Seasonality of bronchiolitis in newborns and young infants in pandemic times by SARS-CoV-2

Resumo

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Objetivos: Comparar a frequência de recém-nascidos e lactentes jovens internados com bronquiolite em uma unidade de terapia intensiva neonatal externa antes e durante o primeiro ano de pandemia pelo SARS-CoV-2. Métodos: Estudo retrospectivo, incluindo crianças de até 45 dias de vida, com bronquiolite, internados nos anos de 2018, 2019 e 2020. Foram selecionados os prontuários: sexo; idade e peso à admissão; agente etiológico; tempo de internação e desfecho. Análise estatística: comparação entre grupos por frequência (qui-quadrado), por média (ANOVA), por mediana (Mann-Whitney). Resultados: Em 2018, a frequência de internações por bronquiolites foi de 6,4%, em 2019, 4,2% e em 2020, 1,3%. Peso médio à admissão (gramas) (2018 - 2978, 2019 - 3855 e 2020 - 3873); Agente viral isolado (2018 - 28,5%, 2019 - 55,5% e 2020 - 66,6%); ventilação mecânica invasiva (2018 - 14,3%, 2019 - 44,4% e 2020 - 100%); tempo médio de internação (dias) (2018 - 8 [7-12], 2019 - 5 [4-10], 2020 - 12 [8-16]); alta hospitalar em 100% dos casos. Conclusão: Em 2020, houve uma redução drástica no número de internações por bronquiolite, justificada pelo isolamento social que resultou em menor circulação de vírus respiratórios.

Keywords: Bronquiolite, Bronquiolite Viral, Estações do Ano, Infecções por Coronavírus, Criança.

Abstract

Objetivos: To compare frequency of newborns and young infants hospitalizad with bronchiolitis in an external neonatal intensive care unit before and during the first year of the SARS-CoV-2 pandemic. Methods: Retrospective study, including children up to 45 days of life, with bronchiolitis, hospitalized during the years of 2018, 2019, and 2020. From medical records were selected: gender; age and weight at admission; etiological agent; type of ventilatory support; hospitalization time and outcome. Statistical analysis: comparison between groups by frequency (chi-square), by mean (ANOVA), by median (Mann-Whitney). Results: In 2018, bronchiolitis was 6.4% of the hospitalizations, 2019 (4.2%), and 2020 (1.3%). Mean age at hospitalization (days) (2018 - 33.7, 2019 - 33.7, 2020 - 31.6); average weight at admission (grams) (2018 - 2,978, 2019 - 3,855, and 2020 - 3,873); Isolated viral agent (2018 - 28.5%, 2019 - 55.5%, and 2020 - 66.6%); invasive mechanical ventilation (2018 - 14.3%, 2019 - 44.4%, and 2020 - 100%); median hospitalization time (days) (2018 - 8 [7-12], 2019 - 5 [4-10], 2020 - 12 [8-16]); hospital discharge - 100% of the cases. Conclusion: In 2020, there was a drastic decrease in the number of hospitalizations due to bronchiolitis, justified by the social isolation that resulted in a lower circulation of respiratory viruses.

Keywords: Bronchiolitis, Bronchiolitis, Viral, Seasons, Coronavirus Infections, Infant.
INTRODUCTION

Bronchiolitis is an inflammatory disease of the airways with obstruction of the lower respiratory tract, caused almost exclusively by viral infections in children under two years of age, presenting a peak of incidence between two and six months of age. Symptomatology begins with rhinitis or nasal congestion and cough, and may develop into respiratory failure. Its severity can range from mild symptoms that can be controlled at home, to acute respiratory failure requiring invasive ventilation. Moreover, this pulmonary condition is responsible for most hospitalizations in the first year of life. Among these factors, prematurity is one of the most important, since premature newborns present incomplete pulmonary development and can be submitted to mechanical ventilation with high oxygen fractions, leading to a higher risk of respiratory changes.

Infants with risk factors such as chronic lung diseases (bronchopulmonary dysplasia, cystic fibrosis, congenital anomalies), congenital heart diseases, Down syndrome, neuromuscular diseases, immunodeficiencies, anatomical changes in the airways, and prematurity are more likely to develop severe bronchiolitis. Among these factors, prematurity is one of the most important, since premature newborns present incomplete pulmonary development and can be submitted to mechanical ventilation with high oxygen fractions, leading to a higher risk of respiratory changes.

Exposure to cigarette smoke and attending day care centers are also pointed out as risk factors and increased severity of bronchiolitis and some studies suggest genetic predisposition. The usage of molecular detection techniques made it possible to identify a wide variety of viral agents causing bronchiolitis. Respiratory syncytial virus (RSV) is undoubtedly the most identified, being detected in up to 80% of children with this pathology, followed by human rhinoviruses. Adenovirus, metapneumovirus, influenza, parainfluenza, entero and bocavirus can also cause bronchiolitis.

The clinical features of bronchiolitis caused by the various virus are generally similar, although each virus demonstrates a small variation in seasonality and geographical distribution. Some studies suggest that RSV can cause a more severe illness and others show even a greater severity when infection occurs by two or more viruses.

The epidemiology of RSV differs globally based on seasonality. In the Northern hemisphere infection rates increase between the end of October and April and the peak occurs between January and February. In the Southern hemisphere bronchiolitis prevail between April and September, with peak in the months of June and July. As this infection occurs in cold months, it is worth mentioning that its transmission and severity can be boosted by agglomerations in closed environments, by the impairment of the ciliary function of the respiratory epithelium caused by cold air and by the variability of the innate antiviral immune responses (reduction of IgA activity) in lower temperatures; in tropical or semitropical climates RSV outbreaks tend to be more common during the rainy season.

In Brazil, the prevalence of RSV ranges from 23.1% to 42.2%, depending on the methodology used, population and region studied. In a study on Sao Paulo city, 41.8% of the children hospitalized with lower respiratory tract infection were positive for RSV; in the neonatal period, this positivity increased to more than 90%

One of the main ways to prevent bronchiolitis is to keep children from staying indoors and poorly ventilated areas or in places with agglomerations of people with respiratory conditions. Contagion by the viruses causing this disease occurs through contact with droplets expelled from the mouth or nose of the infected person or by objects contaminated by the same droplets. Another measure indicated for prevention is constant hygiene of the hands, using soap or hand sanitizer.

The year 2020 marked the beginning of the pandemic by SARS-CoV-2. In view of the need for social withdrawal, which coincided with the seasonality of respiratory viruses in the city of Sao Paulo, the circulation of these viruses decreased greatly.

Thus, this study aimed to compare frequency and severity of newborns and young infants hospitalized with bronchiolitis in an external neonatal intensive care unit before and during the first year of the pandemic by SARS-CoV-2.

METHODS

This is a retrospective and descriptive study, including children up to 45 days of life, diagnosed with bronchiolitis and need for hospitalization in an external neonatal intensive care unit, during the years of 2018, 2019, and 2020.

The study was carried out at the Neonatal Intensive Care Center 2 of the Children’s Institute of the Clinics Hospital, Faculty of Medicine, University of Sao Paulo. Neonatal Intensive Care Center 2 is a tertiary-level neonatal intensive care unit that provides care to a high range of newborns, integrated with teaching and research; it has 16 operating beds (two isolation beds), with individualized box and multiparametric monitoring. The criterion of hospitalization in this center consists of newborns and young infants under the age of 45 days of life who require clinical and/or surgical intensive care. Because it is an external neonatal intensive care unit, Neonatal Intensive Care Center 2 receives children born in the maternity of Clinics Hospital, born in other services and from home.

The project was approved by the ethics committee of the department of pediatrics and the research project analysis committee of clinics hospital (protocol 4.636.766-CAAE: 44742021.8.0000.0068), and the informed consent form was waived because it is a collection of data from the medical records of these newborns.

From the medical records of newborns and young infants, were selected: gender; birth weight (in grams); gestational age (in weeks), for subsequent classification in relation to prematurity (gestational age less than 37 weeks) and nutritional adequacy (adequate, small, or large for gestational age); age on the admission (in days) and weight (in grams). At admission in the Neonatal Intensive Care Center 2 were selected: clinical findings; etiologic agent, when identified; source of contagion (siblings, parents, cousins, etc.).
neighbors, etc.); type of ventilatory support (inhaled oxygen, non-invasive ventilation, invasive ventilation); use of antivirals and antibiotics; hospitalization time (in days) and outcome (hospital discharge or death).

The sample size was not calculated because it is a convenience sample. The results are expressed in percentages, means with standard deviation and medians with interquartile range values. All continuous variables were tested for normality using the Kolmogorov-Smirnov test. The chi-square test was used to compare the frequencies between groups, ANOVA for comparison of means and Mann-Whitney for comparison of medians. The level of significance adopted was 0.05.

RESULTS

In 2018, 7 bronchiolitis (6.4% of hospitalizations) were admitted, in 2019, 9 cases, 4.2% of total hospitalizations and in 2020 only 3 children with this pulmonary condition, making up 1.3% of total hospital admissions. The hospitalizations in 2018 occurred between April and September and 2019, between March and October, that is, within the seasonality of viral respiratory infections. However, the three hospitalizations in 2020 occurred in February, March (both before the onset of the pandemic by SARS-CoV-2), and December, outside the seasonality of respiratory viruses.

Table 1 shows the variables gender, birth weight, prematurity rate, nutritional adequacy, age and weight at admission, time of hospitalization and outcome.

Table 2 describes the variables sources of contagion, isolated agents, use of antivirals and antibiotics, and type of ventilatory support used.

Regarding symptomatology, it was observed: runny nose (36.4% of cases), produced cough or not (71.9%), fever above 38°C (18.2%), and respiratory failure (68.2%).

The isolated viral agents were: VSR, rhinovirus, bocavirus, H1N1, and coronavirus. The most prevalent viral agent was RSV with a positivity of 36.8%; three children (15.7%) were infected by two viruses. The antibiotics used were found to be amikacin, ampicillin, azithromycin, cefpime, ceftriaxone, clarithromycin, meropenen, oxacillin, crystalline penicillin, and vancomycin.

Table 1. Description of the variables gender, birth weight, prematurity rate, nutritional adequacy, age and weight at admission, time of hospitalization and outcome in 2018, 2019, and 2020.

<table>
<thead>
<tr>
<th>Variable</th>
<th>2018 (n=7)</th>
<th>2019 (n=9)</th>
<th>2020 (n=3)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>5 (71.4)</td>
<td>8 (88.8)</td>
<td>2 (66.7)</td>
<td>0.593*</td>
</tr>
<tr>
<td>Birth weight (grams), average (SD)</td>
<td>2294 (704)</td>
<td>3288 (449)</td>
<td>3151 (815)</td>
<td>0.015*</td>
</tr>
<tr>
<td>Prematurity rate (%)</td>
<td>4 (57.1)</td>
<td>7 (77.7)</td>
<td>0 (0)</td>
<td>0.139*</td>
</tr>
<tr>
<td>Adequate for gestational age (%)</td>
<td>7 (100)</td>
<td>7 (77.7)</td>
<td>1 (33.3)</td>
<td>0.153*</td>
</tr>
<tr>
<td>Age at admission (days), mean (SD)</td>
<td>33.7 (15.8)</td>
<td>33.7 (14.3)</td>
<td>31.6 (19)</td>
<td>0.978*</td>
</tr>
<tr>
<td>Weight at admission (grams), average (SD)</td>
<td>2778 (603)</td>
<td>3855 (889)</td>
<td>3873 (970)</td>
<td>0.057*</td>
</tr>
<tr>
<td>Hospital stay (days), median (IQR)</td>
<td>8 (7 - 12)</td>
<td>5 (4 - 10)</td>
<td>12 (8 - 16)</td>
<td>0.441*</td>
</tr>
<tr>
<td>Outcome (hospital discharge) (%)</td>
<td>7 (100)</td>
<td>9 (100)</td>
<td>3 (100)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

*p-value

Chi-square test; ANOVA; Mann-Whitney test; IQR - Interquartile range.

DISCUSSION

The neonatal intensive care unit, which this work was performed, is in a tertiary hospital and its capacity consists of 16 beds. The pathologies admitted in the service are predominantly surgical, over than 50% (gastroschisis, omphalocele, congenital diaphragmatic hernia, among others), providing care to high complexity newborns and for this reason the number of patients with non-surgical pathologies up to 45 days of life is limited.

The hospitalizations in 2018 occurred between April and September and in 2019 between March and others, that is, within the seasonality of viral respiratory infections. However, the three hospitalizations in 2020 occurred in February and March, being before the beginning of the pandemic by SARS-CoV-2 and the last in December, which would be out of seasonality.

Males were the most frequent gender in our study consisting of 72.6% on pre pandemic years and 66.6% in 2020. According to Ben-Shmuel et al. (2018) study that evaluated the association between the sex of the newborn and the risk of respiratory morbidity, the greater involvement of males in respiratory disorders is multifactorial cause, but it is believed that the growth of the airways in males being delayed in relation to the development of the pulmonary parenchyma leads to a discrepancy between the airways and the size of the lung. In addition, associate outcomes such as prematurity, preeclampsia, fetal distress, and even perinatal mortality to the male gender.

The analyses of the birth weight of hospitalized patients diagnosed with bronchiolitis shows in 2018 children with lower birth weight with statistically significant difference (p=0.015), compared to the other years of the study. Shi et al. (2015) report a significant association in a metaanalysis between low birth weight and bronchiolitis caused by RSV, however, the patients’ weight of admission was not statistically significant.

The analyses of weight adequacy for gestational age shows that newborns adequate for gestational age do not have statistically significant difference between the groups (p=0.153). The literature did not describe any studies that...
In Brazil, the social isolation started in mid-March, lasting up to the present moment, to decrease the SARS-CoV-2 pandemic. In the city of Sao Paulo, where the present study was carried out, the isolation rate during the year 2020 ranged from 25% to 58%, according to official data. Among the isolation measures, classes at schools and universities were suspended as well as attendance to daycare. The population was educated about the use of masks and other hygiene needs that contributed to decrease the circulation of the SARS-CoV-2 and other respiratory viruses involved on bronchiolitis.

On the meta-analysis carried out by Kenmoe et al. (2020), social distancing measures undertaken on the pandemic have shown a significant reduction in child hospitalizations due to acute bronchiolitis between the pre-pandemic and pandemic eras, as demonstrated in the present study.

Nascimento et al. (2020) carried a study in the city of Sao Paulo to analyze hospitalized children and adolescents from 0 to 17 years old due to respiratory diseases, in which bronchiolitis was included. They found that among children under 5 years old, pre-pandemic hospitalization represented 81.3% and during the pandemic period it decreased to 45% of total hospitalizations, with statistical significance (p=0.005). In 2018, CTIN-2 had 6.4% of bronchiolitis hospitalizations, 4.2% in 2019 and in 2020, 1.3% of total admissions. Regarding the length of hospital stay, the same authors observed a reduction in the length hospitalization (p=0.005), but in the present study there was no statistical difference in this data (p=0.441).

Friedrich et al. (2020) conducted a Brazilian study that assessed the incidence of bronchiolitis in Brazil before and during the pandemic by SARS-CoV-2. In children under one year of age, bronchiolitis represented 28.2% of hospitalizations for respiratory diseases between January 2016 and June 2020. However, in 2020 there was an important decline in hospitalizations that coincides with the implementation of social distance measures, being represented by a 70% reduction, suggesting that the control measures for SARS-CoV-2 had an important impact on the spread of bronchiolitis.

A study carried in the United States by Pelletier et al. (2021) evaluated changes in pediatric hospitalization patterns by comparing the year 2020 with the previous decade. Among the reasons for hospitalization was bronchiolitis. In this the present study, there was a decrease in the number of hospitalizations in early March 2020 with the nadir in April

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Table 2. Description of the variables sources of contagion (yes or no), clinical picture, isolated viral agents, use of antivirals and antibiotics and type of ventilatory support used (invasive ventilation).

<table>
<thead>
<tr>
<th>Variable</th>
<th>2018 (n=7)</th>
<th>2019 (n=9)</th>
<th>2020 (n=3)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of contagion (%)</td>
<td>2 (28.5)</td>
<td>5 (55.5)</td>
<td>1 (33.3)</td>
<td>0.525a</td>
</tr>
<tr>
<td>Isolated viral agent (%)</td>
<td>2 (28.5)</td>
<td>5 (55.5)</td>
<td>2 (66.6)</td>
<td>0.431a</td>
</tr>
<tr>
<td>Use of antivirals (%)</td>
<td>1 (14.2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.411a</td>
</tr>
<tr>
<td>Use of antibiotics (%)</td>
<td>6 (85.7)</td>
<td>5 (55.5)</td>
<td>3 (100)</td>
<td>0.230a</td>
</tr>
<tr>
<td>Invasive mechanical ventilation (%)</td>
<td>1 (14.3)</td>
<td>4 (44.4)</td>
<td>3 (100)</td>
<td>0.041a</td>
</tr>
</tbody>
</table>

Sources of contagion reported: parents, siblings, cousins; aChi-square test.

correlates this finding. However, Shi et al. (2015) analyzing risks factors in bronchiolitis in children younger than five years old relate that the association between prematurity (gestational age less 37 weeks) and RSV was 1.96 (95%CI: 1.44-2.67).

As described in the results, the clinical findings runny nose (36.4%), productive cough or not (71.9%), fever above 38°C (18.2%), respiratory failure (68.2%) agreed with the pathology studied in the present study.

In our tertiary-level neonatal unit, viral panels are not always available, so it was not possible to identify or collect that screening from all patients in the unit. However, in those it was possible to identify, RSV was predominant, representing 36.8%, while in 15.7% of cases two viral agents was found. However, no statistically significant difference was found in the identification of the viral agent in the groups before and during the coronavirus pandemic (p=0.431). According to Kenmoe et al. (2020) RVS was the most detected virus in 59.2% (95% CI: 54.4; 63.3), followed by rhinovirus 19.3% (95% CI: 16.7; 22), and the most codetections were RVS and RV (7.1%, 95% 4.6;9.9).

The use of broad-spectrum antibiotics is justified because they are children with respiratory insufficiency requiring ventilatory support without a defined etiological agent. In cases that the viruses were identified, this therapeutic measure was suspended depending on the clinical condition and severity of the case, when associated bacterial infection was excluded.

All patients required non-invasive or invasive ventilatory support. The analyses of the use of mechanical ventilation were lower in 2018, progressively higher in 2019 and finally in 2020, 100% of the cases required this ventilatory support, which statistically significant difference between the groups (p=0.041). Despite the lower number of cases during the coronavirus pandemic, we observed greater severity in all cases.

In the sample studied, there were no cases of death (100% hospital discharge) and none of these children presented pathologies that increased mortality in bronchiolitis. Mortality among cases requiring hospitalization is relatively low, but in children with previous diseases such as pulmonary dysplasia and immunodeficiencies, lethality can reach quite high. About 10% of children develop bronchiolitis in the first year of life and about 10% of those required hospitalization in semi-intensive or intensive care units. Mortality in hospitalized patients is 4% to 7% and affects 35% in children with congenital heart diseases.

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of the same year, representing a drop of 45.4%. There was an increase in admissions in May and June despite remaining below the average of previous years. All the considerations made suggest that the rates of respiratory disorders in children may be modifiable with changes in isolation measures. In addition, the study also associates the reduction in the volume of patients with financial instability caused by the economic crisis caused by the pandemic\textsuperscript{21}.

CONCLUSION

In conclusion, although the sample of the present study is small, the results agree with other published studies, where it was shown that social isolation due to the pandemic by SARS-CoV-2 drastically decreases the circulation of other respiratory viruses that cause bronchiolitis, such as RSV and rhinovirus. In addition, other measures contributed to these results, such as hand hygiene, whether with soap and water or hand sanitizer, body and hygiene utensils, and the use of face masks.

REFERENCES