>
</tr>
<tr>
<td>RSV+</td>
<td>77.9</td>
<td>75.8</td>
<td>80.7</td>
<td>0.096</td>
</tr>
</tbody>
</table>

ABSS, acute bronchiolitis severity scale; LOS, length of stay; PICU, paediatric intensive care unit; RSV, respiratory syncytial virus; SpO2, oxygen saturation; UTI, urinary tract infection.

Significant p-values presented in boldface.
Approaches and Apnoea

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ward. In our hospital, we do not use high-flow nasal cannula therapy in the paediatric ward due to its cost and the lack of evidence on its efficacy and safety. Patients that required high-flow therapy were admitted to the PICU, which did not result in a larger proportion of PICU admissions relative to previous studies, in which it ranges between 6% and 13%. Although it is used widely and has shown promising results, it has not yet been recommended for use at the ward level in a recent review.

Our findings relating to heart disease, neurologic disease and bronchopulmonary dysplasia were similar to those of other studies. Their presence was an independent risk factor for admission to the PICU and prolonged length of stay. For that reason, we excluded these cases from our analysis of length of stay.

The presence of siblings in the household, a family history of atopy and the time elapsed since the onset of disease were not associated with the aetiology of AB or length of stay. Out of the remaining variables summarised in Table 4, multivariate logistic regression analysis identified the following as risk factors for increased length of stay: low birth weight, age, history of apnoea prior to admission and reduction in oral intake by more than 50% (Table 5). This was highly consistent with the previous literature.

Bacterial co-infection of the lower respiratory tract, in an epithelium destroyed by a virus like RSV, in patients too young for vaccination against pneumococcus or with incomplete vaccination is not given the importance it deserves in the various studies published to date, although the current evidence suffices to assert that it is frequently involved in cases that require admission to the PICU. Co-infection is a clear risk factor for increased length of stay. Recent studies have found a prevalence of co-infection of up to 29% in children with viral illness. In our series, the clinical diagnosis of respiratory bacterial co-infection, whether confirmed or suspected, was substantially more frequent than the diagnosis of severe UTI.

Our study has the limitations inherent in all retrospective studies, including the challenges posed by data collection and missing data. We must also add the fact that the study was restricted to hospitalised patients and to a single centre. We did not collect information on potential visits to primary care facilities prior to admission, which amount to 21% of patients per year in other case series. We also did not take into account the effects of viral co-infection, which is estimated to occur in 30% of cases, although their presence, as we already noted, is not required for diagnosis. Lastly, bacterial co-infections are particularly difficult to discern in respiratory illness, as acute phase reactants may be elevated in some viral infections.

Conclusions

We found that in our region the timing of outbreak onset varied within a range of four weeks. Five years from the implantation of the CPG, the incidence of hospitalisation is of around 2.3% and seems stable in relation to previous studies. The mean age of patients has decreased to 2.4 months, although the proportion of patients admitted to the PICU remains similar, at 8.5%.

The independent risk factors for an increased length of stay found in our study were low birth weight, age less than 1 month, history of apnoea prior to admission, reduction in oral intake of more than 50% and severe bacterial co-infection, in which the prevalence of respiratory infection was greater than that of severe UTI.

Conflict of interests

The authors have no conflict of interests to declare.

References


