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ORIGINAL ARTICLE

Hospital admission due to respiratory viral infections in moderate preterm, late preterm and term infants during their first year of life

I. Olabarrieta[a], E. Gonzalez-Carrasco[a], C. Calvo[a], F. Pozo[b], I. Casas[b], M.L. García-García[a,*]

[a] *Department of Neonatology and Department of Pediatrics, Severo Ochoa Hospital, Leganés, Madrid, Spain*
[b] *Influenza and Respiratory Viruses Laboratory, National Centre of Microbiology, Instituto de Salud Carlos III, Madrid, Spain*

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Abstract
Background: Respiratory viral infections are a major cause of hospitalisation in infants <1 year and might cause severe symptoms in preterm infants. Our aim was to analyse admissions due to respiratory infections in moderate, late and term infants, and to identify risk factors for hospitalisation in preterm versus term.
Methods: Prospective study in a cohort of moderate and late preterm, and term infants born between October/2011 and December/2012. Admissions due to respiratory infections during the first year of life were analysed and compared among moderate (32–33), late (34–36) and term infants. Sixteen respiratory viruses were detected by RT-PCR. Clinical data were collected.
Results: 30 (20.9%) out of 143 preterm infants required admission for respiratory infection, versus 129 (6.9%) of 1858 term infants born in the same period ($p < 0.0001$, OR: 3.6 CI 2.0 to 5.0). Hospitalised children had a higher prevalence of hyaline membrane disease (HMD) at birth ($p < 0.001$, OR: 7.7 CI: 2.121 to 27.954) and needed more mechanical ventilation ($p < 0.001$, OR: 5.7 CI: 1.813 to 18.396). Virus was identified in 25/30 (83%) preterm babies, and in 110/129 (85%) term infants. The most frequent viruses in preterm infants were RSV (76%) rhinovirus (20%). Clinical and epidemiological characteristics among term and preterm infants were similar.
Conclusions: The risk of respiratory admissions during the first year of life is up to 3.6 times higher in moderate and late preterm. Once admitted, clinical features of respiratory episodes requiring hospitalisation are similar among term and preterm infants. Hyaline membrane disease and mechanical ventilation were also risk factors for respiratory admissions.

* Corresponding author.
E-mail address: marialuz.hso@gmail.com (M.L. García-García).

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Introduction

Respiratory tract viral infection continues to be among the most common reasons for visits to the emergency department and hospitalisation in children, particularly in the case of infants younger than one year. These infections can cause severe symptoms in preterm infants, such as respiratory distress with high morbidity and mortality. Lower respiratory viral infections (LRTI), especially due to respiratory syncytial virus (RSV), are the leading cause of hospital admissions among infants.[1] Having a history of prematurity (less than 32 weeks of gestational age) is a risk factor for severe LRTI in early childhood, and late preterm babies have been considered in the same risk group.[2] Nevertheless, this issue is under investigation and some research groups have not found a higher risk in late preterm infants (more than 336 weeks of gestational age (GA).[3] Respiratory distress syndrome at birth could be a risk factor for hospitalisation in this group.[4] Other authors have not found association between prematurity and hospitalisation during the first two years of life.[5]

Throughout the years, clinicians have considered respiratory syncytial virus followed by influenza as the most common pathogens responsible for respiratory infections. Over the past decade, new viruses have been discovered through more specific testing. This includes human metapneumovirus (HMPV), rhinovirus (RV), human bocavirus (HBoV) and others.[6]

We designed a prospective study in a cohort of moderate-late preterm and term infants. Our aim was to evaluate incidence and clinical characteristics of hospitalisation due to respiratory tract infections associated to a panel of 16 different respiratory viruses during the first year of life.

Patients and methods

This was a systematic prospective study conducted at Severo Ochoa Hospital (Leganes, Madrid, Spain) to assess the incidence, epidemiology and clinical characteristics of respiratory viral infections that needed hospitalisation in a cohort of moderate and late preterm infants during the first year of life. 143 preterm infants born between 32_0 and 36_6 weeks were followed up by phone, and hospitalisation incidence due to respiratory viral infections was compared with the 1858 term babies born during the same period in our hospital. The enrolment period was October 2011 to December 2012. The study was funded by FIS (Fondo de Investigaciones Sanitarias – Spanish Health Research Fund) Grant 09/00246 and approved by The Medical Ethics Committee. Parents were informed and consent was obtained.

Clinical assessment

Patients hospitalised due to respiratory symptoms were evaluated by an attending physician. During the hospital stay, and as part of the study, a physician filled out a study-questionnaire with the following variables: age, sex, clinical diagnosis, history of prematurity and underlying chronic diseases, need for oxygen therapy assessed by transcutaneous oxygen saturation, axillary temperature $\geq 38\,^{\circ}C$, presence of infiltrates/atelectasis in radiographs, administration of antibiotic therapy, duration of hospital stay, total white blood cell (WBC) count, C-reactive protein (CRP) serum values, and result of blood culture if performed. Oxygen therapy was provided in order to achieve oxygen saturation $\geq 94\%$.

Upper respiratory tract infection (URTI) was defined as the presence of rhinorrhoea and/or cough in the absence of wheezing, dyspnoea, crackling rales or use of bronchodilator, with or without fever. The classic criteria, presence in an initial episode of acute onset expiratory dyspnoea with previous signs of viral respiratory infection (whether or not this was associated to respiratory distress or pneumonia), were applied in diagnosing *bronchiolitis*.[7] Children with wheezing, breathlessness and obstruction of the airways, in whom similar episodes had previously been diagnosed and treated by a physician, were diagnosed as *recurrent wheezing*. Cases with focal infiltrates and consolidation in chest radiographs, in the absence of wheezing, were classified as *pneumonia*.

Only infants born before 28 weeks of GA receive treatment with palivizumab.

Virological study

Specimens of nasopharyngeal aspirates (NPA) were taken from each patient upon admission and sent for virological study at the Respiratory Virus and Influenza Unit (WHO-National Influenza Centre-Madrid, ISCIII, Madrid, Spain). Specimens were processed within 24 h of collection. Three RT-nested PCR assays were performed to detect a total of sixteen respiratory viruses. In these assays, reverse transcription (RT) and first amplification round were carried out in a single tube using the Qiagen® OneStep RT-PCR kit (Qiagen, Hilden, Germany). Influenza A, B and C viruses were detected using a previously described method including the primer sets specific to amplify influenza viruses in a multiplex PCR assay.[8] From 2003, this assay was used directly in respiratory samples as the routine method for the establishment of primary influenza A, B and C diagnosis at the National Influenza Centre-Madrid. A second multiplex PCR was used to detect parainfluenza viruses 1–4, human coronaviruses 229E and OC43, enteroviruses and rhinoviruses.[9] Presence of RSV-A and B types, HMPV, HBoV and adenoviruses were investigated by a third multiplex RT-nested PCR method.[10]

An internal amplification control was included in the reaction mixture to exclude false-negative results due to specimen inhibitors and/or extraction failure. Given the high sensitivity of nested PCR, precautions had to be taken to prevent reaction tubes from becoming contaminated with previously amplified product as well as to protect target RNA, or DNA, from other specimens and controls. All procedures were performed in safety cabinets located in separated laboratories, all well away from the area where amplified products were analysed. Detection levels of 0.1 and 0.01 $TCID_{50}$ of influenza A and B viruses and 1–10 molecules of cloned amplified products of influenza C virus, RSV A and B, and adenovirus serotype 1 were achieved.

Statistical analysis

Incidence and clinical characteristics of infections in preterm babies were compared with those associated to