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Risk of asthma in children diagnosed with bronchiolitis during infancy: Protocol of a longitudinal cohort study linking emergency department-based clinical data to provincial health administrative databases

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ABSTRACT

Introduction The Canadian Bronchiolitis Epinephrine Steroid Trial (CanBEST) and the Bronchiolitis Severity Cohort (BSC) study enrolled infants with bronchiolitis during the first year of life. The CanBEST trial suggested that treatment of infants with a combined therapy of high-dose corticosteroids and nebulised epinephrine reduced the risk of admission to hospital. Our study aims to—(1) quantify the risk of developing asthma by age 5 and 10 years in children treated with high-dose corticosteroid and epinephrine for bronchiolitis during infancy, (2) identify risk factors associated with development of asthma in children with bronchiolitis during infancy, (3) develop asthma prediction models for children diagnosed with bronchiolitis during infancy.

Methods and analysis We propose a longitudinal cohort study in which we will link data from the CanBEST (ISRCTN56745572, post-results) and BSC study with routinely collected data from provincial health administrative databases. Our outcome is asthma incidence measured using a validated health administrative data algorithm. Primary exposure will be treatment with a combined therapy of high-dose corticosteroids and nebulised epinephrine for bronchiolitis. Covariates will include type of viral pathogen, disease severity, medication use, maternal, prenatal, postnatal and demographic factors and variables related to health service utilisation for acute lower respiratory tract infection. The risk associated with development of asthma in children treated with high-dose corticosteroid and epinephrine for bronchiolitis will be assessed using multivariable Cox proportional hazards regression models. Prediction models will be developed using multivariable logistic regression analysis and internally validated using a bootstrap approach.

Ethics and dissemination Our study has been approved by the ethics board of all four participating sites of the CanBEST and BSC study. Finding of the study will be disseminated to the academic community and relevant stakeholders through conferences and peer-reviewed publications.

Strengths and limitations of this study

- Our study provides an opportunity to specifically examine whether treatment of infants with bronchiolitis with combined high-dose corticosteroids and nebulised epinephrine reduces the risk of future asthma.
- Linkage of data from clinical studies to health service utilisation data may provide objective, prospectively collected measures and outcomes that are free of recall bias and minimise loss to follow-up and data missingness.
- Diagnosis of asthma using health service utilisation data is a proxy method, but we will use a validated health-administrative algorithm for the detection of asthma.

INTRODUCTION

A multitude of controlled follow-up studies has established that viral bronchiolitis during infancy is associated with on-going respiratory morbidity. Infants with bronchiolitis have an increased risk of developing wheeze-associated disorders, including asthma, in later life.^{1,2} Respiratory syncytial virus (RSV) is the most common aetiological agent detected in infants with bronchiolitis.³ Studies have shown 20%–54% of infants with bronchiolitis develop asthma.^{4–12} A multivariate evaluation of possible risk factors for asthma showed that RSV bronchiolitis during infancy had the highest independent OR for asthma (OR: 12.7, 95% CI 3.4 to 47.1).¹ However, a more recent systematic review has reported that this association may not be causal.¹³ This association appears most pronounced during the first 5 years of life but may extend up to



10 years of age.^{114–16} The mechanism through which RSV contributes to asthma is not fully understood but appears to relate to the viral injury, disease severity, pre-existing abnormal lung function, genetic susceptibility, altered immunology and environmental factors.¹¹³

A number of risk factors have been found to be associated with the development of asthma among children with a history of bronchiolitis in early life. These include the child's clinical course of bronchiolitis (severity of illness and viral pathogen), prenatal (maternal asthma control and smoking during pregnancy) and postnatal factors (prematurity, congenital heart disease, pre-existing impaired lung function, personal history of atopy) and early childhood (breastfeeding, daycare attendance), parental (family history of atopy and asthma), household (moisture, dust, mite, tobacco smoke) and demographic factors (men, lower socioeconomic status, immigrant status).^{12 17 18} In addition to these, the pattern of health service utilisation by children during their preschool years and the services they receive for prevention of respiratory disorders during the first 2 years of life may also be associated with later development of asthma.¹⁹

It has been postulated that the immune response followed by viral bronchiolitis may induce long-lasting detrimental effects and contribute to postbronchiolitis wheezing and asthma.^{20–23} For example, severe RSV bronchiolitis in young infant may shift the T-helper (Th)1/Th2 balance in favour of a Th2 cytokine pattern, leading to development of allergic sensitisation and persistent asthma.⁴²⁴ As a result, it has been suggested that immunomodulating drugs such as corticosteroids might prevent the development of asthma.^{25 26} Most follow-up studies in bronchiolitis, however, have found no association between corticosteroid use and the degree of respiratory sequelae after bronchiolitis.^{25–28} However, these studies primarily examined admitted patients who may have had more severe disease and were at a later stage in the disease process. The majority of studies also had relatively small samples and were likely underpowered to detect possible beneficial effects. Importantly, corticosteroids alone appear to have no immediate benefit in the treatment of bronchiolitis^{27–29} and, thus, are not recommended for the treatment of bronchiolitis.^{30–33}

The Canadian Bronchiolitis Epinephrine Steroid Trial (CanBEST)²⁹ and the Bronchiolitis Severity Cohort (BSC)³⁴ study enrolled infants with bronchiolitis during their first year of life. These studies have established a bronchiolitis cohort where detailed clinical data, including the management and clinical outcomes for infants with bronchiolitis, are known. Results from the CanBEST trial suggested that the combined therapy of high-dose corticosteroids and nebulised epinephrine may reduce admissions to hospital for children with bronchiolitis through a synergistic effect between the two medications.²⁹ Basic science evidence supports a synergistic effect of corticosteroid and epinephrine in modulating the immune system through several mechanisms: (1) β_2 -adrenoceptor agonists synergistically

upregulate mRNA production of anti-inflammatory genes by enhanced translocation of the glucocorticoid receptor into the nucleus^{35 36} and (2) corticosteroids enhance and markedly extend upregulation of mRNA for regulation of G-protein signalling 2 by β_2 -adrenoceptor agonists.³⁷ Clinical studies in asthma have also demonstrated that combined administration of high-dose corticosteroid and epinephrine results in anti-inflammatory and bronchoprotective effects that are unachievable by either drug alone.³⁶³⁷ Given the potential benefit seen in the acute management of bronchiolitis and the clinical and basic science evidence of true synergy between beta-agonists and corticosteroids, it is important to examine whether any longer term benefit of such treatment in acute phase bronchiolitis exists.

Early identification of children who later develop asthma may improve their quality of life by appropriate preventive measures, regular monitoring and appropriate drug treatment.³⁸ Predictive models have been shown to help physicians to identify asthma, particularly in children under 5 years.^{39–41} However, the majority of these prediction models have targeted children in the general population rather than children with bronchiolitis per se.^{41 42} There is evidence to suggest that simple clinical parameters, such as—age, sex, history of atopy, family history of asthma and early frequent wheezing during the first 3 years of life, can identify children at high risk of developing asthma by age 6, specifically in children diagnosed with RSV bronchiolitis during infancy.⁴³ In addition, the level of healthcare utilisation during the bronchiolitis episode has been found to correlate with the risk of subsequent asthma, with the greatest risk of asthma following bronchiolitis hospitalisation.^{44–46} A study has shown that children who develop asthma have high intensity health service utilisation during preschool years.⁴⁷

Our proposed study aims to link CanBEST and BSC data to provincial health administrative databases (HAD). The unique combination of these data sources can provide objective, prospectively collected measures and outcomes that are free of recall bias. Moreover, it minimises loss to follow-up and data missingness, as individuals are consistently followed in HAD. This study will allow us to examine the long-term effect of high-dose corticosteroid and epinephrine treatment on the respiratory health of children diagnosed with bronchiolitis during infancy as well as develop the most parsimonious asthma prediction models specifically for children diagnosed with bronchiolitis during infancy. Our three objectives are:

Objective 1: to quantify the risk of developing asthma by age 5 and 10 years in children treated with high-dose corticosteroid and epinephrine for bronchiolitis during infancy.

Objective 2: to identify risk factors associated with the development of asthma in children diagnosed with bronchiolitis during infancy.

Objective 3: to develop asthma prediction models for children diagnosed with bronchiolitis during infancy.

METHODS

Study design

We will conduct a longitudinal cohort study by linking clinical data from two emergency department (ED)-based bronchiolitis studies (CanBEST and BSC) with routinely collected HAD.

Study population

Our study will include children recruited from Ontario and Alberta sites of the CanBEST and BSC study (all sites are members of the research collaboration Pediatrics Emergency Research Canada). CanBEST and BSC study recruited participants from paediatric EDs from 2004 to 2007 (CanBEST, N=720; BSC, N=724). Inclusion criteria for this study are children who were diagnosed with bronchiolitis at age ≤ 12 months and participated in the CanBEST or BSC study (inclusion and exclusion details of CanBEST and BSC study available elsewhere).^{29 34} Exclusion criteria are subjects without a valid Ontario or Alberta health card number for data linkage, subjects without an ON or AB residence code (at the time of enrolment into the trial) or those who could not be linked.

Data sources

Clinical data: a bronchiolitis cohort will be created by pooling data from the CanBEST and BSC study. CanBEST was a multicentre, double-blind, placebo-controlled randomised trial in which infants with bronchiolitis were enrolled from nine paediatric EDs across Canada.²⁹ For our proposed study, data from four sites in two provinces will be used and linked (total sample size 720; Ontario sites: Children's Hospital of Eastern Ontario, Ottawa, and Children's Hospital London Health Sciences Centre, London; Alberta sites: Alberta Children's Hospital, Calgary and Stollery Children's Hospital, Edmonton). In CanBEST, participants were randomly assigned to one of four intervention groups. Group 1: epinephrine—high-dose oral corticosteroid, group 2: epinephrine, group 3: high-dose oral corticosteroid and group 4: placebo. Total follow-up was 22 days after enrolment in the study and the primary outcome was hospital admission up to 7 days after enrolment. The BSC study cohort (total sample size for Ontario and Alberta 724) included infants with bronchiolitis who were either ineligible for CanBEST or those who did not consent to participation in CanBEST.³⁴ The baseline data for both studies included clinical, demographic, historical and environmental data. Follow-up data for children in CanBEST included laboratory investigation for viral pathogen, admission to hospital, length of hospital stay and intensive care unit (ICU) admission. The BSC study children received treatment for bronchiolitis following standard guidelines with treatments and outcomes recorded. These data are currently housed in a repository in Ontario, at the Children's Hospital of Eastern Ontario, Ottawa.

Health administrative data: in Ontario, data from the bronchiolitis cohort described above will be linked to six Ontario-based HAD housed and accessible through ICES.

ICES is an independent non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyse healthcare and demographic data, without consent, for health system evaluation and improvement. The following databases will be used: (1) Ontario Health Insurance Plan database, which contains information on all fee-for-service billings for physician services rendered, (2) National Ambulatory Care Reporting System database (NACRS), which contains data for hospital-based and community-based emergency and ambulatory care, (3) Ontario Registered Persons Database, which includes information on demographics and on the time period for which each participant was eligible to receive publicly funded provincial healthcare, (4) Discharge Abstract Database (DAD), which provides information on all acute care hospitalisations; (5) Ontario Asthma Surveillance Information System (OASIS), a validated registry that uses administrative databases to identify and follow individuals with asthma; and (6) MOMBABY database, which contains information from hospital admission records for mothers linked with their newborns at the time of birth. In Alberta, the bronchiolitis cohort will be linked to provincial HAD housed at and accessible through the Enterprise Data Warehouse, maintained by Alberta Health Services (AHS) Analytics. The Enterprise Data Warehouse contains the CIHI DAD, NACRS, Alberta physician claims and Alberta Pharmaceutical Information Network. AHS Analytics has created coding that creates a linked data set of all Alberta mothers and their infants from FY 2002/2003 up to present day. Children's health service utilisation data will be drawn from this linked data set of all Alberta mothers and their infants.

Data linkage and transfer

Individual records from the bronchiolitis cohort will be deterministically linked to HAD within each province. In Ontario, we will use the unique Ontario health insurance number for linkage and access to data housed at ICES. In Alberta, the Alberta Unique Lifetime Identifier will be used to link and access data in Alberta-based HAD housed in the Enterprise Data Warehouse, AHS. In Alberta, the data set created for these patients will be deidentified and transferred via Services Secure File Transfer Protocol to the secure analytical environment at ICES to create a combined two-province study data set. The linked data sets from the two provinces will then be pooled within the secure analytical environment at ICES to create an Integrated Pediatric Health Data Repository (see online supplemental file 1). While we anticipate a high success rate of linking the bronchiolitis clinical data sets to HAD, it is possible that some children may not be matched due to unavailability of health card number. If we identify a significant number of patients with an unavailable health card number, we will use a probabilistic approach for these patients to link their bronchiolitis clinical trial data to HAD.

Data storage and analysis

Once the data have been transferred and linked, it will be retained in the secure environment of ICES. ICES will assign an ICES key number (IKN) for each subject in the linked database. Only the IKN will be provided in the data set containing the various variables for analysis, the Ontario health card number will not be provided. Data analysis will be performed through ICES Data & Analytic Services.

Outcome measures and predictors

Outcome measure

Our *primary outcome* is the cumulative incidence of asthma by age 5 and 10 years. We will define asthma using a validated health administrative case definition, which has been shown to have 89% sensitivity and 72% specificity to identify asthma in children aged 0–17 years.^{48 49} Previous studies have used this case definition to identify asthma in the paediatric population,^{18 50} and it has also been used by the Canadian Chronic Disease Surveillance System to identify asthma cases from provincial HAD that includes Ontario and Alberta.⁵¹

Covariates

Important covariates (all measured in CanBEST and BSCS) will include clinical risk factors: gestational age at birth, birth weight, age at bronchiolitis diagnosis, infant sex, personal history of atopy, maternal and family history of asthma, smoking exposure (maternal and environmental), breastfeeding, daycare attendance, respiratory distress assessment index (RDAI), receipt of RSV immunoglobulin, presence of comorbidities, type of viral pathogen, disease severity (based on hospital admission or ICU admission) and type and dosage of medications. Socioeconomic status will be measured using the Canadian/Ontario marginalisation index.⁵² We will use HAD to measure: respiratory-related health service use (number of hospitalisations, ED or physician office visits) for acute lower respiratory tract infections (LRTI), total days of hospital admission for acute LRTI and receipt of primary immunisations. Counts for respiratory-related health service use will be accrued from the time the child is diagnosed with bronchiolitis until reaching 2 years of age.

Approaches and analysis

Objective 1: quantify the risk of developing asthma by age 5 and 10 years in children treated with high-dose corticosteroid and epinephrine for bronchiolitis during infancy.

1. Risk estimation: risk of asthma by age 5 and 10 years will be assessed by comparing children diagnosed with bronchiolitis who received high-dose corticosteroid and epinephrine (exposed group, N=180) to those who did not receive high-dose corticosteroid and epinephrine for treatment of bronchiolitis (nonexposed group, N=1050). The nonexposed group will comprise: (1) children in CanBEST who received only epinephrine or only placebo as treatment and (2) children in the BSC study (none of whom received high-dose corticosteroid treatment). To determine incident asthma

by age 5 and 10 years (the primary outcome) of these children, their health service utilisation record will be followed through the HADs. Asthma incidence will be ascertained when the child is of 2 years of age.

2. Statistical analysis: the unadjusted effects of high-dose corticosteroid and epinephrine on later asthma development will be assessed using Cox proportional hazards regression analysis. Because treatment assignment will be nonrandom, we will compare outcomes after controlling for clinical and health service utilisation-related factors using multivariable adjustment analysis. For our risk-adjusted comparison, multivariable Cox proportional hazards regression modeling will be performed to determine the effect of high-dose corticosteroid and epinephrine after simultaneously adjusting for prespecified risk factors. Adjusted HR with 95% CI will be generated to estimate the effect of high-dose corticosteroid and epinephrine. Since asthma incidence has been shown to decrease with age, we plan to perform separate analyses for diagnosis of asthma by age 5 and 10 years.¹

Objective 2: identify risk factors associated with development of asthma by age 5 and 10 years in children diagnosed with bronchiolitis during infancy.

1. Probable risk factors include clinical factors: age at diagnosis of bronchiolitis, sex, RDAI score on ED presentation with bronchiolitis, receipt of RSV immunoglobulin, presence of comorbidities, specific viral pathogen, disease severity (based on hospital admission or ICU admission); early childhood factors (breastfeeding and daycare); environmental factors (tobacco smoke at home); sociodemographic factors and health service utilisation-related factors: respiratory-related health service use (number of hospitalisations, ED or physician office visits) in the 2-year period following bronchiolitis for acute LRTI, total days of hospital admission for acute LRTI and receipt of primary immunisations by age 2 years.

2. Statistical analysis: multivariable Cox proportional hazards regression analysis will be performed to identify significant covariates. Risk estimate of covariates will be presented as adjusted HR with 95% CI.

Objective 3: develop asthma prediction models for children diagnosed with bronchiolitis during infancy.

1. Prediction modelling: models predicting asthma at age 5 and 10 will be generated using multivariable logistic regression analysis. A forward stepwise method (with entrance tolerances of 0.05) will be used to determine significant predictors for inclusion in the regression models. Collinearity and correlation will be analysed before model fitting. We will internally validate our models and assess their predictive accuracy by discrimination (area under the curve) and calibration (by plotting observed vs predicted number of outcomes). Internal validation will be performed using bootstrapping method.⁵³ Potential clinical predictors: age < 6 months at diagnosis of bronchiolitis, sex, high RDAI score on ED presentation with bronchiolitis, receipt

of RSV immunoglobulin, presence of comorbidities such as congenital heart disease, presence of RSV viral pathogen, severe disease (based on hospital admission or ICU admission), breastfeeding <3 months, no daycare attendance, tobacco smoke at home and low socioeconomic status. Potential health service utilisation-related predictors: volume of respiratory-related health service use (number of hospitalisations, ED or physician office visits) for acute LRTI >7 days of hospital admission for acute LRTI and complete receipt of primary immunisations by age 2 years.

2. Comparison between models developed using only clinical predictors to those developed using both clinical and health service utilisation-related predictors: we will compare the incremental performance of models developed using only clinical variables to those developed using both clinical and health service utilisation-related variables. Incremental improvement in outcome prediction will be determined by examining the change in the area under the receiver–operating characteristic curve, net reclassification index and integrated discrimination improvement.⁵⁴

Study power

Objective 1: risk of developing asthma by age 5 and 10 years in children treated with high-dose corticosteroid and epinephrine for bronchiolitis during infancy. Evidence has shown in children diagnosed with bronchiolitis during infancy, the proportion of children with asthma between the ages of 5 and 10 years to range from 20% to 54%.^{4–12} With 180 subjects in the exposed group (total number of children who received combined therapy of high-dose corticosteroid and epinephrine in CanBEST) and a minimum of 180 subjects in the nonexposed group and assuming an asthma proportion of 35% in the nonexposed group, we will have >80% power to detect an absolute difference in proportion of at least 14% between the exposed and nonexposed group. A sensitivity analysis showing the power for varying proportions of children with asthma in the exposed group is included in online supplemental file 2.

Objective 3: develop asthma prediction models for children diagnosed with bronchiolitis during infancy. We will use data from CanBEST and BSCS studies (N=1440). A well-used ‘rule of thumb’ for multivariable prediction model sample size is to ensure at least 10 outcome events per predictor before selection of the model. We will follow criteria set by Riley *et al* to account for minimum overfitting of data.^{55 56}

PATIENT AND PUBLIC INVOLVEMENT

Patients were not involved in the development of the study research question, outcome methods or design of the study and will not be involved in the conduct of the study.

ETHICS AND DISSEMINATION

We have received ethics approval of our study from all four sites of the study. ICES is an independent, nonprofit research

institute whose legal status under Ontario’s health information privacy law allows it to collect and analyse healthcare and demographic data, without consent, for health system evaluation and improvement. As part of our integrative knowledge translation plan, we have consulted clinicians across the spectrum of paediatric care in the development of the study and will continue this consultation at key stages of the study (eg, evaluating results). Our end-of-grant knowledge translation plan includes dissemination of study findings to the academic community, relevant stakeholders and to the public through presentations at international paediatric, emergency medicine and respirology meetings and publication in peer-reviewed journals.

DATA DISPOSITION

The data set from this study will be held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS. The full data set creation plan and underlying analytic code will be available from the authors on request, understanding that the computer programs may rely on coding templates or macros that are unique to ICES and, therefore, either inaccessible or may require modification.

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Correction notice This article has been corrected since it was published. The trial registration number has been removed from the Abstract as it relates to CanBEST study mentioned under Methods and analysis section of Abstract and not the main article.

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Collaborators Pediatric Emergency Research Canada: Terry P Klassen; Andrew Dixon; Troy Turner and Rhonda Correll

Contributors KA and ACP co-designed the study, scientific content, obtained funding, developed protocol and study materials, obtained necessary approvals for the study and critically revised this manuscript. DBF and DR contributed to the design, scientific content, contributed to grant application development and review of the manuscript. SH contributed to statistical planning. DWJ, PM, TT, GJ contributed to review of the manuscript.

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