Canadian Anaphylaxis Network-Predicting Recurrence after Emergency Presentation for Allergic REaction (CAN-PREPARE): a prospective, cohort study protocol

Waleed Alqurashi, Marcus Shaker, George A Wells, Gary Stephen Collins, Matthew Greenhawt, Janet A Curran, Roger Zemek, Suzanne Schuh, Anne Ellis, Jennifer Gerdz, Cheryl Kreviazuk, Andrew Dixon, Mohamed Eltorki, Stephen B Freedman, Jocelyn Gravel, Naveen Poonai, Margitta Worm, Amy C Plint

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Largest prospective cohort study on paediatric biphasic anaphylaxis conducted to date.
⇒ Sample size calculation and statistical analysis plan are based on the highest methodological standard for prediction modelling research.
⇒ We established an international, multidisciplinary expert team encompassing paediatrics, emergency medicine, allergy/immunology, research methodology and statistics, and knowledge translation.
⇒ We instituted an advisory council of external parents, youth and clinicians end-users and community partners to monitor milestones, identify potential barriers and enablers for future implementation, and guide future decision aid tools.
⇒ This study is not designed to generalise our findings to settings outside of an academic paediatric emergency department; this limitation may be mitigated when we yield a clinically useful and statistically sensitive model that may be externally validated.

INTRODUCTION

Anaphylaxis is the most severe form of allergic reaction that rapidly affects multiple body systems and can be fatal. The highest incidence is in children and adolescents. In Canada, approximately every 10 min, there is an emergency department (ED) visit for food allergy. Up to 80% of anaphylactic reactions in children are triggered by food. 

ABSTRACT

Introduction Anaphylaxis is a severe, potentially fatal multiorgan system manifestation of an allergic reaction. The highest incidence of anaphylaxis is in children and adolescents. Biphasic anaphylaxis (BA) is defined as the recurrence of allergic symptoms after resolution of an initial reaction. It has been reported to occur in 10%–20% of cases within 1–48 hours from the onset of the initial reaction. The dilemma for physicians is determining which patients with resolved anaphylaxis should be observed for BA and for how long. Guidelines for duration of postanaphylaxis monitoring vary, are based on limited evidence and can have unintended negative impacts on patient safety, quality of life and healthcare resources. The objectives of this study are to derive a prognostic model for BA and to develop a risk-scoring system that informs disposition decisions of children who present to emergency departments (ED) with anaphylaxis.

Methods and analysis This prospective multicentre cohort study will enrol 1682 patients from seven paediatric EDs that are members of the Paediatric Emergency Research Network Canada network. We will enrol patients younger than 18 years of age with an allergic reaction meeting anaphylaxis diagnostic criteria. Trained ED research assistants will screen, obtain consent and prospectively collect study data. Research assistants will follow patients during their ED visit and ascertain, in conjunction with the medical team, if the patient develops BA. A standardised follow-up survey conducted following study enrolment will determine if a biphasic reaction occurred after ED disposition. Model development will conform to the broad principles of the PROGRESS (Prognosis Research Strategy) framework and reporting will follow the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis Statement.

Ethics and dissemination Ethics approval has been received from all participating centres. Our dissemination plan focuses on informing clinicians, policy makers and parents of the results through publication in peer-reviewed journals and broadcasting on multiple media platforms.

Trial registration number NCT05135377.
and 8% of allergy-related ED visits are due to anaphylactic shock.3

According to the Canadian Institute for Health Information, the rate of children visiting Ontario and Alberta EDs for anaphylaxis more than doubled between 2007 and 2014.3 Among 13–17 years, ED visits increased significantly (from 23/100 000 in 2007 to 59/100 000 in 2014). The highest annual rate of ED visits was among children aged 4 and younger.3 Similarly, the Cross-Canada Anaphylaxis Registry reported a steady increase in paediatric ED visits: from 1.8/1000 in 2011 to 4.5/1000 in 2015.10 12 These estimates are higher than data from the USA and Europe.13 14

As the volume of anaphylaxis-related ED visits continues to rise,10 12 ambiguity in how physicians manage anaphylaxis increases the healthcare burden and may contribute to ED crowding. Current Canadian and international guidelines recommend that all patients with anaphylaxis present to the ED, and after initial reactions have been treated, remain there for a prolonged period to be monitored for biphasic anaphylaxis (BA, also called delayed or late-phase anaphylaxis).13–17 BA is a second wave of symptoms after initial resolution.16 17 The reported incidence of this potentially serious phenomenon varies from 10% to 20%; the majority occur within 1–24 hours from onset of the initial reaction.16–47 However, these studies vary considerably in their design (prospective vs retrospective), enrolled population (adults vs children or mixed), settings (ED vs outpatient allergy clinics), and definition and severity of anaphylaxis and biphasic reaction. Recent systematic review and meta-analyses58–60 underline these epidemiological factors that explain the significant clinical heterogeneity between previous observational studies. This inconsistency of the literature creates dilemma for ED physicians in deciding which patients should be observed and the optimum duration of observation.51 As a result, guidelines for postanaphylaxis care vary,16 17 are based on poor or little evidence, and have negative impacts on patient safety and quality of life.18 19 52 53 This clinical uncertainty originates from the lack of validated clinical predictors for BA. Consequently, many children are hospitalised or undergo prolonged monitoring in the ED after resolution of initial anaphylaxis.53 54

In the USA, ED care and hospitalisations are the largest drivers of annual direct medical costs (US$1.9 billion) for food allergic children.55 The incremental cost of extended ED observation of resolved anaphylaxis (6 hours vs 1 hour) is US$62 374 per case of BA identified (US$68 411 from the societal perspective). ED monitoring beyond 6 hours of patients who quickly stabilise after treatment is associated with an incremental cost-effectiveness ratio of US$230 202 per case observed (societal perspective).56 As ED crowding and visits for anaphylaxis increase, current postanaphylaxis clinical practice is neither sustainable nor cost-effective.57 58

Providing the best evidence-based value care at the lowest cost is critical to optimise resource stewardship and eliminate wasteful spending in healthcare. In alignment with national and international research priorities,57–61 our goal is to derive a prognostic clinical prediction model that identifies children with anaphylaxis who are at heightened risk of BA. This model will address a gap in current knowledge and practice, with anticipated benefits for patient care and health system efficiency worldwide.

METHODS AND ANALYSIS

Study design

We will conduct a prospective multicentre cohort study. Prospective data collection is necessary to minimise research waste in prediction modelling, accurately assess the risk and impact of BA on patients and the healthcare system, and derive a clinically useful prediction rule. Our design ensures consistency and precision of data collection of all clinically relevant potential predictors and enables accurate assessment of critical outcomes. Our methods follow established guidelines for developing clinical prediction rules.62–71 We conform to the PROGRESS (Prognosis Research Strategy) methods of prediction modelling.59 72–74

Study population

All children aged 0–17 years who present to a participating ED will be screened for study enrollment based on the following criteria:

Inclusion criteria

1. Age <18 years.
2. Presenting to ED with an allergic reaction that matches diagnostic criteria for anaphylaxis as defined by the World Allergy Organization (WAO) in 2019.75 Anaphylactic reaction is a multisystem allergic reaction characterised by one or more clinical features involving the respiratory or cardiovascular systems and associated with one or more clinical features involving the skin or gastrointestinal tract. These criteria are universally accepted and endorsed by most international allergy and emergency medicine organisations.57 76 The 2019 WAO guidelines clarify the involvement of two organ systems is not always requisite for diagnosis: ‘Although the diagnosis of anaphylaxis usually depends on the involvement of multiple organ systems, anaphylaxis may present as an acute cardiac or respiratory event as the only manifestation of anaphylaxis.’75 Thus, an individual with isolated hypotension, bronchospasm, or upper airway obstruction after exposure to a known or potential trigger will be deemed to have anaphylaxis, even if typical skin features are absent.75 77
3. Language proficiency in English or French

Exclusion criteria

1. Anaphylactic reaction that occurred in the context of a suicidal attempt or intoxication.
2. Anaphylactic reaction that began in hospital and managed outside the ED (inpatient or outpatient unit).
3. Inability or unwillingness of individual and/or caregiver to complete the follow-up surveys post-ED discharge.

### Study setting
Between April 2022 and June 2024, the study will enrol participants in EDs from seven hospitals: CHU Sainte-Justine, Children’s Hospital of Eastern Ontario, Hospital for Sick Children, McMaster Children’s Hospital, Children’s Hospital–London Health Sciences Centre, Alberta Children’s Hospital and Stollery Children’s Hospital. These EDs are members of Paediatric Emergency Research Canada (PERC; https://www.perc-canada.ca). Research staff will follow site-specific Research Ethics Boards’ guidelines for approaching potential participants and families for research studies, screening for eligibility and obtaining consent.

### Outcome
The primary outcome is development of BA. As per the recently published consensus definition, to be classified as BA, an anaphylactic reaction must meet three criteria: (1) initial anaphylactic reaction followed by resolution of all initial manifestations for ≥1 hour, with no new symptoms or treatment administered in that time; (2) second phase of new or recurrent symptoms or signs that meet the consensus definition of anaphylaxis occurring within 1–48 hours from complete resolution of initial symptoms or signs and (3) new or recurrent symptoms or signs not caused by antigen re-exposure. We will capture any new or recurrent symptoms or signs, but only clinical manifestations that meet diagnostic criteria for anaphylaxis will be defined as anaphylactic biphasic responses. This definition focuses on clinically important or major biphasic reactions. Mild symptoms that involve only the skin (eg, urticarial rash) will be captured and classified as minor biphasic responses, but they do not meet our case definition for BA.

### Data collection in ED
A research assistant (RA) or research nurse (RN) in the ED will approach potential participants to screen for eligibility and provide a study overview. When the prescreen has been completed, the RA/RN will consult with the attending physician to confirm that the symptoms are consistent with anaphylaxis. If the attending physician considers the signs and symptoms to be more in line with another diagnosis (eg, gastroenteritis), the patient will be excluded. After confirming participant eligibility, the RA/RN will obtain written informed consent (and assent as appropriate) and proceed with data collection. Table 1 lists the independent variables that will be collected.

The RA/RN will review the physical exam findings with the clinical team (treating ED physician/bedside nurse). Because anaphylaxis is a clinical diagnosis, participants or caregivers will be asked about the spectrum of symptoms and signs experienced before and on arrival in the ED. The RN/RA will verbally administer a structured questionnaire to participants or caregivers to collect demographics, medical history, risk factors, reaction characteristics, and symptoms. Information from the participant and from the medical record about treatment before and after ED arrival, and BA events during the ED monitoring period, will be captured by the RN/RA. Missing data will be obtained by questioning the participant, caregiver or treating ED team. To capture

### Table 1: Data collection variables

| From clinical history | Demographics: age, sex, date of birth and self-identified race |
|-----------------------|---------------------------------------------------------------|
|                       | A medical history (eg, cardiac disease, bronchial asthma, eczema) |
|                       | Previous ED visits for anaphylaxis |
|                       | Current anaphylaxis augmenting factors (eg, physical exercise, viral illness or fever, menses in female, drugs such as non-steroidal anti-inflammatory drugs, antacid, β-blockers and ACE inhibitors) |
|                       | Allergen trigger (eg, type, time of exposure and onset of symptoms, location) |
| From physical examination | Participant weight |
|                       | Vital signs at triage (heart rate, respiratory rate, blood pressure, and oxygen saturation) |
|                       | Triage score (based on Canadian Paediatric Triage and Acuity Scale) |
|                       | Physical exam findings on arrival at ED |
| From prehospital and initial ED intervention, and disposition | Treatment interventions (eg, epinephrine, bronchodilators) received before arrival at ED and during transport by paramedics (if applicable) |
|                       | Non-pharmacological/supportive interventions (such as intubation and intravenous fluids) and timeline |
|                       | Pharmacological interventions (including dose, route, frequency and time administered) |
|                       | Disposition time, location (home or hospitalisation), list of discharge medications and outpatient allergy referral |
| From ED monitoring period | Presence and description of new/recurrent symptoms/signs |
|                       | Time of new recurring symptoms/signs |
|                       | Management interventions given for biphasic reaction |
| From follow-up email/phone call after ED disposition | Presence and description of new/recurrent symptoms/signs |
|                       | Time of new/recurrent symptoms/signs |
|                       | Management interventions given for biphasic reaction, including visits to ED/primary care providers |
| From 6 month follow-up (if applicable) | If patient was seen by allergist |
|                       | If seen by allergist, was allergic agent identified? |

ED, emergency department.
all BA events and ascertain symptom recurrence while participants are being monitored, the research RN/RA will follow the participant/caregiver throughout the ED visit. Events occurring outside study team hours will be captured in the follow-up questionnaire.

First follow-up after ED discharge or hospital admission
Published data have reported symptom recurrence up to 48 hours from anaphylaxis onset.26 44 We will contact participants by telephone or email 2–5 days after enrolment to complete a standardised questionnaire that will capture the nature and timing of new and recurrent symptoms or signs, follow-up with health providers, return ED visits and treatments received. Events that took place in-hospital, but were not previously captured by the study team (eg, outside study team hours), will be verified from the participant’s medical chart.

Second follow-up after ED discharge or hospital admission
Participants whose anaphylaxis trigger or culprit allergen was unknown at the time of study enrolment will be contacted 6–9 months after enrolment. We will determine if the participant had been assessed by an allergy specialist in the interim, and if so, whether an allergic agent had been identified.

Strategies for retention
For the follow-up survey, the families of participants will be asked: (1) their preferred mode of contact (email or telephone) and (2) the best time to reach them and contact number. Based on their preferences, we will send the follow-up questionnaire as an automated REDCap survey to the parent/caregiver email address or administer the survey by telephone. If the e-surveys is not completed within 24 hours, a second email will be sent. If there is no response to a second email, experienced staff will contact the participant for a telephone interview. A similar schedule of repeat calls will be used to reach those who selected telephone follow-up.

Sample size
Based on our research,35 48 49 estimates from prospective ED studies28 44 45 86 and published data from large adult and paediatric studies,81 82 10% is a conservative estimate of the population-wide event rate of BA. Our systematic reviews of potential predictors48 and other relevant studies identified 19 potential predictive variables.88 Recent BMJ and Stat in Med articles offer practical guidance for calculating the sample size required for the development of clinical prediction models.84 85 Following these guidelines, we considered sample size from four perspectives, with the largest being selected as the sample size needed. The four calculations are based on: the approximate 95% CI for the overall outcome proportion 0.10 in the study population (calculated sample size needed n=139); the mean absolute prediction error of the average error in the model’s outcome (n=274); achievement of an expected uniform shrinkage factor of ≤10% (n=1529); and ensuring a small, expected optimism in the apparent proportion of overall variation explained R2 (n=719). Details of these calculations with the selection of the parameter estimates and sensitivity considerations are provided in online supplemental material A. Taking the largest sample size that meets all four criteria, we need to enrol 1529 participants with anaphylaxis. Based on previous studies by our network, we anticipate 10% lost to follow-up.56 87 Thus, our estimated sample size is 1682 participants.

Dependent predictors selection for analysis
Table 2 lists the 19 candidate-dependent predictors that we will include in the analysis. We chose these 19 variables based on clinical studies of predictors of BA by our team and by others,16–47 two systematic reviews,48 49 the meta-analysis from the 2020 anaphylaxis practice parameter69 and clinical experience. These predictors encompass recently published BA predictors from the European Anaphylaxis Registry retrospective data.48 Given the direct association between initially severe anaphylaxis and subsequent BA, we also include risk factors of severe anaphylaxis.49

Data analysis
The statistical analysis will be performed using R statistical software V.4.0.5 (R Core Team, Vienna, Austria).90 Descriptive analysis will be used to summarise baseline participant demographics, anaphylaxis clinical manifestations and management characteristics. Although race and indigenous status will be collected as demographic characteristics, we will not perform race-based analysis; these variables will be used as descriptors to demonstrate the diversity and representativeness of our sample.

| Table 2 | Candidate-dependent predictors that will be included in the analysis |
|----------|------------------------------------------------------------------|
| Allergen predictors | Patient predictors |
| Peanut trigger13 | Age34 35 36 89 |
| Venom trigger49 | Male sex49 115 |
| Drug trigger31 49 80 115–118 | Previous anaphylaxis51 36 39 |
| Unknown trigger31 49 50 88 | Uncontrolled asthma or chronic lung disease48 49 78 89 115 117 |
| ≥30 min from exposure to trigger to onset of symptoms48 | Exercise as cofactor for anaphylaxis1 |
| Disease predictors | Treatment predictors |
| Signs of severe anaphylaxis22 23 25 27 | Treatment of initial reaction with a dose of epinephrine49 123 |
| Wide pulse pressure49 123 | Treatment of initial reaction with epinephrine49 123 35 44 124 |
| Respiratory distress or wheezing49 | Systemic steroids44 49 |
| Gastrointestinal manifestations49 123 | Epinephrine administration >60 min from onset of reaction49 123 35 39 126 127 |
| Cutaneous manifestations49 73 | |

Include (as defined by Brown’s severity grading score174): cyanosis or SpO2≤92%, hypotension, confusion, collapse, loss of consciousness or incontinence.

BA, biphasic anaphylaxis.
Multivariable regression analysis will be used to derive a predictive model for BA. As recommended by Royston et al., our modelling strategy will follow six steps.

1. Evaluate data quality. Predictors found to be complete (<10% missing data) will be used in a full model approach. Missing data will be considered Missing at Random. If any potential predictor has >10% missing value, a multiple imputation procedure will be followed to replace these values. If >50% data are missing, the variable will be omitted from the analysis.

2. Handle and model continuous predictors. To maximise the predictive ability of the regression model, we will maintain continuous variables such as age. Collinearity between predictors will be evaluated with correlation coefficient (r) and variance inflation factors (VIFs), which measure the degree to which collinearity degrades the precision of estimate coefficients. Strongly correlated predictors (r>0.8 or VIF>10) will be combined in a single variable. In accordance with Harrell and Steyerberg, we will use Penalised maximum likelihood (PML) estimation to perform shrinkage reduction (reduction of the regression coefficients to improve prediction quality). Maximising a modified Akaike’s information criterion will be used to choose the optimal penalty factor for PML and select the best model. This approach includes a penalty against large models to deal with the trade-off between overfitting and model simplicity. The added benefit of this approach is that we could use more penalty factor if we found significant interaction.

3. Develop final model (predictor selection). Predictors that match the above two criteria will be entered in a ‘full model’ that contains the main effects of all candidate predictors. The objective of predictors reduction is to find the best combinations of variables for accurate prediction (low mean squared error) in a model that is easy for clinicians to use and that contains as few variables as possible. Therefore, we will assess for collinearity and use shrinkage technique as a method of variable reduction. Collinearity between predictors will be evaluated with correlation coefficient (r) and variance inflation factors (VIFs), which measure the degree to which collinearity degrades the precision of estimate coefficients. Strongly correlated predictors (r>0.8 or VIF>10) will be combined in a single variable. In accordance with Harrell and Steyerberg, we will use Penalised maximum likelihood (PML) estimation to perform shrinkage reduction (reduction of the regression coefficients to improve prediction quality). Maximising a modified Akaike’s information criterion will be used to choose the optimal penalty factor for PML and select the best model. This approach includes a penalty against large models to deal with the trade-off between overfitting and model simplicity. The added benefit of this approach is that we could use more penalty factor if we found significant interaction.

4. Assess model performance with three measures. Calibration refers to the accuracy of absolute risk estimates. Model calibration will be assessed by calibration slope, and graphically, by locally weighted scatterplot smoothing (LOESS) plots of observed vs predicted probabilities of the outcome. The slope of the calibration curve is a measure of overoptimism of the model predictions.

5. Validate model
   - Internal validation. Recruiting from geographically separated sites enhances generalisability and supports internal validation of the model. To correct for overfitting and quantify optimism in model performance, our model will be validated internally using bootstrapping through the following steps: (1) After developing the prediction model using the entire original sample and determining apparent performance, we will generate a bootstrap sample by sampling individuals with replacement from the original sample; (2) Develop a model using the bootstrap sample (applying the same modelling and predictor selection in step 3 above); (3) Determine the apparent bootstrap performance of this model (performance of bootstrap model in the original sample and calculate the optimism as the difference between bootstrap performance and test performance); (4) Repeat steps 1 through 3 at least 500 times and (5) Average the estimates of optimism in step 4, and subtract the value from the apparent performance obtained in step 1 to obtain an optimism-corrected estimate of performance.

   - External validation: Before broad clinical implementation, our derived rule requires external validation. Lack of external validation is a limitation of many clinical prediction models. For two reasons, this proposal focuses only on model derivation: (1) Requesting funding for external validation may be premature. Before embarking on external validation, we need proof that our a priori risk factors yield a clinically useful and statistically sensitive model and (2) The validation phase should be broader, in different settings, with other participant, and with different clinicians. Our ultimate goal is to validate our model and risk score in an international setting. Such validation is feasible because PERC is a member of the Paediatric Emergency Research Networks (PERN), and member networks have a history of collaboration.

6. Present model. As described by Sullivan et al.: we will use the regression coefficient in our final fitted model to generate a clinical decision rule that enables point-of-care risk assessment of BA. To develop a points score system, we will follow the steps described in a recent BMJ paper: (1) Multiply and round regression coefficients of binary predictors; (2) Search for score for continuous predictors to determine the difference in regression units; (3) Estimate multiplication factor for the scores; (4) Use decision curve analysis to assign participants to risk groups and quantify any deterioration in discriminative performance and (5)
Present accompanying table of probabilities to allow points score to be translated into a predicted risk. The anticipated stoplight scoring system (green=low→discharge; yellow=moderate→monitor in ED/preference-sensitive care; red=high→admit to hospital) will inform evidence-based disposition decisions by clinicians and anticipatory guidance to families.

Patient and public involvement
Patients and/or the public were involved in the design and dissemination plans for this research. To promote uptake of our results, potential knowledge users have been and will be engaged throughout the project.109 We have a multiphase approach to maximise collaboration and opportunities for diverse knowledge users to interact at various research phases.110 Our multisite team includes ED clinicians as typical end-users and champions for future implementation. We have established an advisory council of external end-users (parents, youth, ED clinicians) and community partners (Food Allergy Canada, Canadian Society of Allergy & Clinical Immunology) to monitor milestones, identify potential barriers and enablers for future implementation, and guide future decision aids study. The leadership team at Food Allergy Canada has reviewed and supports this proposal. To improve study operation and minimise the burden on patients and families, we sought feedback from the Patients and Families Advisory Committee at the Children’s Hospital of Eastern Ontario Research Institute.

Ethics and dissemination
Ethics
Ethics approval has been received from all recruiting centres. Written informed consent, and/or assent when appropriate, will be obtained from all participants or legal guardians.

The study is registered at ClinicalTrials.gov (NCT05135377). Results information from this study will be submitted to ClinicalTrials.gov.

End-of-grant KT (knowledge translation)
ED personnel, providers, allergists, clinical researchers, administrators and government policy makers can use our study outputs to improve healthcare delivery. KT will focus on informing clinicians, other key user groups, and parents and participants. Our plan has three goals: increase knowledge awareness, inform/change practice and inform future research.111 112

We have a powerful infrastructure to disseminate our results. Study investigators are senior members of PERC and PERN, networks that include paediatric ED researchers worldwide (>100 hospitals across 6 PERN networks),113 practicing clinicians, medical educators and healthcare administrators. PERC is closely tied to the Translating Emergency Research Knowledge for Kids Network of Centres of Excellence,114 a partnership for knowledge exchange between general EDs and PERC sites. Our reporting/publication of the study results will conform to the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis checklist.102

Author affiliations
1Department of Pediatrics and Emergency Medicine, University of Ottawa Faculty of Medicine, Ottawa, Ontario, Canada
2Children’s Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada
3Section of Allergy and Clinical Immunology, Children’s Hospital at Dartmouth-Hitchcock, Lebanon, New Hampshire, USA
4Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Ottawa, Ontario, Canada
5School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada
6Centre for Statistics in Medicine, University of Oxford Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, Oxford, UK
7Section of Allergy and Clinical Immunology, Children’s Hospital Colorado, Aurora, Colorado, USA
8Pediatrics, IWK Health Centre, Halifax, Nova Scotia, Canada
9Pediatrics, The Hospital for Sick Children, Toronto, Ontario, Canada
10Division of Allergy and Immunology, Queen’s University, Kingston, Ontario, Canada
11Food Allergy Canada, Toronto, Ontario, Canada
12Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada
13McMaster Children’s Hospital, Hamilton, Ontario, Canada
14Departments of Pediatrics and Emergency Medicine, Albert Children’s Hospital, University of Calgary Cumming School of Medicine, Calgary, Alberta, Canada
15Centre Hospitalier Universitaire Sainte-Justine, Universite de Montreal, Montreal, Quebec, Canada
16Departments of Paediatrics, Internal Medicine, Epidemiology & Biostatistics, Western University, London, Ontario, Canada
17Division of Allergy and Immunology, Department of Dermatology and Allergy, Charite Universitätsmedizin Berlin, Berlin, Germany

Acknowledgements
We are grateful to the Patients and Family Advisory Committee at the Children’s Hospital of Eastern Ontario Research Institute, and Food Allergy Canada for the insightful comments and feedback on the recruitment approach and data collection forms. We are also grateful to the following research coordinators and research managers for the operational support of the study at their institutions: Candice McGahren, Jena Shank, Judith Sweeney, Kamary Coriolano DaSilva, Patricia Candelaria, Redjana Cucurumaru and Stéphanie Pellerin.

Collaborators
The Pediatric Emergency Research Canada (PERC) Network members include the following: Waleed Alqurashi, MD, MSc, Roger Zemek, MD, and Amy Plint, MD, MSc (Children’s Hospital of Eastern Ontario, Ottawa, Ontario, Canada); Janet Curran, PhD, RN (IWK Health Centre, Halifax, Nova Scotia, Canada); Suzanne Schuh, MD (The Hospital for Sick Children, Toronto, Ontario, Canada); Andrew Dixon, MD (Stollery Children’s Hospital, Edmonton, Alberta, Canada); Mohamed Eltorki MBCHB (McMaster Children’s Hospital, Hamilton, Ontario, Canada); Stephen B. Freedman, MD, CM, MSc (Alberta Children’s Hospital, Calgary, Alberta, Canada); Jocelyn Gravel, MD, MSc (Sainte-Justine Pédiatrica, Montreal, Quebec, Canada); and Naveen Poonai, MD, MSc (Western University, London, Ontario, Canada).

Contributors
WA and ACP conceived the study idea. WA, ACP and MS wrote the protocol with input from GAW, GSC, MG, JAC, RZ, SS, AE, JG, CK, AD, ME, SF, JG, NP and MW. All authors provided input into the methodology and analysis plan. All authors approved the final protocol manuscript. ACP and GAW are the supervisors of the study.

Funding
This work is supported by the Canadian Institutes of Health Research (CIHR), grant number PJT-175057. This work is also supported by the Children’s Hospital Academic Medical Organization (CHAMO) Innovation Fund, grant number N/A.

Competing interests
All authors have read and understood BMJ policy on declaration of interests and have no relevant interest to declare. ACP is supported by a Tier I University of Ottawa Research Chair. SF is supported by the Alberta Children’s Hospital Professorship in Child Health and Wellness.

Patient and public involvement
Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication
Not applicable.
induced anaphylaxis in US children. *Pediat Allergy Immunol* 2018;29:538–44.
14 Grabenhenrich LB, Dölle S, Moneret-Vautrin A, et al. Anaphylaxis in children and adolescents: the European anaphylaxis registry. *J Allergy Clin Immunol* 2016;137:1129–37.
15 Canadian Society of Allergy and Clinical Immunology. Anaphylaxis in Schools & Other Settings, 2016. Available: http://csaci.ca/wp-content/uploads/2017/11/Anaphylaxis-in-Schools-Other-Settings- [Accessed 10 Dec 2016].
16 Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis—a practice parameter update 2015. *Annals of Allergy, Asthma & Immunology* 2015;115:341–84.
17 Muraro A, Roberts G, Worm M, et al. Anaphylaxis: guidelines from the European Academy of allergy and clinical immunology. *Allergy* 2014;69:1026–45.
18 Lieberman P. Biphasic anaphylactic reactions. *Ann Allergy Asthma Immunol* 2005;95:217–26.
19 Tole JW, Lieberman P. Biphasic anaphylaxis: review of incidence, clinical predictors, and observation recommendations. *Immunol Allergy Clin North Am* 2007;27:309–26.
20 Lertnawapan R, Maek-a-nantawat W. Anaphylaxis and biphasic phase in Thailand: 4-year observation. *Allergol Int* 2011;60:283–9.
21 Orhan F, Canitez Y, Bakirtas A, et al. Anaphylaxis in Turkish children: a multi-centre, retrospective, case study. *Clin Exp Allergy* 2011;41:1767–76.
22 Inoue N, Yamamoto A. Clinical evaluation of pediatric anaphylaxis and the necessity for multiple doses of epinephrine. *Asia Pac Allergy* 2013;3:106.
23 Lee J, Garrett JPD, Brown-Whitehorn T. Biphasic reactions in children undergoing oral food challenges. *Allergy and Asthma Proceedings*, 2013: 220–6.
24 Nagano C, Ishiguro A, Yotani N. Anaphylaxis and biphasic reaction in a children Hospital. *Japanese J Allergy* 2013;62:163–70.
25 Vezir E, Eroçoşoğlu M, Kaya A. Characteristics of anaphylaxis in children referred to a tertiary care center. *Allergy and Asthma Proceedings*, 2013: 239–46.
26 Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380–4.
27 Liew WK, Chiang WC, Goh AE, et al. Paediatric anaphylaxis in a Singaporean children cohort: changing food allergy triggers over time. *Asia Pac Allergy* 2013;3:29.
28 Brown SGA, Stone SF, Fatovich DM, et al. Anaphylaxis: clinical patterns, mediator release, and severity. *J Allergy Clin Immunol* 2013;132:1141–9.
29 Grunau BE, Li J, Yi TW, et al. Incidence of clinically important biphasic reactions in emergency department patients with allergic reactions or anaphylaxis. *Ann Emerg Med* 2014;63:736–44.
30 Rohacek M, Edenhoffer H, Bircher A, et al. Biphasic anaphylactic reactions: occurrence and mortality. *Allergy* 2014;69:791–7.
31 Lee S, Bellolio MF, Hess EP, et al. Predictors of biphasic reactions in the emergency department for patients with anaphylaxis. *J Allergy Clin Immunol Pract* 2014;2:281–7.
32 Oya S, Nakamori T, Kinoshita H. Incidence and characteristics of biphasic reactions: occurrence and mortality. *Allergy* 2014;69:791–7.
33 Manuyakov W, Benjaponpitak S, Kamchaisinthikul W, et al. Pediatric anaphylaxis: triggers, clinical features, and treatment in a tertiary-care Hospital. *Asian Pac J Allergy Immunol* 2015;33:8–13.
34 Rihani A-M. Further evaluations of factors that may predict biphasic reactions in emergency department anaphylaxis patients. *Pediatrics* 2018;142:2222–3.
35 Kim T-H, Yoon SH, Lee S-Y, et al. Biphasic and protracted anaphylaxis to iodinated contrast media. *Eur Radiol* 2018;28:1242–52.

**REFERENCES**

1 Simons FER, Ardusso LRF, Biló MB, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J* 2011;4:13–57.
2 Castells M. Diagnosis and management of anaphylaxis in precision medicine. *J Allergy Clin Immunol* 2017;140:321–33.
3 CIHI. Anaphylaxis and allergy in the emergency department, 2015. Available: https://secure.cihi.ca/free_products/Anaphylaxis_Infosheet_en.pdf [Accessed 18 Dec 2015].
4 Sheikh A, Hippsley-Cox J, Newton J, et al. Trends in national incidence, lifetime prevalence and adrenaline prescribing for anaphylaxis in England. *J R Soc Med* 2008;101:139–43.
5 Wood RA, Camargo CA, Lieberman P, et al. Anaphylaxis in America: the prevalence and characteristics of anaphylaxis in the United States. *J Allergy Clin Immunol* 2014;133:461–7.
6 Moro-Moro M, Múgica-García MV, Tejedor-Alonso MA. Epidemiology of anaphylaxis: contributions from the last 10 years. *J Invest Allergol Clin Immunol* 2015;25:163–75.
7 Simons FER, Sampson HA. Anaphylaxis epidemic: fact or fiction? *J Allergy Clin Immunol* 2008;122:1166–8.
8 Lieberman P, Camargo CA, Bohlke K, et al. Epidemiology of anaphylaxis: findings of the American College of allergy, asthma and immunology epidemiology of anaphylaxis Working group. *Ann Allergy Asthma Immunol* 2006;97:596–602.
9 Canada S. The impact on emergency department utilization of the CFHI healthcare collaborations and initiatives, 2013. Available: https://www.cfhi-facs.ca/sf-docs/default-source/reports/risk-analytica.pdf?sfvrsn=bb4d1f4f_2
10 Hochstadter E, Clarke A, De Schryver S, et al. Increasing visits for anaphylaxis and the benefits of early epinephrine administration: A 4-year study at a pediatric emergency department in Montreal, Canada. *J Allergy Clin Immunol* 2016;137:1888–90.
11 Gabrielli S, Clarke A, Morris J, et al. Evaluation of prehospital management in a Canadian emergency department anaphylaxis cohort. *J Allergy Clin Immunol Pract* 2019;7:2322–8.
12 Lee AYM, Enarson P, Clarke AE, et al. Anaphylaxis across two Canadian pediatric centers: evaluating management disparities. *J Asthma Allergy* 2011;10:1–7.
13 Motosue MS, Bellolio MF, Van Houten HK, et al. National trends in emergency department visits and hospitalizations for food-
41 Brady WJ, Luber S, Carter CT, et al. Multifaceted anaphylaxis: an uncommon event in the emergency department. *Acad Emerg Med* 1997;4:193–7.
42 Popa VT, Lerner SA. Biphasic systemic anaphylactic reaction: three illustrative cases. *Ann Allergy* 1984;53:151–5.
43 Stark BJ, Sullivan TJ. Biphasic and protracted anaphylaxis. *J Allergy Clin Immunol* 1986;78:76–83.
44 Ellis AK, Day JH. Incidence and characteristics of biphasic anaphylaxis: a prospective evaluation of 103 patients. *Ann Allergy Asthma Immunol* 2007;98:64–9.
45 Scraton SE, Gonzalez EG, Waihel KH. Incidence and characteristics of biphasic reactions after allergen immunotherapy. *J Allergy Clin Immunol* 2009;123:493–8.
46 Mehr S, Liew WK, Tey D. Clinical predictors for biphasic reactions in children presenting with anaphylaxis. *Clin Exp Allergy* 2010;40:83.
47 Conflino-Cohen R, Goldberg A. Allergic immunotherapy-induced biphasic systemic reactions: incidence, characteristics, and outcome: a prospective study. *Ann Allergy Asthma Immunol* 2010;104:73–8.
48 Alqurashi W, Ellis AK. Do corticosteroids prevent biphasic anaphylaxis? *J Allergy Clin Immunol Pract* 2017;5:1194–205.
49 Shaker MS, Wallace DV, Golden DBK, et al. Anaphylaxis-a 2020 practice parameter update, systematic review, and grading of recommendations, assessment, development and evaluation (GRADE) analysis. *J Allergy Clin Immunol* 2020;145:1082–123.
50 Lee S, Belloflo MF, Hess EP, et al. Time of onset and predictors of biphasic anaphylactic reactions: a systematic review and meta-analysis. *J Allergy Clin Immunol Pract* 2013;5:408–16.
51 Kemp SF. The post-anaphylaxis dilemma: how long is long enough to observe a patient after resolution of symptoms? *Curr Allergy Asthma Rep* 2008;8:45–8.
52 Lee S, Sadosty AT, Campbell RL. Update on biphasic anaphylaxis. *Curr Opin Allergy Clin Immunol* 2016;16:346–51.
53 Parlaman JP, Cron AP, Uspal NJ, et al. Emergency and hospital care for food-related anaphylaxis in children. *Hosp Pediatr* 2016;6:269–74.
54 Michelson KA, Monuteaux MC, Neuman MI. Variation and trends in anaphylaxis care in United States children’s hospitals. *Acad Emerg Med* 2016;23:623–8.
55 Gupta R, Holdford D, Bilaver L, et al. The economic impact of childhood food allergy in the United States. *JAMA Pediatr* 2013;167:1026–31.
56 Shaker M, Wallace D, Golden DBK, et al. Simulation of health and economic benefits of extended observation of resolved anaphylaxis. *JAMA Netw Open* 2019;2:191392.
57 Simons FE, Aradusso LR, Biló MB, et al. International consensus on (icon) anaphylaxis. *World Allergy Organ J* 2014;7:9.
58 Sicherer SH, Allen K, Lack G, et al. Critical issues in food allergy: a national academies consensus report. *Pediatrics* 2017;140.
59 National Academies of Sciences and Medicine E. Finding a path to safety in food allergy: assessment of the global burden, causes, prevention, management, and public policy. Washington: National Academies Press, 2017.
60 National Institute for Health and Clinical Excellence. Anaphylaxis: assessment and referral after emergency treatment / guidance and guidelines | NICE, 2016. Available: https://www.nice.org.uk/guidance/cg134/chapter/4-Research-recommendations-the-frequency-and-effects-of-biphasic-reactions [Accessed 12 Dec 2016].
61 Bialy L, Plint AC, Freedman SB, et al. Pediatric emergency research Canada (PERC): Patient/Family-informed research priorities for pediatric emergency medicine. *Acad Emerg Med* 2018;25:1365–74.
62 Stell IG, Wells D, Vandemheen K, et al. The Canadian CT head rule for patients with minor head injury. *Lancet* 2001;357:1931–6.
63 McGinn TG, Guyatt GH, Wyer PC, et al. Users’ guides to the medical literature: XXII: how to use articles about clinical decision rules. evidence-based medicine Working group. *JAMA* 2000;284:77; quiz 81-2.
64 Wynants L, Collins GS, Van Calster B. Key steps and common pitfalls in developing and validating risk models. *BJOG* 2017;124:423–32.
65 Reilly BM, Evans AT. Translating clinical research into clinical practice: impact of using prediction rules to make decisions. *Ann Intern Med* 2006;144:201–9.
66 Green SM, Schriger DL, Yealy DM. Methodologic standards for interpreting clinical decision rules in emergency medicine: 2014 update. *Ann Emerg Med* 2014;64:286–91.
67 Steyerberg EW. Toward better clinical prediction models: seven steps for development and an ABCD for validation. *Eur Heart J* 2014;35:1925–31.
68 Steyberg EW, Uno H, Ioannidis JPA, et al. Poor performance of clinical prediction models: the harm of commonly applied methods. *J Clin Epidemiol* 2018;98:133–43.
69 Riley R. Prognostic model research, 2020. Available: https://www.prognosissurvey.org.
70 Harrell FE. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. In: Publishing Sl, ed. 2015.
71 Steyberg EW. Clinical prediction models: a practical approach to development, validation, and updating. Int.: Springer, 2009.
72 Riley RD, Hayden JA, Steyberg EW, et al. Prognosis research strategy (progress) 2: prognostic factor research. *PLoS Med* 2013;10:e1001380.
73 Steyberg EW, Moons KGM, van der Windt DA, et al. Prognosis research strategy (progress) 3: prognostic model research. *PLoS Med* 2013;10:e1001581.
74 Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *Br J Surg* 2015;102:148–58.
75 Turner PJ, Worm M, Ansotegui IJ, et al. Time to revisit the definition and clinical criteria for anaphylaxis? *World Allergy Organ J* 2019;12:100066.
76 Campbell RL, Li JTC, Nicklas RA, et al. Emergency diagnosis and treatment of anaphylaxis: a practice parameter. *Ann Allergy Asthma Immunol* 2014;113:599–608.
77 Australian Society of Clinical Immunology and Allergy, Acute management of anaphylaxis. 2021. Available: https://allergy.org.au/images/ASCA_HP_Guidelines_Acute_Management_Anaphylaxis_2021.pdf.
78 Bialy L, Plint A, Zemek R, et al. Pediatric emergency research Canada: origins and evolution. *Pediatr Emerg Care* 2018;34:138–44.
79 Dribin TE, Sampson HA, Camargo CA, et al. Persistent, refractory, and biphasic anaphylaxis: A multidisciplinary Delphi study. *Journal of Allergy and Clinical Immunology* 2020;146:1089–96.
80 Muñoz-Cano R, Pascall M, Araujo G, et al. Mechanisms, cofactors, and augmenting factors involved in anaphylaxis. *Front Immunol* 2017;8:1193.
81 Nagata S, Obbe H, Jo T, et al. Glucocorticoids and rates of biphasic reactions in patients with Adrenaline-Treated anaphylaxis: a propensity score matching analysis. *Int Arch Allergy Immunol* 2022;183:939–45.
82 Gupta RS, Sehgal S, Brown DA, et al. Characterizing biphasic food-related allergic reactions through a US food allergy patient registry. *J Allergy Clin Immunol Pract* 2021;3:717–27.
83 Alqurashi W, Anaphylaxis. *B. Epidemiology, Predictors, and Management*. In: Ellis AK, ed. Anaphylaxis: A Practical Guide. Springer Nature, 2020: 43–60.
84 Riley RD, Ensor J, Snell KIE, et al. Calculating the sample size required for developing a clinical prediction model. *BMJ* 2020;366:m441.
85 Riley RD, Snell KIE, Ensor J, et al. Minimum sample size for developing a multivariable prediction model: Part I - Continuous outcomes. *Stat Med* 2019;38:1262–75.
86 Schuh S, Babi FE, Dalziel SR, et al. Practice variation in acute bronchiolitis: a pediatric emergency research networks study. *Pediatrics* 2017;140.
87 Dalziel SR, Thompson JM, Macias CG, et al. Predictors of severe H1N1 infection in children presenting within pediatric emergency research networks (PERN): retrospective case-control study. *BMJ* 2013;347:g4836.
88 Kraft M, Scherer Hofmeier K, Ruelle F, et al. Risk factors and characteristics of biphasic anaphylaxis. *J Allergy Clin Immunol Pract* 2020;8:3388–95.
89 Worm M, Fransuzik W, Renaudin J-M, et al. Factors increasing the risk for a severe reaction in anaphylaxis: an analysis of data from the European anaphylaxis registry. *Allergy* 2018;73:1322–30.
90 Core Team R. R: a language and environment for statistical computing. R found. STAT. Comput. 2021. Available: https://www.r-project.org/.
91 Rosyten P, Moons KGM, Altman DG, et al. Prognosis and prognostic research: developing a prognostic model. *BMJ* 2009;338:b604.
92 Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361–87.
93 Steyberg EW, Eijkemans MJ, Harrell FE, et al. Prognostic modeling with logistic regression analysis: in search of a sensible strategy in small data sets. *Med Decis Making* 2001;21:45–56.
94 Vadas P, Perelman B, Liss G. Platelet-Activating factor, histamine, and tryptase levels in human anaphylaxis. J Allergy Clin Immunol 2013;131:144–9.
95 Vadas P, Perelman B. Effect of epinephrine on platelet-activating factor-stimulated human vascular smooth muscle cells. J Allergy Clin Immunol 2012;129:1329–33.
96 Alba AC, Agoritsas T, Walsh M, et al. Discrimination and calibration of clinical prediction models: users’ guides to the medical literature. JAMA 2017;318:1377–84.
97 Vickers AJ, Van Calster B, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. BMJ 2016;352:i6.
98 Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 2010;21:128.
99 Steyerberg EW, Harrell FE. Prediction models need appropriate internal, interval-external, and external validation. J Clin Epidemiol 2016;69:245–7.
100 Toll DB, Janssen KJM, Vergouw Y, et al. Validation, updating and impact of clinical prediction rules: a review. J Clin Epidemiol 2008;61:1085–94.
101 Steyerberg EW, Harrell FE, Borsboom GJ, et al. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol 2001;54:774–81.
102 Moons KGM, Altman DG, Steyerberg EW, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPD): explanation and elaboration. Ann Intern Med 2015;162:W1–73.
103 Grady D, Berkowitz SA. Why is a good clinical prediction rule so hard to find? Arch Intern Med 2011;171:1701–2.
104 Collins GS, de Groot JA, Dutton S, et al. External validation of multivariable prediction models: a systematic review of methodological conduct and reporting. BMC Med Res Methodol 2014;14:1–12.
105 Ban J-W, Emparanza Ji, Urreta I, et al. Design characteristics influence performance of clinical prediction rules in validation: a meta-epidemiological study. PLoS One 2016;11:e0145779.
106 Alsic E, Hoysted C, Kassam-Adams N, et al. Psychosocial care for injured children: worldwide survey among hospital emergency department staff. J Pediatr 2016;170:227–33.
107 Sullivan LM, Massaro JM, D’Agostino Sr RB. Likelihood Modelling: Presentation of Multivariate Data for Clinical Use: The Framingham Study Risk Score Functions. In: D’Agostino Sr RB, ed. Tutorials in Biostatistics: Statistical Modelling of Complex Medical Data. Wiley Online Library, 2004: 445–76.
108 Bonnett LJ, Snell KIE, Collins GS, et al. Guide to presenting clinical prediction models for use in clinical settings. BMJ 2019;365:l3774.
109 Bowen S, Graham ID. Integrated knowledge translation. In: Graham ID, Strauss SE, Tetroe J, eds. Knowledge translation in health care: Moving from evidence to practice. Wiley Blackwell Oxford, 2013: 14–21.
110 Gagliardi AR, Berta W, Kothari A, et al. Integrated knowledge translation (IKT) in health care: a scoping review. Implementation Sci 2015;11:1–12.
111 CIHR. Guide to knowledge translation planning in CIHR: integrated and evidence-informed approaches. 2012. Available: http://www.cihr-irsc.gc.ca/e/45321.html#A5 [Accessed 11 Apr 2016].
112 Lomas J, Diffusion LJ. Diffusion, Dissemination, and implementation: who should do what? Ann N Y Acad Sci 1993;703:226–37.
113 PERN-Globall.com P. Available: https://www.pern-global.com/ [Accessed 11 Apr 2016].
114 TREKK.ca Tca. Available: http://trekk.ca/ [Accessed 10 Jan 2017].
115 Turner PJ, Gowland MH, Sharma V, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. J Allergy Clin Immunol 2015;135:956–63.
116 Motoussis MS, Bellolio MF, Van Houten HK, et al. Risk factors for severe anaphylaxis in the United States. Ann Allergy Asthma Immunol 2011;107:56–61.
117 Mullens RJ, Wainstein BK, Barnes EH, et al. Increases in anaphylaxis fatalities in Australia from 1997 to 2013. Clin Exp Allergy 2016;46:1099–110.
118 Xing Y, Zhang H, Sun S, et al. Clinical features and treatment of pediatric patients with drug-induced anaphylaxis: a study based on pharmacovigilance data. Eur J Pediatr 2018;177:145–54.
119 Smith PK, Hourihane Jonathan O’B, Lieberman P. Risk multipliers for severe food anaphylaxis. World Allergy Organ J 2015;8:30–6.
120 Hompes S, Köhl A, Nemat K, et al. Provoking allergens and treatment of anaphylaxis in children and adolescents--data from the anaphylaxis registry of German-speaking countries. Pediatr Allergy Immunol 2011;22:568–74.
121 Niggemann B, Beyer K. Factors augmenting allergic reactions. Allergy 2014;69:1582–7.
122 Dinh DV, Attkisson AH, Rainer TH. Anaphylaxis presentations to an emergency department in Hong Kong: incidence and predictors of biphasic reactions. J Emerg Med 2005;28:381–8.
123 Brazil E, MacNamara AF. “Not so immediate” hypersensitivity--the danger of biphasic anaphylactic reactions. Emergency Medicine Journal 1998;15:252–3.
124 Oya S, Kinoshita K, Daya M, et al. Characteristics of anaphylactic reactions: a prospective observational study in Japan. J Emerg Med 2020;59:812–8.
125 Campbell RL, Bashore CJ, Lee S, et al. Predictors of repeat epinephrine administration for emergency department patients with anaphylaxis. J Allergy Clin Immunol Pract 2015;3:576–84.
126 Lee JM, Greenes DS. Biphasic anaphylactic reactions in pediatrics. Pediatrics 2000;106:762–6.
127 Petchyapranukorn O, Poapichanachorn C. Incidence of anaphylaxis in the Emergency department: a 1-year study in a university hospital. Asian Pacific J allergy Immunol 2006;24:111.
128 Brown SGA. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol 2004;114:371–6.