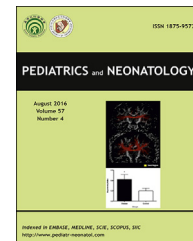


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Original Article

# Respiratory syncytial virus associated hospitalizations in children with congenital diaphragmatic hernia

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## Key Words

respiratory syncytial virus;  
congenital diaphragmatic hernia;  
respiratory tract infection;  
hospitalization

**Background:** To evaluate the risk of RSV infection in infants and children with congenital diaphragmatic hernia (CDH) over two consecutive RSV seasons.

**Methods:** Retrospective, single-center cohort study from southern Austria including infants with CDH born between 1993 and 2012. Infants were retrieved by searching via ICD-10 codes Q79.0 and Q79.1 and by using a local electronic database. Children were followed over 2 years of life including at least two consecutive RSV seasons (November to April). We also defined a group of hypothetical RSV infections with the following criteria: 70% of the admissions due to a respiratory infection (diagnosis of bronchiolitis and/or LRI score  $\geq 3$ ) during the RSV seasons over the first 2 years of life, when no test for RSV was performed.

**Results:** Twenty-nine of 45 infants with CDH comprised the study population (6 were lost to follow-up and 10 died) of whom 9 (31%) exhibited 17 hospitalizations due to respiratory illness. Two hospitalized infants (6.9% of the study population) tested RSV positive, one during the first and the other during the second RSV season. Nine of 29 infants (31%) had documentation of palivizumab prophylaxis, none (0%) had proven RSV hospitalization compared to 1 of 20 (5%) without prophylaxis during the first RSV season ( $p = 0.256$ ). Including the hypothetical cases, we calculated 0 of 9 (0%) in the palivizumab group and 4 of 20 (20%) in the group without prophylaxis ( $p = 0.079$ ).

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**Conclusions:** We found a moderate rate of proven RSV hospitalizations in infants with CDH, and palivizumab prophylaxis led to a non-significant reduction of proven and hypothesized RSV hospitalizations.

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## 1. Introduction

Morbidity due to respiratory syncytial virus (RSV) disease is still high in infants and children worldwide during the first 2 years of life. In recent years several rare diseases have been identified demonstrating high morbidity associated with RSV disease. These include children with malignancy, congenital and acquired immune deficiency, Down syndrome, neuromuscular impairment, cystic fibrosis, and congenital diaphragmatic hernia (CDH). Thus, the extension of guidelines for prophylaxis with palivizumab for these patients with special conditions has increasingly been discussed.<sup>1–3</sup>

The most common long-term complications observed in children after CDH repair are recurrent infections of the respiratory tract, lung hypoplasia, pathological gastrointestinal reflux, somatic growth abnormalities, and skeletal deformations.<sup>4</sup> Recurrent respiratory tract infections were observed in one third of children after CDH repair (on average six to eight times a year), and these children required synthetic patch placement during hernia repair, high frequency oscillation ventilation in the neonatal period, and prolonged artificial ventilation significantly more often.<sup>4</sup> A similar rate of 39% of frequent respiratory tract infections, which were alleviated with increasing age, was reported some years ago; additionally, comparable neonatal risk factors were found.<sup>5</sup>

There exists only one study focusing on the risk of RSV infection, which demonstrated a 23.8% rate of RSV infections in children with CDH (5 of 21 survivors with severe CDH) with three of them needing hospitalization (RSV hospitalization rate 14.3%) due to bronchiolitis during the follow-up period.<sup>6</sup> In two children the recurrence of CDH following RSV infection resulted in the need to perform a re-operation for CDH, and all three children needing hospitalization suffered from chronic wheezing requiring medication after the first RSV infection.

Eighty-six infants with CDH born in three French reference tertiary centers between January 2009 and March 2013 were identified and analyzed regarding the rate of hospitalization for wheezing.<sup>7</sup> In total, 116 wheezing episodes requiring a doctor's visit occurred in 50 infants (58%) before 24 months of age. RSV was present in 6 of 15 children (40%) with available nasal samples at first readmission and in 1 of 5 (20%) at second readmission. Thoracic herniation of the liver, low gestational age, longer initial hospitalization, the need for oxygen therapy at home, and eczema were all significantly associated with readmission for wheezing exacerbation. Fifty-three infants (62%) had received palivizumab prophylaxis, but the authors found no association with the overall rate of readmission for wheezing exacerbation or RSV-related hospitalization.

Due to the lack of data on RSV hospitalizations and on the effects of palivizumab prophylaxis in infants with CDH, the Delphi study concluded that further studies are needed to add evidence to the most frequent and clinically oriented scenarios including CDH.<sup>3</sup> Therefore, we aimed to evaluate the risk of RSV infection in infants with CDH over two consecutive RSV seasons by means of a retrospective cohort study including a long period.

## 2. Methods

All infants with a diagnosis of CDH born between January 1, 1993 and December 31, 2012 at the Department of Pediatrics of the Medical University Graz, a tertiary care center in the southern part of Austria, were included retrospectively for analysis. The study started in June 2014 following approval by the ethics committee of the Medical University of Graz (number 26–145 ex 13/14). We searched for CDH using ICD-10 codes Q79.0 and Q79.1 and in the local electronic database.

Children were all followed for 2 years including at least two consecutive RSV seasons from November to April according to long-term epidemiological data from Austria.<sup>8</sup> Children were excluded for analysis if they were lost to follow-up or in case of death during the first 2 years of life. Data were collected from the local electronic database openMedocs regarding gender, date of birth, gestational age, birth weight, and small for gestational age (defined as birth weight below the 10th percentile), month of discharge, location of CDH, neonatal course of disease, and history of palivizumab prophylaxis.

RSV hospitalization was defined as hospitalization associated with lower respiratory tract infection (LRTI) and a positive RSV test result. RSV testing was performed from nasopharyngeal aspirates using RSV-ELISA (Directigen EZ RSV Test, Becton Dickinson, USA; sensitivity 66.7–87.2%; specificity 85.5–91.6%). Data were collected regarding days of hospitalization due to respiratory illness, age at admission in months, month of RSV hospitalization, days of oxygen requirement, days in the intensive care unit (ICU), days of respiratory support (either nasal continuous positive airway pressure or mechanical ventilation). Severity of LRTI was measured using the modified lower respiratory illness/infection (LRI) score ranging from 1 to 5.<sup>9</sup> In detail 1 = upper respiratory tract infection, 2 = mild LRTI without respiratory distress (tachypnea, retractions), 3 = moderate LRTI with respiratory distress without oxygen demand, 4 = LRTI with oxygen demand, and 5 = assisted ventilation.

We also defined a group of hypothetical RSV infections with the following criteria: admission due to a respiratory infection (diagnosis of bronchiolitis and/or LRI score  $\geq 3$ ) during the RSV seasons over the first 2 years of life, when no

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