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Canadian infants presenting with Brief Resolved Unexplained Events (BRUEs) and validation of clinical prediction rules for risk stratification: a protocol for a multicentre, retrospective cohort study

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ABSTRACT

Introduction Brief Resolved Unexplained Events (BRUEs) are a common presentation among infants. While most of these events are benign and self-limited, guidelines published by the American Academy of Pediatrics inaccurately identify many patients as higher-risk of a serious underlying aetiology (positive predictive value 5%). Recently, new clinical prediction rules have been derived to more accurately stratify patients. This data were however geographically limited to the USA, with no large studies to date assessing the BRUE population in a different healthcare setting. The study's aim is to describe the clinical management and outcomes of infants presenting to Canadian hospitals with BRUEs and to externally validate the BRUE clinical prediction rules in identified cases.

Methods and analysis This is a multicentre retrospective study, conducted within the Canadian Paediatric Inpatient Research Network (PIRN). Infants (<1 year) presenting with a BRUE at one of 11 Canadian paediatric centres between 1 January 2017 and 31 December 2021 will be included. Eligible patients will be identified using diagnostic codes. The primary outcome will be the presence of a serious underlying illness. Secondary outcomes will include BRUE recurrence and length of hospital stay. We will describe the rates of hospital admissions and whether hospitalisation was associated with an earlier diagnosis or treatment. Variation across Canadian hospitals will be assessed using intraclass correlation coefficient. To validate the newly developed clinical prediction rule, measures of goodness of fit will be evaluated. For this validation, a sample size of 1182 is required to provide a power of 80% to detect patients with a serious underlying illness with a significance level of 5%.

Ethics and dissemination Ethics approval has been granted by the UBC Children's and Women's Research Board (H21-02357). The results of this study will be disseminated as peer-reviewed manuscripts and presentations at national and international conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will be the largest to describe the Brief Resolved Unexplained Events (BRUE) population outside of the USA, and the first in a Canadian setting, including the prevalence of serious underlying etiologies in this population.
⇒ This study will allow the generalisability of the findings observed by the BRUE Quality Improvement and Research Collaborative (BRUE-QIRC) beyond the US healthcare system.
⇒ The study will provide the first external validation of the BRUE clinical prediction rules outside the cohort from where the rules were derived.
⇒ By identifying practice patterns, trends and clinical outcomes across Canada, we can provide a basis to identify areas of improvement (ie, practice standardisation and reduction of unnecessary admission or investigations).
⇒ Limitations of this study include its retrospective design with a reliance on the interpretation of medical record documentation. The heterogeneity of serious underlying diagnoses identified in the cohort may preclude the identification of the association of risk factors with a specific disorder (eg, airway abnormality and abnormal breathing pattern).

INTRODUCTION

Infants under the age of 1 year commonly exhibit brief events associated with changes in their breathing pattern, tone and colour, or level of consciousness.[1] Most of these events are benign and self-limited, however they can be quite concerning for parents.[2–4] In 2016, the American Academy of Padiatrics (AAP) provided guidelines on the management of these events, and coined a more specific term

Brief Resolved Unexplained Events (BRUEs).[5] BRUEs were defined as a resolved event involving one or more of (1) cyanosis or pallor, (2) apnoea or irregular respirations, (3) change in tone or (4) altered level of consciousness, with no clinical explanation after a full history and physical examination. To meet criteria, the infant must be back to their baseline by the time of evaluation by a medical professional. The AAP clinical practice guidelines stratified infants presenting with BRUE as lower-risk and higher-risk. A patient is considered at a lower-risk if they fulfil all of the following: (1) age>60 days; (2) gestational age≥32 weeks and corrected to ≥45 weeks; (3) event<1 min; (4) a history of only one event, with (5) no cardiopulmonary resuscitation (CPR) administered and (6) no concerning features on history or (7) physical examination. The guidelines provided recommendations for the evaluation and management of patients considered at a lower-risk, and deferred the management of higher-risk patients to individual providers, due to the lack of evidence.[5] For the lower-risk BRUE group, the AAP guidelines recommended against extensive laboratory investigations, consultation or hospital admissions for cardiorespiratory monitoring. They instead recommended a focus on patient and family-centred care and the use of a shared decision making model to inform care.[5]

Following the publication of the AAP guidelines, studies showed that while the majority of infants presenting with a BRUE (87%–92%) met at least one higher-risk criteria, only a small proportion have a serious underlying diagnosis (4%).[2 6–8] Analysis of the AAP criteria identified a history of a similar event, event clusters, CPR use and abnormal medical history to be associated with a serious underlying diagnosis. Meanwhile, patients younger than 60 days were less likely to have a serious diagnosis identified.[8] Given the lack of recommendations for patients meeting higher-risk criteria, and who represent the majority of the BRUE population, clinicians may feel inclined to admit these patients and perform multiple tests to rule out a serious underlying process, despite what is now understood to be of low likelihood. In addition to inflicting psychological stress on caregivers and unnecessary harm to the infant, the admission of otherwise well infants for diagnostic clarity and management is associated with significant healthcare costs (mean USD$15 409).[9]

In 2018, 15 children's hospitals across the USA convened to create BRUE Quality Improvement and Research Collaborative (BRUE-QIRC) network.[6–8 10 11] Using an administrative database (Pediatric Health Information System), the collaboration was able to retrospectively identify the largest cohort of patients with BRUE described to date (n=3283). The collaborative developed and validated an approach to identifying BRUE patients based on diagnostic codes.[10] Furthermore, they were able to describe the cohort's characteristics,[6] any identified diagnoses[7] and the yield of diagnostic testing in this population.[11] Work by the BRUE-QIRC demonstrated the AAP guidelines have a 98% negative predictive value (NPV) for identifying a serious underlying medical condition, but only had a 5% positive predictive value (PPV).[8] This highlighted the need for a new validated clinical prediction rule to more accurately identify patients presenting with a BRUE at higher-risk of recurrent events or serious underlying diagnosis.[12] Based on these findings, the BRUE-QIRC has recently derived and validated such clinical prediction rules that considered patient and BRUE characteristics to predict recurrence or serious diagnosis.[8] Compared with the current AAP guidelines, the derived rules showed better discrimination (area under the curve (AUC) of 0.68 vs 0.54). Instead of relying on one cut-off for defining lower-risk and higher-risk groups, the rules offered families and clinicians a shared decision-making tool to decide on the next steps in management based on their risk tolerance.

While the study was large, it was geographically limited to the USA.[8] No large studies to date have assessed the BRUE population outside of the USA, particularly since the publication of the new 2016 AAP guidelines. Previous reports targeting bronchiolitis, gastroenteritis or traumatic brain injuries have identified variability in the rate of admissions and diagnostic testing between the USA and other countries, particularly Canada.[13–18] As such, studies conducted in different healthcare settings are required to generalise the findings observed by the BRUE-QIRC.

The proposed study aims to describe the population of children presenting with a BRUE to Canadian hospitals, where the healthcare system is significantly different from the USA (eg, public vs privately funded healthcare). This multisite retrospective cohort study will additionally provide the first external validation of the BRUE clinical prediction tools outside of the cohort from where the rules were derived. Furthermore, by identifying practice patterns, trends and clinical outcomes across Canada, we can provide a basis to identify areas of improvement (ie, practice standardisation and reduction of unnecessary admission or investigations).[19]

METHODS AND ANALYSIS

Study design

This multisite retrospective cohort study will use hospital health records as the data source. This study will be conducted at 11 sites within the Canadian Paediatric Inpatient Research Network (PIRN), which includes 19 children's and community hospitals across Canada.[20] Potentially eligible participants will be identified first using administrative data based on their admission or discharge diagnoses. Eligibility will then be determined by whether the patient meets the AAP criteria for BRUE after review of the medical record. The clinical prediction rules will then be retrospectively applied to these eligible infants for risk stratification and correlated to outcomes. The description of the cohort will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort

studies.[21] Validation of the clinical prediction rules will be reported according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[22]

Time period

This study will include patients presenting to the emergency department (ED) between 1 January 2017 and 31 December 2021 inclusive. This timeframe is based on the 5-year period following the publication of the AAP guideline on BRUE in May 2016.[5] Charts will be reviewed until 31 March 2022 inclusive, which allows monitoring for clinical outcomes up to 90 days from presentation, for a patient presenting on the last day of the eligibility window.

Inclusion criteria

Eligibility criteria were adapted from the BRUE-QIRC study.[6] Patients will be included if they are an infant (<365 days old) who experienced an event which the observer describes as a sudden, brief and now-resolved episode involving one or more of (1) cyanosis or pallor, (2) apnoea or irregular respirations, (3) change in tone or (4) altered level of consciousness with no clinical explanation after a full history and physical examination.[5]

Exclusion criteria

Children will be excluded if they meet any of the following criteria:

1. Extreme prematurity (<28 weeks gestation), given the high prevalence of comorbidities that can present similar to a BRUE (eg, apnoea of prematurity, feeding difficulties intraventricular haemorrhage).
2. Presented for care for a reason unrelated to BRUE.
3. Prior diagnosis of a comorbid condition known to contribute to BRUE, including neurologic abnormalities, genetic conditions (eg, trisomy 21), serious congenital heart disease or arrhythmia or congenital airway abnormality.
4. Documentation of symptoms by history (within 48 hours prior to the event) precluding a diagnosis of BRUE, including fever or persistent respiratory symptoms.
5. Documentation of substantially abnormal vital signs on presentation to the emergency department (ED).
6. Documentation of objective abnormalities on physical examination precluding a diagnosis of BRUE.

Participant identification

Patient records with International Classification of Diseases, Tenth Revision, Canada (ICD-10-CA) admission or discharge codes related to the following will be reviewed: (1) BRUE or Apparent Life-Threatening Event (ALTE); (2) codes consistent with BRUE characteristics (eg, choking, altered consciousness, apnoea or change in muscle tone or colour). This selection strategy has been previously validated and identified BRUE patients with a sensitivity of 98.8%–98.9%, specificity of 33.4%–43.2% and PPV of 46.6%–48.4%.[10]

Each site investigator will instruct a local health records department to identify eligible patients based on the ICD-10-CA codes outlined in online supplemental appendix 1 within the specified time period. We will exclude patients with codes indicating extreme prematurity: (1) extremely low birth weight (999 g or less) (P07.0); or (2) extreme immaturity (less than 28 completed weeks/less than 196 completed days of gestation) (P07.2).

Total number of sites

To identify the maximum number of patients, describe the variation in care and outcomes of children presenting with BRUEs, and generate findings generalisable to all Canadian children, this study will be conducted at multiple hospitals across Canada. All members of PIRN were invited to join the study, and 11 agreed to participate. The study's primary site is BC Children's Hospital (Vancouver, BC). Current additional sites include IWK Health Centre (Halifax, NS), Centre Hospitalier de l'Université Laval (Quebec City, QC), CHU Sainte-Justine (Montreal, QC), Montreal Children's Hospital (Montreal, QC), Children's Hospital of Eastern Ontario (Ottawa, ON), Kingston Health Sciences Centre (Kingston, ON), North York General Hospital (Toronto, ON), Hospital for Sick Children (Toronto, ON), Stollery Children's Hospital (Edmonton, AB), Alberta Children's Hospital (Calgary, AB). These sites span five of 13 Canadian provinces and include eight of the 10 largest Canadian paediatric centres, with a median annual ED visit volume of 49 000 patients (range: 13 000–80 000). All included sites are in an urban setting and most represent tertiary academic centres (n=10), including seven freestanding children's hospitals. Additional hospital sites from PIRN may join. Recruitment will be closed prior to starting data analysis.

Data collection

A case report form (CRF) will be used for data extraction (online supplemental appendix 2). The CRF has been pilot tested in the US study completed by the BRUE-QIRC.[6] Each site investigator will identify a research assistant (a medically trained trainee/student/nurse) and train that individual in data identification and extraction. Trained individuals will enter deidentified data directly using the electronic CRF into a secure REDCap online database managed at BC Children's Hospital Research Institute in Vancouver, BC.[23] If a reviewer is uncertain regarding the patient's eligibility or the presence of an outcome of interest, they can defer this chart to be reviewed by an adjudication team composed of the study leads, research coordinator and site leads. Cases will be reviewed until a consensus is achieved.

Baseline characteristics

We will collect data on a number of relevant baseline characteristics that are important in the description of clinical presentation of BRUE. Demographic information including date of birth, age (in days) and sex will

be collected. Relevant medical history including medical history, perinatal complications, gestational age at birth, concerning family or social histories, symptoms preceding presentation to ED and history of transfer from community hospital will be collected.

Regarding the BRUE characteristics, we will extract whether there was a history of prior similar episodes (ie, not the first event), a history of multiple or cluster of events in the last 24 hours or performed CPR. If CPR is performed, we will collect whether it was indicated. To characterise the event, we will collect details on duration and associated symptoms such as colour change (blue or white), abnormal respiratory pattern (absent, decreased or irregular breathing), change in tone or altered responsiveness. We will collect any abnormality noted in the ED with regard to vital signs, and concerning signs on physical examination or history.

Study outcomes

Our primary outcome of interest is the presence of a serious underlying illness, defined as one or more conditions that could explain the presenting events and require a timely diagnosis, and where delay could potentially cause significant morbidity or mortality (online supplemental appendix 3).[6 24] Examples of serious underlying illnesses include epilepsy requiring treatment with antiepileptics, serious bacterial infections requiring antimicrobials, airway abnormalities requiring surgery and non-accidental injury. The diagnosis could have been made during the index hospital presentation or at a later encounter in the 90 days following the initial presentation.

Secondary outcomes include:

1. Documented event recurrence, defined as one or more events consistent with a BRUE during the index ED visit or hospital admission.[6]
2. Length of hospital stay for hospitalised patients, defined in hours using time of admission and time of discharge.
3. Admission to the intensive care unit (ICU) and length of stay in the ICU (in days).
4. Mortality within 90 days of index presentation.
5. ED revisit (at index hospital) for any reason within 90 days of index presentation.
6. Hospital readmission (at index hospital) within 90 days of index presentation.

Diagnostic tests

We will collect information on diagnostic tests completed, including whether they were normal/abnormal and whether they contributed to the diagnosis. Abnormal values will be defined based on local reference ranges. If multiple tests were ordered during the initial encounter (eg, multiple complete blood count (CBC)), then we will document the first one. Investigations of interest include routine bloodwork and metabolic testing (eg, CBC, electrolytes and blood gas), inflammatory markers, toxicology, blood and urine cultures, pertussis and viral respiratory testing and testing of the cerebrospinal fluid (CSF). We will also assess imaging modalities such as chest X-ray, echocardiogram, head ultrasound, brain CT, brain MRI upper gastrointestinal study, barium swallow study and skeletal survey. Ancillary tests of interest include electroencephalogram, 12 lead ECG (EKG/ECG), pH probe, overnight oximetry, polysomnography and continuous pulse oximetry/or cardiorespiratory monitoring.

Consultations

Information will be extracted regarding any specialty consultations (eg, otorhinolaryngology (ENT), neurology, cardiology, gastroenterology, respirology and child protection) or involvement of allied healthcare providers (eg, dietician and social worker). When a consultation is completed, we will collect information on whether a diagnosis was confirmed as a cause for the BRUE.

Interventions

We will collect details on interventions initiated during hospitalisation or at the time of discharge, including antimicrobials, anti-epileptics, medication for acid suppression or antireflux, caffeine, intravenous fluids, nasogastric tube feeding, oxygen (low flow nasal prongs or high-flow), positive pressure ventilation.

Complications

We will collect information on any documented complications or adverse events during the hospital stay. This includes IV extravasation, medication side effects, feeding tube dislodgement, non-clinically significant events on cardiorespiratory monitors or significant surgical complications.

Diagnoses

We will collect information on any diagnoses identified during the initial presentation or at a later encounter in the following 90 days. We will collect information on whether the diagnosis was identified in the inpatient or outpatient setting, and whether the diagnosis fits the serious diagnosis criteria. For serious diagnoses requiring treatment, we will collect the timing in days for treatment initiation from the date of initial presentation.

Sample size

For the descriptive aims of the study, we will pursue purposive sampling, including all available cases within our specified date range. Our aim is to provide descriptive data across a wide range of Canadian hospitals and to validate the clinical prediction rules in different settings. A centre that is over-represented in the cohort would limit generalisability and the reliability of the observations. As such, no single site will recruit more than 25% of the eligible population. Random sampling may be required at sites where the number of eligible patients exceeds this limit. Based on the number of sites involved at present, we anticipate a sample size of 1820–2564. For the validation of the BRUE clinical prediction rules, a sample size of 1182 is required to provide a power of 80% to detect patients with a serious underlying illness with a significance level

of 5%. This is calculated using a prevalence rate of 4.6%, and an AUC of 0.61 (data from the original derivation study conducted by the BRUE-QIRC).[8]

Proposed statistical methods

Baseline demographic characteristics and study outcomes will be collected and summarised using descriptive statistics. Events will be classified as lower-risk or higher-risk based on the AAP guidelines.[5] Means (with SD), medians (with IQR and ranges will be used to describe continuous variables (eg, age). Counts and proportions will be used to describe categorical variables (eg, gender). Where appropriate, 95% CIs will be provided around estimates.

We will describe the rates of admissions among patients presenting with BRUEs to the ED and whether hospitalisation was associated with an earlier diagnosis or treatment for those with a serious underlying diagnosis. Time to appropriate treatment will be estimated among patients with a serious diagnosis by the Kaplan Meier method.[25] Death prior to treatment will be considered as a competing event, and stratified survival curves will be provided. Rates will be compared between those admitted to hospital after index BRUE and those discharged from the ED with the log rank test.

Variation across Canadian hospitals will be assessed using intraclass correlation coefficient, estimated from a generalised mixed effects model. We will illustrate the trends in the outcomes of interest over time in a figure, graphing the mean (SD) or median (IQR) of each calendar quarter for the 5-year period. Linear models for change over time may be considered including adjustment for autocorrelation.[26]

We will use univariate analysis to determine the association between the outcome of interest, and the independent variables (patients and BRUE characteristics). Two outcomes will be assessed separately as the dependent variable (serious underlying diagnosis and event recurrence). The effect of individual predictors of each of the outcomes will be reported as ORswith 95% CIs.

We will assess the prognostic accuracy of the AAP higher-risk criteria in Canada. For each of the binary outcomes (serious underlying diagnosis, event recurrence, ICU admission, mortality, ED revisit and hospital readmission), we will calculate the sensitivity, specificity, PPV, NPV, AUC of the AAP classification. We will calculate the 95% CI using the Wilson method.

External validation of the derived prediction rule

The previously derived models (BRUE clinical prediction rules)[8] will be applied to the new data to estimate (1) the external discrimination and (2) the external calibration.[27–31] For external discrimination, we will use the Area Under Receiver Operating Characteristic curve (AUROC) as a summary measure.[32] Calibration will be assessed using risk stratification tables, calibration slope and intercept and visually with calibration plots.[33] Recalibration of the model will be considered if performance is suboptimal. Heterogeneity in model performance across sites, and other relevant strata will be assessed and in cases where large differences occur, factors not included in the model may be examined. All model performance statistics will be reported with 95% CIs. In the case of poor external validation metrics, we may consider rederivation steps on external data to assess similarities and differences in derived models. If this is required, rederivation will include internal validation based on the non-parametric bootstrap. Model summaries (AUROC, sensitivity, specificity and calibration) will be assessed across bootstrap samples to measure model uncertainty and optimism.[34] Variables selected will also be assessed for internal consistency. Missing predictor data may be imputed using multiple imputation by chained equations. Imputation models will include all predictors, outcome and any other variables related to the missing values.[35]

Sensitivity analysis

We will conduct the above analyses separately for patients presenting to freestanding children's hospitals versus general EDs. We will conduct the above analyses separately excluding children that were transferred given the possibility of missing details from initial presentation and double counting patients transferred from community hospitals to a tertiary care facility. In all sensitivity analyses, we will compare summary statistics for discrimination (AUROC) and calibration (slope, intercept) between subgroups of interest. ROC curves and calibration plots will also be stratified.

Patient and public involvement

Patients were not involved in the development of the research question or study design and will not be involved in the conduct of the study given its retrospective nature.

ETHICS AND DISSEMINATION

Ethical considerations

Ethics approval was granted by the University of British Columbia's Children's and Women's Research Board (H21-02357). Prior to the launch of the study, approval of the institutional ethics review committee responsible for research ethics oversight at each participating site is required. The principal investigator overseeing the study site and the individual Site Investigators will be responsible for ensuring that each site has fulfilled its local ethics requirements.

This retrospective study does not involve contact with human subjects and thus will not incur any major risks to the patients who provided the data. No medical record number or other personal identification information will be extracted. The main risk to participants is a breach of privacy/confidentiality. In order to minimise this risk, each subject will be given a unique identification code. The code breaking information will be kept at individual sites, separate from the data extraction files and totally inaccessible to individuals outside the local research team. No identifying data

will be sent to the centralised data at BC Children's Hospital. The analytical clinical database will contain no patient identifiers and will fulfil the definition of a deidentified data set as defined by the Health Insurance Portability and Accountability Act in the USA. For data safety and security, the electronic data will be maintained under secure, password-protected conditions while hard copy records will be kept in a locked office, and access will only be given to authorised study personnel.

Record retention

Records relating to the research conducted shall be retained for at least 5 years after completion of the research at BC Children's Hospital or according to each site's policy (whichever is longer). Completion of the research for this protocol is anticipated to include the planned analyses, as well as subsequent derivative analyses. Finally, completion of the research also entails completion of all publications relating to the research. After 5 years, hard copies will be shredded and electronic data will be securely deleted, unless a decision is made to extend the retention period. No data will be sent outside the institution.

Dissemination plan

Results of this study will be disseminated locally at individual participating institutions to allow for quality improvement initiatives and development of local pathways to standardise clinical practice. Additionally, we plan on completing manuscripts for publication in peer-reviewed journals. Abstracts will also be submitted for presentation at national and international conferences.

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Competing interests None declared.

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