Severe bronchiolitis profiles and risk of asthma development in Finnish children

Orianne Dumas, Riku Erkkola, Eija Bergroth, Kohei Hasegawa, Jonathan M Mansbach, Pedro A Piedra, Tuomas Jartti, Carlos A Camargo

Online repository

Severe bronchiolitis profiles and risk of asthma development in Finnish children

Orianne Dumas, PhD,[1] Riku Erkkola, MD,[2] Eija Bergroth, MD, [3,4] Kohei Hasegawa, MD,[5] MPH, Jonathan M Mansbach, MD, MPH,[6] Pedro A Piedra, MD,[7] Tuomas Jartti, MD,[2,8,9] Carlos A Camargo, Jr, MD, DrPH[5]

Author affiliations:

1. Université Paris-Saclay, UVSQ, Inserm, CESP, Equipe d'Epidémiologie Respiratoire Intégrative, 94807, Villejuif, France

2. Department of Children and Adolescents, Turku University Hospital and University of Turku, Turku, Finland

3. Department of Pediatrics, Kuopio University Hospital, Kuopio, Finland

4. Department of Pediatrics, Central Hospital of Central Finland, Jyväskylä, Finland

5. Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

6. Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA

7. Departments of Molecular Virology and Microbiology and Pediatrics, Baylor College of Medicine, Houston, Texas, USA

8. PEDEGO Research Unit, Medical Research Center, University of Oulu, Oulu, Finland

9. Department of Children and Adolescents, Oulu University Hospital, Oulu, Finland

Table of Contents

MATERIAL AND METHODS

Study design and data collection

The 30th Multicenter Airway Research Collaboration (MARC-30) Finland study is a prospective, multicenter cohort study of children hospitalized with bronchiolitis, which was run parallel to the primary MARC-30 study in the United States.[1,2] Both cohort studies were coordinated by the Emergency Medicine Network (EMNet; Boston, USA). Children were recruited from the pediatric wards or intensive care units of Kuopio, Tampere, and Turku University Hospitals during the winter seasons 2008 to 2010. The children were younger than 24 months on admission. The Institutional Ethical Board of Turku University Hospital approved the study. The institutional ethical boards of other participating hospitals confirmed this approval. The parents or guardians gave written informed consent to the study.

During hospitalization, the guardians were interviewed using a structured questionnaire, including demographic, environmental, and medical history. Clinical data on the acute illness were also collected. Researchers collected nasopharyngeal aspirates on hospitalization by using a standardized protocol. Testing was performed for a large panel of respiratory tract viruses by using real-time PCR assays.[1,2] Of 564 eligible children with bronchiolitis, 410 (73%) were enrolled. Two enrolled subjects were excluded from all analyses because of incomplete data, leaving a total of 408 subjects in the analytical cohort.

Follow-up of the children was conducted through different methods: parent questionnaire/interviews combined with review of medical records four to five years after hospitalization, and linkage to a national social insurance database (Kela) seven to nine years after hospitalization, as detailed below.

Four to five years after hospitalization, study questionnaires, including partially modified questions from the International Study of Asthma and Allergy in Childhood,[3] were sent to all

participants (4-year follow-up).[4] If the parents did not respond within 6 months, participants were contacted by telephone and interviewed. Data on respiratory symptoms and asthma medication since index hospitalization were collected. If regular prescription or use of inhaled corticosteroids or leukotriene receptor antagonists ever was reported (positive answer to the question "In the previous 12 months, was your child prescribed a regular controller medication for recurrent wheezing or prolonged cough or asthma?"), the patient's files (ie, hospital records or inquiries sent to private sector pediatricians) of reported medical encounters were reviewed for the exact prescription time of medication.

Seven to nine years after hospitalization, MARC-30 Finland data were linked to the Finnish Social Insurance Institution of Finland (Kela) database (7-year follow-up).[5] Briefly, this database records benefits including discount from drug purchase, which can be applied to children who have had continuous asthma medication for 6 months, and need to continue treatment. Asthma-related benefits and drug purchase were evaluated at the time of the child's 7th birthday.

More specifically, the diagnosis and Kela special reimbursement criteria for asthma are described as follows (https://www.kela.fi/laake203): "Asthma of school age (7 years and older) children is diagnosed based on the same criteria as adults. The diagnoses of children under 7 years should be confirmed with pulmonary function tests. The pulmonary function testing is usually successful in children aged 5 years or older. The pulmonary function test results must be presented in the medical certificate. The diagnosis of asthma in children under 3 years of age is based on the symptoms and clinical findings. In small children, findings indicative of asthma are: recurrent expiratory wheezing, recurrent dyspnoea, and alleviation of symptoms with the use of bronchodilators. Characteristics supporting the diagnosis of asthma are the need of bronchodilators more than twice a week and recurrent asthma exacerbations requiring increase in medication at least every six weeks. For small children with physician-confirmed recurrent

dyspnoea 2–3 times a year, a clinical index based on the risk factors may be used to support the asthma diagnosis. The probability of asthma is increased in the presence of one primary criterion or two secondary criteria. The primary criteria are: 1) maternal or paternal asthma, 2) physician-confirmed atopic eczema, 3) IgE-mediated food allergy. The secondary criteria are: 1) physician-confirmed allergic rhinitis, 2) expiratory wheezing without infection, 3) eosinophilia (blood eosinophil percentage >4%). If the dyspnoea recurs at least 4 times a year, the regular anti-inflammatory pulmonary medication is indicated. In small children, special methods (oscillometry for example) indicating alternating bronchial obstruction, or special methods indicating elevated expiratory nitrogen indicating eosinophilic respiratory inflammation may provide additional information supplementing the evaluation. In order to be granted the special reimbursement entitlement the patient is required to have used anti-inflammatory pulmonary medication for 6 months."

Bronchiolitis profiles at baseline

Bronchiolitis profiles at baseline were determined by using latent class analysis (LCA) based on medical history, clinical course of bronchiolitis, and viral etiology, as described earlier.[6] Three bronchiolitis profiles were identified and were labelled 'A', 'BC' and 'D', to match with profiles identified in a similar cohort in the US (MARC-30 US, four profiles identified: 'A', 'B', 'C' and 'D'). Briefly, profile A was characterized by history of wheezing, history of eczema, wheezing at the ED presentation and rhinovirus infection. Profile BC was characterized by a low probability of children with history of wheezing or eczema, indicators of severe illness (inadequate oral intake, hospital length of stay ≥3 days) and RSV infection. Profile D was the least severely ill group and included mostly children without wheezing at ED presentation and who tended to have rhinovirus infection.

Main outcomes and clinical definitions

Current asthma at 4-year follow-up was defined as the prescription of regular asthma control medication (inhaled corticosteroids or leukotriene receptor antagonists) in the past 12 months, based on parental report and review of medical records. Current asthma at 7-year follow-up was defined as current benefit recorded in Kela database with repeated purchase of asthma control medication in the past 12 months.

Statistical analyses

Associations between bronchiolitis profiles and current asthma at 4-year and 7-year follow-ups were evaluated by using logistic regression. Main models were adjusted for age and sex. Secondary models were further adjusted for number of siblings at home, exposure to environmental tobacco smoke, maternal smoking during pregnancy, gestational age and breastfeeding, and accounted for a potential center effect (patient clustering at the hospital level) A 2-sided P-value of less than .05 was considered statistically significant.

References

1. Mansbach JM, Piedra PA, Teach SJ, Sullivan AF, Forgey T, Clark S, et al. Prospective multicenter study of viral etiology and hospital length of stay in children with severe bronchiolitis. Arch Pediatr Adolesc Med. 2012;166:700–6.
2. Jartti T, Aakula M, Mansbach JM, Piedra PA, Bergroth E, Koponen P, et al. Hospital length-of-stay is associated with rhinovirus etiology of bronchiolitis. Pediatr Infect Dis J. 2014;33:829–34.
3. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International study of asthma and allergies in childhood (ISAAC): Rationale and methods. Eur Respir J. 1995;8:483–91.
4. Bergroth E, Aakula M, Elenius V, Remes S, Piippo-Savolainen E, Korppi M, et al. Rhinovirus Type in Severe Bronchiolitis and the Development of Asthma. J Allergy Clin Immunol Pract. 2020;8:588-595.e4.
5. Sonninen K, Jyrkkä J, Martikainen JE, Malmström K, Mäkelä MJ, Sepponen K. Age-related off-label use of nasal corticosteroids for allergies is relatively common in Finnish children with asthma. Acta Paediatr Int J Paediatr. 2017;106:1830–6.
6. Dumas O, Hasegawa K, Sullivan AF, Piedra PA, Camargo CA Jr. A clustering approach to identify bronchiolitis profiles among children hospitalized with bronchiolitis. Thorax. 2016;71:712–8.