Predictors of hospitalization for acute lower respiratory infections during the first two years of life in a population of preterm infants with bronchopulmonary dysplasia

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ABSTRACT

Background: There have been few research studies aimed at obtaining a better understanding of the prediction of subsequent respiratory morbidity at follow-up in infants with a previous history of bronchopulmonary dysplasia (BPD) living in low- and middle-income countries (LMIC). The aim of the present study was to identify predictors of hospitalization for acute lower respiratory infections (ALRIs) in a population of infants with a history of BPD living in a LMIC.
Methods: In a prospective cohort study, we determined independent predictors of the number of hospitalizations for ALRIs during the first two years of life in a population of infants with a history of BPD living in Bogota, Colombia. In multivariate analyses, we included both clinico-demographic variables and underlying disease characteristics as predictor variables of hospitalization for ALRIs.
Results: Of a total of 138 patients included in the study, 83 (60.1%) had at least one hospitalization for ALRI during the follow-up period. Independent predictors of the number of hospitalizations for ALRIs included duration of neonatal ventilatory support (IRR 1.02; CI 95% 1.00–1.03; p = 0.010), duration of subsequent ambulatory oxygen therapy (IRR 2.06; CI 95% 1.16–3.64; p = 0.013), and breastfeeding in females (IRR 0.35; CI 95% 0.14–0.84; p = 0.019).
Conclusions: Duration of mechanical ventilation, duration of subsequent ambulatory oxygen therapy, and breastfeeding in females were independently associated with the number of hospitalizations for ALRIs in our population of infants with a history of BPD.

1. Introduction

Bronchopulmonary dysplasia (BPD) is the most common cause of chronic lung disease in children born prematurely [1]. When compared to patients without BPD, premature infants with BPD have significantly higher rates of respiratory problems at follow-up, including respiratory symptoms, chronic respiratory morbidity, and recurrent wheezing and other asthma symptoms, often leading to the need for respiratory medications and increased healthcare utilization, including hospitalizations for acute lower respiratory infections (ALRIs) [2]. Hospital admissions for ALRIs are a significant problem, not only because of the

possibility of progression to life-threatening conditions, but also because of the significant impact on related healthcare costs and the considerable negative effect on the quality of life of affected children and their families [3]. Although ALRIs pose a significant health problem in high-income countries, they are an even greater problem in low- and middle-income countries (LMICs) and are considered to be the leading cause of death among infants and children living in these countries [4]. Identification of infants with BPD who are at risk for hospitalizations for ALRIs at follow-up is important, because these patients could benefit from more effective and targeted preventive or therapeutic interventions, in an attempt to reduce the significant healthcare and clinical

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burden of ALRIs [5]. Therefore, an essential next step in approaching the problem is to identify predictors of hospitalizations for ALRIs in infants with a history of BPD. Although a variety of predictors of subsequent hospitalizations for ALRIs at follow-up in infants with BPD have been identified, such as male gender, oxygen dependency at 36 weeks post-menstrual age, having older siblings aged less than five years and living in rented accommodations, and passive tobacco smoke exposure [6], comparatively few of these investigations have been performed in LMICs, where the morbidity and mortality attributable to these infections is the greatest [4]. Accordingly, there is still a considerable need for additional studies aimed at obtaining a better understanding of the prediction of subsequent respiratory morbidity at follow-up in infants with a previous history of BPD living in a LMIC.

Therefore, the aim of this study was to identify predictors of hospitalization for ALRIs in a population of infants with a history of BPD living in a LMIC.

2. Materials and methods

2.1. Study site

Bogota, the capital city of Colombia, a tropical LMIC located in South America, contains one fifth of Colombia's population, and is located at an elevation of about 2650 m (8660 ft) above sea level. The city's high altitude makes it necessary to account for the effects of decreased atmospheric pressure, especially the decreased partial pressure of inspired oxygen, which drives gas exchange in the lungs [7]. Although respiratory syncytial virus, the most commonly identified virus in infants with ALRIs, is active in the city throughout the year, it peaks during the 3-month period from March to May, the first rainy period of the year in the city [8]. The Hospital Militar Central and the Hospital Universitario Clinica San Rafael are two tertiary-care university-based hospitals located in the metropolitan area of Bogota, the former with 800 hospital beds and the latter with 320 hospital beds, both of which mainly function as referral centers, with the majority of admissions coming from the emergency department and from inpatient transfers from outlying primary and secondary clinics and hospitals.

2.2. Study design and study population

We conducted a multicenter prospective cohort study that recruited prematures (born at 36 weeks gestation or earlier) with a diagnosis of BPD (defined as persistent oxygen requirement at 36 weeks post-menstrual age) included in the Kangaroo Mother Care (KMC) program of both institutions, born between January 2008 and January 2009. Infants were recruited from the KMC program because in the participating institutions it is now considered to be the most feasible, available, and preferred intervention for decreasing premature morbidity and mortality and because it facilitates the long-term follow-up of premature patients. The KMC Program is an intervention that was begun in 1978 in Bogota, Colombia, in response to overcrowding and insufficient resources in neonatal intensive care units, associated with high morbidity and mortality among low-birthweight infants. The intervention consists of continuous skin-to-skin contact between the mother and the infant, exclusive breastfeeding, and early home discharge in the kangaroo position [9]. Parents of included infants were native Spanish speakers, with widely varied educational background and socioeconomic status, but all of them had at least 5 years of formal education, and some type of health insurance coverage.

Regarding the local BPD epidemiology, in 2004, Ruiz-Pelaez et al. carried out a prospective analytical cohort of preterm newborns (mean gestational age at birth - GAB: 31.9 weeks) from 12 health facilities in Bogota in 2004. They reported an overall BPD incidence of 54.3% (95% CI, 49.4–59.1), as well as a greater risk of developing BPD when compared to a historical control cohort. They further determined the following relative risks (RRs) of developing BPD for various GAB: 1.75

(95% CI, 1.52–2.01) for GAB ≤ 28 weeks, 1.99 (95% CI, 1.71–2.23) for GAB = 29–30 weeks, 2.14 (95% CI, 0.94–2.52) for GAB = 31–32, and 1.87 (95% CI, 1.53–2.29) for GAB = 33–34 weeks [10].

The study protocol was approved by the local ethics board. The procedures followed were in accordance with the ethical standards of the local ethical board and with the Helsinki Declaration of 1975 as revised in 1983. Subjects were excluded from the study if they expected to move out of Bogota within 2 years after inclusion in the study or if the parents refused to sign the consent form. In both institutions, the treating physicians make the decision for hospitalization for ALRIs based on the following criteria: signs of difficult breathing, such as chest indrawing, rapid breathing, stridor (especially in a calm child) or wheeze; cyanosis; hemoglobin saturation below 90% in room air or need for oxygen supplementation; feeding problems such as if the child is not able to drink or a young infant stops adequate feeding; and whether the child is abnormally sleepy, difficult to wake, or has convulsions. All of these are criteria for inpatient management in infants not getting any better after an intervention is administered in the ED for a maximum of 24 h.

At baseline, we collected information on the number of courses of antenatal corticosteroids for acceleration of fetal lung maturation, gender, birth weight, GAB, duration of neonatal ventilatory support, number of doses of palivizumab (15 mg/kg of body weight) given monthly by intramuscular injection (0, 1–3 doses, 4–5 doses, 5 or more doses), maternal and parental smoking, doctor-diagnosed maternal and paternal asthma, and doctor-diagnosed maternal and paternal allergic rhinitis. Likewise, during routine follow-up visits performed at 1, 3, 6, and 12 months after birth, and when infants were 24 months (corrected age) old, we prospectively collected the following clinical information: presence and duration of breastfeeding (0–5 months, 6 or more months), duration of ambulatory oxygen therapy (0–89 days, 90–119 days, 120 or more days), maternal and paternal smoking after birth, and the number of hospitalizations for ALRIs. Maternal and paternal smoking was considered to be a factor if there was at least one report of smoking at either the baseline visit or one of the follow-up visits. Categorization of continuous exposure variables was based on a review of prior literature, using well-recognized, published boundaries for the exposure variables [11–13].

2.3. Outcome definition

The number of hospitalizations for ALRIs was considered to be the main measure of the outcome.

A hospitalization for ALRI was defined as an observation-room stay of at least 24 h or an admission to the general ward or the neonatal or pediatric intensive care unit of any duration, after receiving primary care in the Emergency Department for acute manifestations of laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonia, any combination of these, or any of these along with signs or symptoms of upper respiratory infection [14]. If seven or more days had passed since the resolution of the previous ALRI, an episode of ALRI was considered to be a new and separate one.

2.4. Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range, IQR), whichever is appropriate. Categorical variables are presented as numbers (percentage). Differences between continuous variables were analyzed using the unpaired *t*-test or Wilcoxon's signed rank test, whichever was appropriate. Associations between categorical variables were analyzed using the Chi-square test or Fisher's exact test, whichever was appropriate. In order to identify factors independently associated with the number of hospitalizations for ALRIs, we fit the data to negative binomial regression models. This regression technique can be considered to be a generalization of the Poisson regression, since it has the same mean