CHEST

Respiratory Exacerbations in Indigenous Children From Two Countries With Non-Cystic Fibrosis Chronic Suppurative Lung Disease/Bronchiectasis

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BACKGROUND: Acute respiratory exacerbations (AREs) cause morbidity and lung function decline in children with chronic suppurative lung disease (CSLD) and bronchiectasis. In a prospective longitudinal cohort study, we determined the patterns of AREs and factors related to increased risks for AREs in children with CSLD/bronchiectasis.

METHODS: Ninety-three indigenous children aged 0.5 to 8 years with CSLD/bronchiectasis in Australia (n = 57) and Alaska (n = 36) during 2004 to 2009 were followed for > 3 years. Standardized parent interviews, physical examinations, and medical record reviews were undertaken at enrollment and every 3 to 6 months thereafter.

RESULTS: Ninety-three children experienced 280 AREs (median = 2, range = 0-11 per child) during the 3-year period; 91 (32%) were associated with pneumonia, and 43 (15%) resulted in hospitalization. Of the 93 children, 69 (74%) experienced more than two AREs over the 3-year period, and 28 (30%) had more than one ARE in each study year. The frequency of AREs declined significantly over each year of follow-up. Factors associated with recurrent (two or more) AREs included age < 3 years, ARE-related hospitalization in the first year of life, and pneumonia or hospitalization for ARE in the year preceding enrollment. Factors associated with hospitalizations for AREs in the first year of study included age < 3 years, female caregiver education, and regular use of bronchodilators.

CONCLUSIONS: AREs are common in children with CSLD/bronchiectasis, but with clinical care and time AREs occur less frequently. All children with CSLD/bronchiectasis require comprehensive care; however, treatment strategies may differ for these patients based on their changing risks for AREs during each year of care. CHEST 2014; 146(3):762-774

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ABBREVIATIONS: ARE = acute respiratory exacerbation; CF = cystic fibrosis; CSLD = chronic suppurative lung disease; HRCT = high resolution CT

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Chronic suppurative lung disease (CSLD) and bronchiectasis unrelated to cystic fibrosis (CF)[1] are relatively common among indigenous children in both high- and low-income countries.[2-5] One in 68 indigenous children in central Australia[6] and one in 63 indigenous children in Alaska's Yukon Kuskokwim Delta[4] have bronchiectasis. In contrast, the prevalence in European children is one in 7,440 among those < 15 years of age.[7] CSLD and bronchiectasis are both characterized by chronic or recurrent "wet" cough, obstructive lung disease, and recurrent acute respiratory exacerbations (AREs).[8,9] AREs in people with bronchiectasis are associated with hospitalizations, declining lung function, and reduced quality of life.[10] They have also been used as outcome measures in therapeutic trials in adults[11] and children[12] with bronchiectasis. Thus, understanding factors associated with recurrent and severe AREs is important.

We conducted a longitudinal observational study from 2004 to 2009 of a cohort of indigenous children residing in Australia and Alaska with chronic wet cough who were diagnosed with CSLD or bronchiectasis. As part of that study, we compiled data about AREs on children before and after enrollment. The baseline clinical and socioeconomic features and upper airway microbiology of this group have been published previously.[13,14] The purpose of this report is to (1) characterize the pattern of AREs in this cohort of children over at least 3 years of observation and (2) identify clinical features that increased the risk of recurrent and severe AREs requiring hospitalization.

Materials and Methods

Study Participants

Australian Aboriginal and Alaska Native children, aged 0.5 to 8 years, with either bronchiectasis confirmed by high-resolution CT (HRCT)[2,15] scan or CSLD, defined by > 3 months of daily wet cough, were enrolled in the Multicentre Bronchiectasis Study in Australia and Alaska. In the Australian cohort, only children in the placebo arm of a randomized controlled trial nested within the larger study were included in this report.[12] The Australian and Alaska groups were studied concurrently, and definitions for inclusion were chosen a priori for observation during the 5-year period. Figure 1 depicts the enrollment process for eligible children, including those who underwent HRCT scans to diagnose bronchiectasis. Eligible children were identified and recruited sequentially as they presented to their regional pediatric or pulmonary clinics. Children were excluded if they (1) had an underlying cause of bronchiectasis (CF, primary ciliary dyskinesia, or immunodeficiency), (2) received treatment of cancer or diabetes, or (3) had a CNS or neuromuscular disorder that affected respiratory function. Children with at least 3 consecutive years of observation were included to characterize longitudinal trends in AREs.

Human ethics committees and institutional review boards of all participating institutions approved the study (e-Appendix 1). Parents and/or legal caregivers provided written informed consent.

Measurements

At enrollment, study staff interviewed the parent/guardian to obtain a sociodemographic and medical history. At each study encounter, a pediatric pulmonologist or pediatrician reviewed medical records, performed an interval history and physical examination, and updated a respiratory diagnosis. Participants were seen by research staff every 3 to 6 months. Information from birth to enrollment was obtained retrospectively and from enrollment to end of the study prospectively from medical records. Both study sites provided standard clinical care for participants and nonparticipants, which included antibiotics, chest clearance techniques, asthma therapy when indicated, parental smoking cessation advice, childhood immunizations, nutritional support, and management of exacerbating factors, such as gastroesophageal reflux disease and dysphagia.

As described previously,[12] AREs were defined as acute respiratory-related episodes requiring new antibiotic treatment for any of the following reasons: increased cough, dyspnea, increased sputum volume or color intensity, new chest examination or radiographic findings, deterioration in predicted FEV_1 by > 10%, or hemoptysis. We counted all clinical encounters within 2 weeks as a single ARE. If a second presentation occurred > 14 days after the first, two episodes were counted. All medically attended AREs were captured at community-based clinics and hospitals where participants received all of their medical care. Severe AREs were defined as those needing hospitalization for treatment.

Data Management and Statistical Analysis

Data were entered at each site into a password-protected study database on a secure website. A data manager conducted regular data checks and queries to ensure data completeness and accuracy. Study definitions and procedures were identical for both sites of the study. In addition, investigators and research nurses met regularly via teleconference to discuss study progress.

Data were analyzed using the Statistical Package for Social Science v.20 (IBM) and Stata Statistical Software v13.0 (StataCorp LP). We presented means with SDs for normally distributed data, medians with ranges for nonnormally distributed data, and proportions for categorical data. All statistical tests were two-tailed, with 95% CIs calculated where appropriate. Statistical significance was defined as $P < .05$. Outcomes with ARE count data were modeled using negative binomial regression with robust SEs. Main effects included in the model were as follows: (1) age at enrollment (< 3 and ≥ 3 years), (2) country of enrollment, and (3) wheeze present at first examination. Incidence rate ratios were reported.

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