Timing of repeat epinephrine to inform paediatric anaphylaxis observation periods: a retrospective cohort study

Timothy E Dribin, Hugh A Sampson, Yin Zhang, Stephanie Boyd, Nanhua Zhang, Kenneth A Michelson, Mark I Neuman, David C Brousseau, Rakesh D Mistry, Stephen B Freedman, Paul L Aronson, Kelly R Bergmann, Brittany Boswell, Sri S Chinta, Wee-Jhong Chua, Ari R Cohen, Joanna S Cohen, Alicia Daggett, Justin R Davis, Julia F Freeman, Kajal Khanna, Curtis L Knoles, Karen Y Kwan, Chari D Larsen, Juhee Lee, Tamar R Lubell, Ashley M Metcalf, Matthew M Moake, Jo-Ann O Nesiama, Thuy L Ngo, Christian D Pulcini, Christopher J Russo, Nidhi V Singh, Geetanjali Srivastava, Jonathan Strutt, Vandana Thapar, Craig Vander Wyst, Patrick S Walsh, Yonatan Wolnerman, David Schnadower, for the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics

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Division of Emergency Medicine (T E Dribin MD, Prof D Schnadower MD, S Boyd PhD) **and Division of Biostatistics and Epidemiology** (Y Zhang MS, Prof N Zhang PhD), **Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA**; **Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA** (T E Dribin, Prof D Schnadower, Prof N Zhang); **Division of Allergy and Immunology, Icahn School of Medicine at Mount Sinai, New York, NY, USA** (Prof H A Sampson MD); **Division of Emergency Medicine, Ann & Robert Lurie Children's Hospital, Chicago, IL, USA** (K A Michelson MD); **Division of Emergency Medicine, Boston Children's Hospital, Boston, MA, USA** (Prof M I Neuman MD); **Department of Pediatrics, Harvard Medical School, Boston, MA, USA** (Prof M I Neuman); **Department of Pediatrics, Nemours Children's Health Delaware, Wilmington, DE, USA** (Prof D C Brousseau MD, C J Russo MD); **Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA** (Prof D C Brousseau, C J Russo); **Section of Pediatric Emergency Medicine, Departments of Pediatrics and Emergency Medicine, Yale School of Medicine, New Haven, CT, USA** (Prof R D Mistry MD, Prof P L Aronson MD); **Department of Pediatrics** (Prof S B Freedman MDCM) **and Department of Emergency Medicine** (Prof S B Freedman),

Summary

Background Children presenting to the emergency department with anaphylaxis typically receive at least one dose of epinephrine and are observed in the emergency department or monitored for recurrent (biphasic anaphylaxis) or persistent symptoms on hospital wards for variable durations before discharge is considered safe. We aimed to calculate the incidence rate and timing of repeat epinephrine dosing to determine the observation threshold at which the cumulative incidence of repeat epinephrine was less than 2% for every 1 h increase in observation time.

Methods This multicentre, retrospective cohort study across 30 emergency departments in the USA and one emergency department in Canada included children aged 6 months to 17 years who, according to electronic medical records, presented to one of the participating emergency departments with an acute allergic reaction that was treated with intramuscular, subcutaneous, or intravenous epinephrine before arrival at the emergency department or in the emergency department between Jan 1, 2016, and Dec 31, 2019. We excluded patients who had no documentation of symptoms or examination findings before presenting to the emergency department, were transferred from outside health-care facilities, had reactions secondary to medications administered in the emergency department, or had comorbidities requiring tailored management decisions. Demographics, medical history, and emergency department revisits within 72 h of discharge were extracted from electronic medical records. The primary outcome was the time from first to last administration of epinephrine. For patients on intravenous epinephrine infusions, the relevant time interval was from infusion initiation to discontinuation. Kaplan–Meier analyses were used to compare time to last epinephrine dose by initial reaction severity, stratified by respiratory and cardiovascular involvement (no respiratory or cardiovascular involvement, respiratory but no cardiovascular involvement, and cardiovascular involvement).

Findings Of 7717 patients with ICD-10 Clinical Modification codes for anaphylaxis, 5641 were eligible for inclusion (median age 7·9 years [IQR 3·3–13·1]; 2475 [43·9%] female; 3166 [56·1%] male). Of the 5139 patients who reported ethnicity, 1131 (22·0%) identified as Hispanic and 4008 (78·0%) identified as non-Hispanic. 263 (4·7%) of 5641 patients received a repeat epinephrine after 2 h of the first dose, whereas 109 (1·9%) received repeat epinephrine after 4 h, 64 (1·1%) after 6 h, and 46 (0·8%) after 8 h. The observation period at which the increase in cumulative incidence of repeat epinephrine was less than 2% was 115 min (95% CI 105–122) for all patients, 105 min (54–135) for patients without respiratory or cardiovascular involvement (n=1070), 109 min (98–118) for patients with respiratory but no cardiovascular involvement (n=4076), and 161 min (125–249) for patients with cardiovascular involvement (n=495). These findings suggest that 5378 (95·3%) patients in our cohort would have been safely discharged 2 h after receiving the first epinephrine dose and that 5532 (98·1%) patients would have been safely discharged 4 h after the first epinephrine dose.

Interpretation A 2-h observation period is probably safe for most children who present to an emergency department with an acute allergic reaction requiring epinephrine. A 4-h observation period might be enough for patients with cardiovascular involvement who appear well.

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Research in context

Evidence before this study

Anaphylaxis is a potentially life-threatening allergic reaction that frequently presents to the emergency department and might require hospitalisation. No formal systematic review of the literature was done. Approximately 5% of children have recurrent anaphylaxis symptoms after initial resolution (ie, biphasic reaction), but the timing of these events is highly variable. As such, after treatment with epinephrine, patients experience variation in the time spent under observation in the emergency department or hospital. Robust clinical data with accurate predictor and outcome variables are needed to optimise and standardise anaphylaxis observation periods, eliminate variation in clinical practice, and avoid both unnecessarily long emergency department stays and hospitalisations.

Added value of this study

In this 31-center retrospective cohort study of 5641 patients aged 6 months to 17 years who presented to an emergency department with an acute allergic reaction that was treated with epinephrine between Jan 1, 2016, and Dec 31, 2019, we used Kaplan-Meier analyses to determine the timing from initial to last dose epinephrine administration to inform the optimal anaphylaxis observation period. In the entire cohort, 263 (4·7%) patients received repeat epinephrine 2 h after the initial dose, whereas 109 (1·9%) patients received repeat epinephrine after 4 h, 64 (1·1%) after 6 h, and 46 (0·8%) after 8 h. To determine if patients with more severe initial reactions require longer observation periods than patients with less severe reactions, we stratified the cohort by severity groups and found that patients with no cardiovascular involvement were at low risk of receiving repeat epinephrine beyond 2 h after initial epinephrine dose, whereas patients with cardiovascular involvement were at low risk of receiving repeat epinephrine beyond 4 h. Applied to our cohort, these findings suggest that 5378 (95·3%) patients could have been safely discharged 2 h after initial epinephrine dose, and 5532 (98·1%) patients could have been safely discharged 4 h after the initial epinephrine dose.

Implications of all the available evidence

A 2-h observation period after epinephrine is probably safe for most children with anaphylaxis without cardiovascular involvement. Patients with cardiovascular involvement might require a longer observation, but the risk of repeat epinephrine beyond 4 h is low. Incorporating our findings into an appropriate discharge bundle that includes epinephrine prescription and education, allergist referral, and counselling on allergen avoidance might help standardise anaphylaxis care, reduce anaphylaxis observation periods, and limit unnecessary hospitalisations.

Introduction

Anaphylaxis is a potentially life-threatening allergic reaction that frequently demands emergency department assessment and might require hospitalisation.[1] In the USA, from 2008 to 2016 the number of paediatric emergency department visits by children with anaphylaxis increased from 54 visits per million person-years to 163 visits per million person-years (incidence rate ratio 3·23 [95% CI 2·56–3·90]), placing a substantial strain on patients, caregivers, and the health-care system.[2,3] After treatment with epinephrine, patients are observed in the emergency department or monitored on a hospital ward for biphasic reactions. The optimal duration of observation is unknown, and evidence is needed to avoid practice variation, unnecessarily long emergency department stays, avoidable hospitalisations, and inform guidelines.[3–5]

An emergency department study of 294 children with anaphylaxis used the timing of repeat epinephrine as an outcome to inform the optimal duration of observation. The investigators reported that repeat dosing occurred most commonly within 2 h (17%; n=51), and 4% (n=11) of patients received epinephrine more than 4 h after the initial dose.[6] However, this study only included hospitalised patients and had an insufficient sample size to stratify the analysis based on reaction severity.

Our study aimed to determine the incidence rate and timing of repeat epinephrine dosing based on initial reaction severity, because it is hypothesised that patients with severe reactions might need to be observed for longer than patients with less severe reactions. Additionally, we sought to identify predictors of repeat epinephrine administration.

Methods

Study design and participants

We conducted a retrospective cohort study of children aged 6 months to 17 years who, between Jan 1, 2016, and Dec 31, 2019, presented with anaphylaxis to one of 30 emergency departments in the USA and one emergency department in Canada that are part of the Pediatric Emergency Medicine Collaborative Research Committee (appendix p 1). Each participating emergency department received approval for the study from its institutional review board. Patient consent was waived, and data use agreements were obtained when necessary.[7] The study was conducted and reported per STROBE reporting guidelines for observational studies.[8]

Eligible cases were identified from electronic medical records using the ICD-10, Clinical Modification codes for anaphylaxis (appendix p 4).[7] Sites identified the most recent patient encounter up to Dec 31, 2019, and reviewed retrospective visits consecutively until the target of approximately 200 eligible encounters was reached (6000 total encounters across 31 emergency departments). For patients with more than one emergency department

Cumming School of Medicine, University of Calgary, Calgary, AB, Canada; Department of Pediatric Emergency Medicine, Children's Minnesota, Minneapolis, MN, USA (K R Bergmann DO); **Department of Emergency Medicine, Stanford University School of Medicine, Palo Alto, CA, USA** (B Boswell MD, K Khanna MD); **Department of Pediatrics, Section of Pediatric Emergency Medicine, Medical College of Wisconsin, Milwaukee, WI, USA** (S S Chinta MBBS, P S Walsh MD); **Mass General for Children, Boston, MA, USA** (W-J Chua MD, A R Cohen MD); **Massachusetts General Hospital, Boston, MA, USA** (W-J Chua, A R Cohen); **Department of Emergency Medicine, Harvard Medical School, Boston, MA, USA** (W-J Chua, A R Cohen); **Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, MD, USA** (J S Cohen MD); **Department of Pediatrics at Children's Mercy Kansas City, Kansas City, MO, USA** (A Daggett MD); **University of Missouri-Kansas City School of Medicine, Kansas City, MO, USA** (A Daggett); **Pediatric Emergency Medicine, University of Mississippi Medical Center, Jackson, MS, USA** (J R Davis MD); **Children's Hospital Colorado, Aurora, CO, USA** (J F Freeman MD, C Vander Wyst MD); **University of Colorado School of Medicine, Aurora, CO, USA** (J F Freeman, C Vander Wyst); **The Children's Hospital at Oklahoma University Health, Oklahoma City, OK, USA** (C L Knoles MD); **Division of Emergency and Transport Medicine, Department of Pediatrics, Keck School of Medicine of the University of Southern California, Children's Hospital Los Angeles, Los Angeles, CA, USA** (K Y Kwan MD); **Department of Pediatrics Spencer Fox Eccles School of Medicine, University of Utah, Salt Lake City, UT, USA** (C D Larsen MD); **Division of Allergy and Immunology, Children's Hospital of Philadelphia, Philadelphia, PA, USA** (J Lee MD); **Perelman School of Medicine at University of Pennsylvania, Philadelphia, PA, USA** (J Lee); **Division of Pediatric Emergency Medicine,**

Department of Emergency Medicine, Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA (T R Lubell MD); Rady Children's Hospital, University of California San Diego, San Diego, CA, USA (A M Metcalf DO); Division of Pediatric Emergency Medicine, Medical University of South Carolina, Charleston, SC, USA (M M Moake MD); UT Southwestern Medical Center—Children's Medical Center, Dallas, TX, USA (Prof J-A O Nesiama MD); Johns Hopkins University School of Medicine, St Petersburg, FL, USA (T L Ngo DO); Department of Emergency Medicine and Pediatrics, University of Vermont Larner College of Medicine, Burlington, VT, USA (C D Pulcini MD); Division of Pediatric Emergency Medicine, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA (N V Singh MD); Valley Children's Hospital, Madera, CA, USA (G Srivastava MD); Department of Pediatrics, University of Minnesota, St Paul and Minneapolis, MN, USA (J Strutt MD); University of Texas-McGovern Medical School, Houston, TX, USA (V Thapar MD); Albert Einstein College of Medicine—Jacobi Medical Center, Bronx, NY, USA (Y Wolnerman MD)

Correspondence to: Assoc Prof Timothy E Dribin, Division of Emergency Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229, USA
timothy.dribin@cchmc.org

See Online for appendix

encounter for anaphylaxis, only information pertaining to the most recent encounter was included to avoid biasing the standard error estimates and reducing generalisability.[7,9]

Electronic medical records were reviewed manually. Patients were eligible if presenting to an emergency department with an acute allergic reaction that was treated with intramuscular, subcutaneous, or intravenous epinephrine in the pre-emergency department (before arrival at an emergency department) or in the emergency department setting.[7] Treated reactions that did not fulfil the 2006 National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) anaphylaxis criteria (appendix p 5)[10] were eligible because the administration of epinephrine might have mitigated reaction progression.

Patients were excluded if any of the following criteria were met: (1) no documentation of pre-emergency department symptoms or examination findings, (2) patients were transferred from outside health-care facilities, (3) reactions were secondary to medications administered in the emergency department, or (4) if the patient had any comorbidities requiring tailored management decisions (mast cell activation disorders, hereditary angioedema, home oxygen or positive pressure ventilation, or presence of a tracheostomy).[7]

Procedures

Representatives of each participating emergency department abstracted the following information from electronic medical records: demographics (sex, race, ethnicity), insurance status, emergency department and inpatient lengths of stay, medical history, treatments received before arrival at and during stay at emergency department, inpatient treatments, and number of emergency department revisits within 72 h of initial discharge (for revisits data such as reaction features, treatments, and disposition was extracted). A complete list of data elements abstracted from electronic medical records is available in the appendix (p 1).[7] Organ systems considered for involvement were skin or mucosal (urticaria, flushing, angioedema, and facial swelling), gastrointestinal (vomiting, abdominal pain, diarrhoea, and nausea or upset stomach), respiratory (wheezing, stridor, cough, increased work of breathing, dyspnoea, rhinorrhoea, and throat symptoms), and cardiovascular (hypotension, syncope, dizziness, incontinence, and altered mental status).[7]

A second representative of each participating emergency department completed an independent review of key variables for 10% of patient encounters at random to enable assessment of interobserver agreement, which are presented as Kappa values. Block randomisation was conducted based on the exact hospitalisation rates at each study site. 10% of patients were randomly selected into the Kappa portion. If no patients with refractory anaphylaxis were included in this selection, one patient with refractory anaphylaxis was randomly chosen and added to the Kappa portion to ensure representation.

Outcomes

The primary outcome was time between administration of the first and last dose of intramuscular or intravenous epinephrine; for patients on intravenous epinephrine infusions, we considered the time between infusion initiation and discontinuation. Secondary outcomes (appendix p 7) were not mutually exclusive and included biphasic anaphylaxis (complete symptom resolution followed by recurrent symptoms or examination findings that fulfilled NIAID/FAAN anaphylaxis criteria), biphasic non-anaphylaxis (recurrent symptoms or examination findings that did not fulfil NIAID/FAAN criteria), persistent anaphylaxis (persistent symptoms or examination findings that fulfilled NIAID/FAAN criteria), persistent non-anaphylaxis (persistent symptoms or examination findings that did not fulfil NIAID/FAAN criteria), and refractory anaphylaxis (initial reaction treated with at least three epinephrine doses or the initiation of an epinephrine infusion and receipt of symptom-directed medical management such as intravenous fluid bolus for patients with hypotension).[7,12]

Statistical analysis

The present study is part of a larger multicentre network study with multiple objectives, one of which is to derive and validate prediction models for emergency department discharge, for which a sample size of 6000 emergency department encounters was required to detect a 5% prevalence of receiving acute therapies beyond 4 h from the initial epinephrine dose with a CI width of 1%.[7] We used the same sample size for the present study because we believed a priori that it would require the largest sample since it involves developing a prediction model with an uncommon outcome.

We used Kaplan–Meier analyses to derive times between first and last epinephrine dose, by initial reaction severity as defined by symptoms and examination findings from the pre-emergency department setting and initial emergency department evaluation. Initial reaction severity was categorised as (1) all patients, (2) no respiratory or cardiovascular involvement, (3) respiratory but no cardiovascular involvement, and (4) cardiovascular involvement.[7]

A priori, we sought to determine the observation threshold at which there was less than a 2% increase in the cumulative incidence of repeat epinephrine dosing as the observation time increased by 1 h. For example, if this observation threshold occurs at 2 h, the cumulative incidence of repeat dose administration between 2 h and 3 h increases by less than 2%. This threshold risk of repeat epinephrine was deemed clinically acceptable because it represented the optimal balance between prolonged observation with limited benefit and the

likelihood of biphasic anaphylaxis occurring after discharge. We also report observation time thresholds for <1% and <0·5% increases in cumulative incidence of repeat epinephrine and the proportion of patients who received repeat epinephrine every hour after the initial dose, given that clinicians and patients or caregivers might accept different risk thresholds for needing epinephrine after observation.[13]

We did not exclude patients with missing data on timing of epinephrine administration; 199 (3·5%) patients received two or more epinephrine doses with missing times for first or last dose. For these patients, we imputed their last dose as the 90th percentile across the cohort without missing data; this approach would probably overestimate the time to the last dose (appendix p 12).

We used a semiparametric mixture cure model to predict repeat epinephrine administration (appendix pp 2–3).[14] This model extends the Cox proportional hazard model by allowing cure after the first dose and provides odds ratios (ORs) for cure and hazard ratios (HRs) for time to repeat epinephrine. We developed univariable and multivariable cure models. Candidate predictors were selected based on biological plausibility and from known risk factors for repeat epinephrine, refractory, or biphasic anaphylaxis (age in years, history of anaphylaxis, history of anaphylaxis to trigger, severe previous anaphylaxis [ie, intensive care unit admission, vasopressors, non-invasive ventilation, or intubation], asthma, asthma controller medication use, food triggers, unknown triggers, receipt of pre-emergency department epinephrine or antihistamines, or systemic steroids in the emergency department).[6,7,15-18] For the model that included all patients, we included initial reaction respiratory or cardiovascular involvement as predictors. Respiratory involvement was categorised as potentially less severe (throat symptoms, cough, or rhinorrhoea) versus severe (wheezing, stridor, respiratory distress, or hypoxemia [oxygen saturation ≤92%][19]). Cardiovascular involvement was categorised as potentially less severe (dizziness) versus severe (syncope, altered mental status, or hypotension) cardiovascular findings.

We compared characteristics of patients with emergency department lengths of stay of less than 4 h to those of patients who stayed 4 h or longer, and we used Kaplan–Meier analyses employing the following approaches: (1) application of a risk score multiple imputation approach for missing epinephrine timestamps,[20] because single imputation might underestimate variations in estimates (appendix p 1); (2) age quartile stratification; (3) inclusion restricted to participants meeting NIAID/FAAN criteria; (4) comparison of participants with less severe versus severe respiratory and cardiovascular involvement using the severity categories of the cure model; and (5) restriction of clinical findings to those initially present in the emergency department because they might be more reliable than those reported by caregivers. We performed cluster bootstrapping to evaluate the clustering effect across different centres; the process was repeated 100 times.[21] Lastly, to evaluate whether the overall results were influenced by different centres, we excluded each centre one at a time and report the results for the less than 2% risk threshold in a forest plot.

Analyses were conducted using SAS version 9.4 and R version 4.2.1, and the semiparametric mixture cure models were estimated using the smcure package in R.[22]

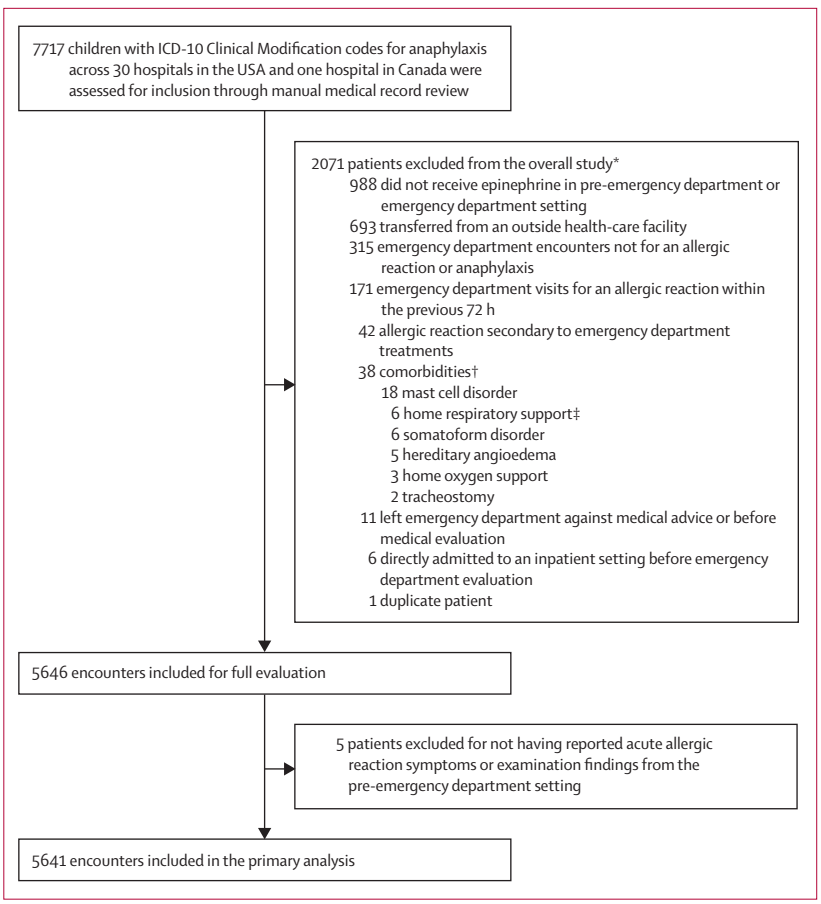


Figure 1: **Cohort development in a study to determine the incidence rate and timing of repeat epinephrine dosing among children with anaphylaxis**
*Patients could have more than one exclusion criterion. †Patients could have more than one comorbidity. ‡Continuous positive airway pressure, Bilevel positive pressure ventilation, or mechanical ventilation.

Role of the funding source
The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Of 7717 children presenting to emergency departments with ICD-10 Clinical Modification codes for anaphylaxis, 5641 were eligible for inclusion (figure 1). Patient and reaction characteristics are summarised in the table. With a median age of 7·9 years (IQR 3·3–13·1), 2475 (43·9%) of 5641 patients were female, and

	Overall (n=5641)	Subgroup*		
		No respiratory or cardiovascular involvement (n=1070)	Respiratory involvement but no cardiovascular involvement (n=4076)	Cardiovascular involvement (n=495)
Site location				
USA (n=30)				
Northeast (n=7)	1340/5641 (23·8%)	286/1070 (26·7%)	949/4076 (23·3%)	105/495 (21·2%)
South (n=9)	1390/5641 (24·6%)	219/1070 (20·5%)	1039/4076 (25·5%)	132/495 (26·7%)
Midwest (n=6)	1171/5641 (20·8%)	225/1070 (21·0%)	862/4076 (21·1%)	84/495 (17·0%)
West (n=8)	1542/5641 (27·3%)	296/1070 (27·7%)	1117/4076 (27·4%)	129/495 (26·1%)
Canada (n=1)	198/5641 (3·5%)	44/1070 (4·1%)	109/4076 (2·7%)	45/495 (9·0%)
Demographics				
Age, years	7·9 (3·3–13·1); 5641	3·4 (1·3–8·0); 1070	8·8 (4·3–13·5); 4076	10·8 (4·7–15·2); 495
Sex				
Female	2475/5641 (43·9%)	441/1070 (41·2%)	1803/4076 (44·2%)	231/495 (46·7%)
Male	3166/5641 (56·1%)	629/1070 (58·8%)	2273/4076 (55·8%)	264/495 (53·3%)
Race†				
White	2349/4717 (49·8%)	441/871 (50·6%)	1707/3455 (49·4%)	201/391 (51·4%)
Black or African American	1396/4717 (29·6%)	216/871 (24·8%)	1071/3455 (31·0%)	109/391 (27·9%)
American Indian	14/4717 (0·3%)	1/871 (0·1%)	12/3455 (0·3%)	1/391 (0·3%)
Asian or Native Hawaiian or Other Pacific Islander	440/4717 (9·3%)	108/871 (12·4%)	297/3455 (8·6%)	35/391 (9·0%)
Other	518/4717 (11·0%)	105/871 (12·1%)	368/3455 (10·7%)	45/391 (11·5%)
Ethnicity†				
Hispanic	1131/5139 (22·0%)	205/972 (21·1%)	815/3740 (21·8%)	111/427 (26·0%)
Non-Hispanic	4008/5139 (78·0%)	767/972 (78·9%)	2925/3740 (78·2%)	316/427 (74·0%)
Insurance				
Private	2802/5464 (51·3%)	560/1044 (53·6%)	2019/3941 (51·2%)	223/479 (46·6%)
Public	2348/5464 (43·0%)	436/1044 (41·8%)	1677/3941 (42·6%)	235/479 (49·1%)
Both private and public	173/5464 (3·2%)	25/1044 (2·4%)	138/3941 (3·5%)	10/479 (2·1%)
Self-pay or uninsured	69/5464 (1·3%)	8/1044 (0·8%)	52/3941 (1·3%)	9/479 (1·9%)
Other	72/5464 (1·3%)	15/1044 (1·4%)	55/3941 (1·4%)	2/479 (0·4%)
Medical history				
Previous anaphylaxis	1561/3885 (40·2%)	258/767 (33·6%)	1153/2774 (41·6%)	150/344 (43·6%)
Number of previous anaphylaxis episodes				
1	415/681 (60·9%)	72/117 (61·5%)	308/498 (61·8%)	35/66 (53·0%)
≥2	266/681 (39·1%)	45/117 (38·5%)	190/498 (38·2%)	31/66 (47·0%)
Previous anaphylactic reaction to the current allergen	685/922 (74·3%)	108/160 (67·5%)	512/669 (76·5%)	65/93 (69·9%)
Asthma	1944/5641 (34·5%)	194/1070 (18·1%)	1576/4076 (38·7%)	174/495 (35·2%)
Reaction characteristics				
Trigger				
Food	4082/4640 (88·0%)	782/878 (89·1%)	2969/3351 (88·6%)	331/411 (80·5%)
Peanut	1003/4082 (24·6%)	197/782 (25·2%)	744/2969 (25·1%)	62/331 (18·7%)
Other nuts	974/4082 (23·9%)	158/782 (20·2%)	732/2969 (24·7%)	84/331 (25·4%)
Multiple food exposure	790/4082 (19·4%)	151/782 (19·3%)	570/2969 (19·2%)	69/331 (20·8%)
Other food	412/4082 (10·1%)	73/782 (9·3%)	295/2969 (9·9%)	44/331 (13·3%)
Egg	272/4082 (6·7%)	101/782 (12·9%)	155/2969 (5·2%)	16/331 (4·8%)
Milk	203/4082 (5·0%)	34/782 (4·3%)	153/2969 (5·2%)	16/331 (4·8%)
Shellfish	200/4082 (4·9%)	25/782 (3·2%)	149/2969 (5·0%)	26/331 (7·9%)
Fish	146/4082 (3·6%)	29/782 (3·7%)	108/2969 (3·6%)	9/331 (2·7%)
Sesame	44/4082 (1·1%)	9/782 (1·2%)	32/2969 (1·1%)	3/331 (0·9%)
Gluten	22/4082 (0·5%)	5/782 (0·6%)	16/2969 (0·5%)	1/331 (0·3%)
Soy	16/4082 (0·4%)	0	15/2969 (0·5%)	1/331 (0·3%)

(Table continues on next page)

	Overall (n=5641)	Subgroup*		
		No respiratory or cardiovascular involvement (n=1070)	Respiratory involvement but no cardiovascular involvement (n=4076)	Cardiovascular involvement (n=495)
(Continued from previous page)				
Unknown	1001/5641 (17·7%)	192/1070 (17·9%)	725/4076 (17·8%)	84/495 (17·0%)
Medications	264/4640 (5·7%)	43/878 (4·9%)	184/3351 (5·5%)	37/411 (9·0%)
Insect stings	140/4640 (3·0%)	38/878 (4·3%)	87/3351 (2·6%)	15/411 (3·6%)
Medications				
Pre-emergency department treatment				
Epinephrine doses				
0	3079/5641 (54·6%)	628/1070 (58·7%)	2206/4076 (54·1%)	245/495 (49·5%)
1	2318/5641 (41·1%)	416/1070 (38·9%)	1692/4076 (41·5%)	210/495 (42·4%)
2	215/5641 (3·8%)	26/1070 (2·4%)	156/4076 (3·8%)	33/495 (6·7%)
≥3	29/5641 (0·5%)	0	22/4076 (0·5%)	7/495 (1·4%)
Antihistamines	3144/5641 (55·7%)	522/1070 (48·8%)	2339/4076 (57·4%)	283/495 (57·2%)
Inhaled bronchodilators	610/5641 (10·8%)	17/1070 (1·6%)	529/4076 (13·0%)	64/495 (12·9%)
Intravenous fluid bolus	99/5641 (1·8%)	4/1070 (0·4%)	64/4076 (1·6%)	31/495 (6·3%)
Emergency department treatment				
Number of epinephrine doses				
0	2165/5641 (38·4%)	403/1070 (37·7%)	1571/4076 (38·5%)	191/495 (38·6%)
1	3255/5641 (57·7%)	632/1070 (59·1%)	2360/4076 (57·9%)	263/495 (53·1%)
2	198/5641 (3·5%)	33/1070 (3·1%)	131/4076 (3·2%)	34/495 (6·9%)
≥3	23/5641 (0·4%)	2/1070 (0·2%)	14/4076 (0·3%)	7/495 (1·4%)
Systemic steroids	3873/5641 (68·7%)	708/1070 (66·2%)	2837/4076 (69·6%)	328/495 (66·3%)
Antihistamines	3117/5641 (55·3%)	620/1070 (57·9%)	2241/4076 (55·0%)	256/495 (51·7%)
Inhaled bronchodilators	994/5641 (17·6%)	23/1070 (2·1%)	874/4076 (21·4%)	97/495 (19·6%)
Intravenous fluid bolus	1194/5641 (21·2%)	166/1070 (15·5%)	844/4076 (20·7%)	184/495 (37·2%)
Inpatient treatment				
Number of epinephrine doses				
0	901/935 (96·4%)	124/124 (100%)	646/678 (95·3%)	131/133 (98·5%)
1	28/935 (3·0%)	0	26/678 (3·8%)	2/133 (1·5%)
2	4/935 (0·4%)	0	4/678 (0·6%)	0
≥3	2/935 (0·2%)	0	2/678 (0·3%)	0
Total number of epinephrine doses (pre-emergency department, emergency department, and inpatient)				
1	4838/5641 (85·8%)	975/1070 (91·1%)	3490/4076 (85·6%)	373/495 (75·4%)
2	668/5641 (11·8%)	88/1070 (8·2%)	487/4076 (11·9%)	93/495 (18·8%)
≥3	135/5641 (2·4%)	7/1070 (0·7%)	99/4076 (2·4%)	29/495 (5·9%)
Median time between first and second epinephrine dose, min (IQR)‡	82·0 (48·0–135·0); 271	91·0 (40·0–130·0); 21	83·0 (50·0–155·0); 209	66·0 (43·0–100·0); 41
Median time between second and third epinephrine dose, min (IQR)‡	55·0 (23·0–136·0); 25	260·0 (260·0–260·0); 1	68·0 (42·0–178·5); 16	16·0 (10·5–74·5); 8
High-acuity therapies (emergency department or inpatient, or both)				
Vasopressors	43/5641 (0·8%)	3/1070 (0·3%)	28/4076 (0·7%)	12/495 (2·4%)
Positive pressure ventilation	14/5641 (0·2%)	0	7/4076 (0·2%)	7/495 (1·4%)
Anaphylaxis courses (outcomes are not mutually exclusive)§				
Biphasic anaphylaxis	86/5641 (1·5%)	6/1070 (0·6%)	62/4076 (1·5%)	18/495 (3·6%)
Biphasic non-anaphylaxis	236/5641 (4·2%)	44/1070 (4·1%)	162/4076 (4·0%)	30/495 (6·1%)
Persistent anaphylaxis	605/5641 (10·7%)	14/1070 (1·3%)	473/4076 (11·6%)	118/495 (23·8%)
Persistent non-anaphylaxis	1400/5641 (24·8%)	330/1070 (30·8%)	958/4076 (23·5%)	112/495 (22·6%)
Refractory anaphylaxis				
Yes	118/5641 (2·1%)	10/1070 (0·9%)	80/4076 (2·0%)	28/495 (5·7%)
No	5520/5641 (97·9%)	1060/1070 (99·1%)	3994/4076 (98·0%)	466/495 (94·1%)
Inconclusive	3/5641 (0·1%)	0	2/4076 (0·0%)	1/495 (0·2%)

(Table continues on next page)

	Overall (n=5641)	Subgroup*		
		No respiratory or cardiovascular involvement (n=1070)	Respiratory involvement but no cardiovascular involvement (n=4076)	Cardiovascular involvement (n=495)
(Continued from previous page)				
Emergency department disposition				
Inpatient hospitalisation	935/5641 (16·6%)	124/1070 (11·6%)	678/4076 (16·6%)	133/495 (26·9%)
Intensive care unit admission	152/935 (16·3%)	15/124 (12·1%)	100/678 (14·7%)	37/133 (27·8%)
Emergency department discharge	4697/5641 (83·3%)	945/1070 (88·3%)	3391/4076 (83·2%)	361/495 (72·9%)
Emergency department revisit related to index encounter	83/5641 (1·5%)	12/1070 (1·1%)	59/4076 (1·4%)	12/495 (2·4%)
Inpatient hospitalisation at revisit	20/83 (24·1%)	4/12 (33·3%)	12/59 (20·3%)	4/12 (33·3%)

Data are n/N (%) or median (IQR); n. NIAID/FAAN=National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network. *Subgroups were defined based on pre-emergency department and initial emergency department symptoms or examination findings. Respiratory was defined as any of the following: wheezing, stridor, cough, increased work of breathing, dyspnoea, rhinorrhoea, or throat symptoms. Cardiovascular was defined as any of the following: hypotension, syncope, dizziness, incontinence, or altered mental status. †Race and ethnicity data were based on documentation in electronic medical records. These variables included race (multiple selection variable), defined as White, Black or African American, American Indian or Alaska Native, Asian or Native Hawaiian or other Pacific Islander, other race (free text variable), or race not documented. Ethnicity was defined as Hispanic, non-Hispanic, or ethnicity not documented (single selection variable). ‡Median time from first to second (and second to third) epinephrine doses in min. §Biphasic anaphylaxis: complete symptom resolution followed by recurrent symptoms or examination findings that fulfil NIAID/FAAN criteria. Biphasic non-anaphylaxis: recurrent symptoms or examination findings that do not fulfil NIAID/FAAN criteria. Persistent anaphylaxis: persistent symptoms or examination findings that fulfil NIAID/FAAN criteria. Persistent non-anaphylaxis: persistent symptoms or examination findings that do not fulfil NIAID/FAAN criteria. Refractory anaphylaxis: the initial reaction treated with three or more epinephrine doses or initiating an epinephrine infusion and receipt of symptom-directed medical management such as an intravenous fluid bolus for patients with hypotension.

Table: **Patient and reaction characteristics**

3166 (56·1%) were male. 4717 patient records included race and ethnicity data; 2349 (49·8%) patients were White, 1396 (29·6%) were Black or African American, 14 (0·3%) were American Indian, 440 (9·3%) were Asian or Native Hawaiian or Other Pacific Islanders, and 518 (11·0%) identified as Other. 1131 (22·0%) of 5139 patients identified as Hispanic and 4008 (78·0%) patients identified as non-Hispanic.

4956 (87·9%) patients fulfilled NIAID/FAAN anaphylaxis criteria.[10] Of the 2562 (45·4%) patients who received pre-emergency department epinephrine, 2158 (84·2%) did not receive repeat epinephrine after emergency department arrival. The Kappa values for interobserver agreement for pre-emergency department and initial emergency department symptoms and examination findings (n=574) were 0·76 and 0·73, respectively, indicating substantial agreement (appendix p 6).[11]

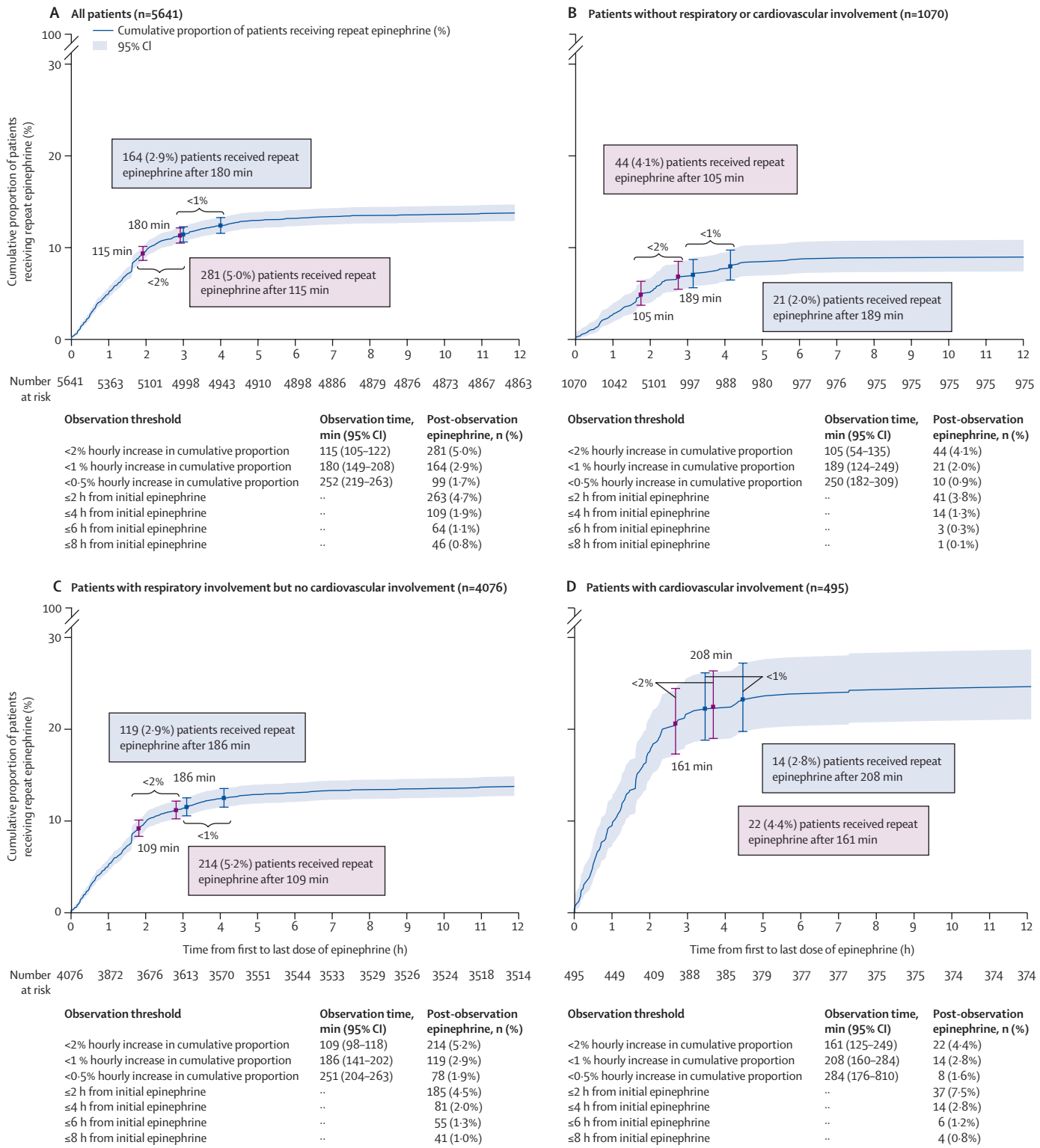
Overall, 86 (1·5%) encounters fulfilled the criteria for biphasic anaphylaxis, 236 (4·2%) for biphasic non-anaphylactic allergic reactions, 605 (10·7%) for persistent anaphylaxis, 1400 (24·8%) for persistent non-anaphylactic allergic reactions, and 118 (2·1%) for refractory anaphylaxis; 3457 (61·3%) of the cohort did not have any of these outcomes. Compared with patients with and without respiratory involvement, patients with cardiovascular involvement had higher rates of biphasic (0·6% *vs* 1·5% *vs* 3·6%), persistent (1·3% *vs* 11·6% *vs* 23·8%), and refractory anaphylaxis (0·9% *vs* 2·0% *vs* 5·7%). At the index emergency department visit, 935 (16·6%) patients were hospitalised. There was one fatality in the cohort that occurred during the index encounter; the patient was intubated in the emergency department and died during inpatient care. Following discharge home, 83 (1·5%) patients had a 72 h emergency department revisit related to the index encounter, of which 33 (39·8%) received epinephrine.

Among all 5641 encounters, 263 (4·7%) patients received repeat epinephrine after 2 h from the initial dose, whereas 109 (1·9%) patients received repeat epinephrine after 4 h, 64 (1·1%) after 6 h, and 46 (0·8%) after 8 h (figure 2A). The observation threshold at which the cumulative incidence of repeat epinephrine was less than 2% was 115 min (95% CI 105–122); 281 (5·0%) patients received repeat epinephrine later than 115 min after the initial dose. Applied to our cohort, this observation threshold suggests that 5378 (95·3%) patients could have been safely discharged 2 h after receiving the first epinephrine dose, and 5532 (98·1%) patients could have been safely discharged 4 h after the first epinephrine dose.

Figure 2: **Cumulative incidence of repeat epinephrine dosing based on pre-emergency department and initial emergency department symptoms or examination findings**

Respiratory involvement was defined as any of the following: wheezing, stridor, cough, increased work of breathing, dyspnoea, rhinorrhoea, or throat symptoms. Cardiovascular involvement was defined as any of the following: hypotension, syncope, dizziness, incontinence, or altered mental status. Purple boxes represent data on the less than 2% risk threshold (a priori outcome), including the time threshold and the number and percentage of patients who received epinephrine after the time threshold. Blue boxes represent data on the less than 1% risk threshold, including the time threshold and the number and percentage of patients who received epinephrine after the time threshold.

For the 1070 patients without respiratory or cardiovascular involvement, 41 (3·8%) patients received repeat epinephrine 2 h after the first dose, 14 (1·3%) after 4 h, three (0·3%) after 6 h, and one (0·1%) after 8 h (figure 2B). The observation threshold at which the cumulative incidence of repeat epinephrine was less



Observation threshold	Observation time, min (95% CI)	Post-observation epinephrine, n (%)
<2% hourly increase in cumulative proportion	115 (105–122)	281 (5·0%)
<1 % hourly increase in cumulative proportion	180 (149–208)	164 (2·9%)
<0·5% hourly increase in cumulative proportion	252 (219–263)	99 (1·7%)
≤2 h from initial epinephrine	..	263 (4·7%)
≤4 h from initial epinephrine	..	109 (1·9%)
≤6 h from initial epinephrine	..	64 (1·1%)
≤8 h from initial epinephrine	..	46 (0·8%)

Observation threshold	Observation time, min (95% CI)	Post-observation epinephrine, n (%)
<2% hourly increase in cumulative proportion	105 (54–135)	44 (4·1%)
<1 % hourly increase in cumulative proportion	189 (124–249)	21 (2·0%)
<0·5% hourly increase in cumulative proportion	250 (182–309)	10 (0·9%)
≤2 h from initial epinephrine	..	41 (3·8%)
≤4 h from initial epinephrine	..	14 (1·3%)
≤6 h from initial epinephrine	..	3 (0·3%)
≤8 h from initial epinephrine	..	1 (0·1%)

Observation threshold	Observation time, min (95% CI)	Post-observation epinephrine, n (%)
<2% hourly increase in cumulative proportion	109 (98–118)	214 (5·2%)
<1 % hourly increase in cumulative proportion	186 (141–202)	119 (2·9%)
<0·5% hourly increase in cumulative proportion	251 (204–263)	78 (1·9%)
≤2 h from initial epinephrine	..	185 (4·5%)
≤4 h from initial epinephrine	..	81 (2·0%)
≤6 h from initial epinephrine	..	55 (1·3%)
≤8 h from initial epinephrine	..	41 (1·0%)

Observation threshold	Observation time, min (95% CI)	Post-observation epinephrine, n (%)
<2% hourly increase in cumulative proportion	161 (125–249)	22 (4·4%)
<1 % hourly increase in cumulative proportion	208 (160–284)	14 (2·8%)
<0·5% hourly increase in cumulative proportion	284 (176–810)	8 (1·6%)
≤2 h from initial epinephrine	..	37 (7·5%)
≤4 h from initial epinephrine	..	14 (2·8%)
≤6 h from initial epinephrine	..	6 (1·2%)
≤8 h from initial epinephrine	..	4 (0·8%)

than 2% was 105 min (95% CI 54–135), and 44 (4·1%) patients received repeat epinephrine later than 105 min after the initial dose.

For 4076 patients with respiratory but no cardiovascular involvement, 185 (4·5%) patients received repeat epinephrine after 2 h of the initial dose, whereas 81 (2·0%) patients received repeat epinephrine after 4 h, 55 (1·3%) after 6 h, and 41 (1·0%) after 8 h (figure 2C). The observation threshold at which the cumulative incidence of repeat epinephrine was less than 2% was 109 min (95% CI 98–118), and 214 patients (5·2%) received repeat epinephrine later than 109 min after the initial dose.

For the 495 patients with cardiovascular involvement, 37 (7·5%) patients received repeat epinephrine after 2 h of the initial dose, whereas 14 (2·8%) patients received repeat epinephrine after 4 h, six (1·2%) after 6 h, and four (0·8%) after 8 h (figure 2D). The observation threshold at which the cumulative incidence of repeat epinephrine was less than 2% was 161 min (95% CI 125–249), and 22 patients (4·4%) received repeat epinephrine later than 161 min after the initial dose.

Predictors of repeat epinephrine based on the multivariable cure model are shown in figure 3; the univariable cure model is shown in the appendix (p 8). For the entire cohort, patients were more likely to receive repeat epinephrine if they had severe respiratory (OR 1·47 [95% CI 1·16–1·84]) or cardiovascular (3·18 [2·35–4·17]) involvement. For the 1070 patients without respiratory or cardiovascular involvement, patients were more likely to receive repeat epinephrine if they received pre-emergency department epinephrine (OR 3·43 [95% CI 2·05–5·78]), steroids in the emergency department (4·13 [2·21–7·43]), or had a history of severe anaphylaxis (HR 4·33 [95% CI 1·50–10·23]). Among the 4076 patients with respiratory but no cardiovascular involvement, asthma controller medication use (OR 1·58 [95% CI 1·21–2·07]), pre-emergency department epinephrine use (5·03 [4·05–6·24]) and emergency department steroid use (2·12 [1·67–2·63]) were associated with receiving repeat epinephrine. The risk of receiving repeat epinephrine was reduced if the reaction trigger was unknown (HR 0·53 [95% CI 0·34–0·87]). For the 495 patients with cardiovascular involvement, a history of anaphylaxis to the current trigger (OR 2·60 [95% CI 1·03–6·12]), a history of severe anaphylaxis (10·27 [3·09–82·37]), pre-emergency department epinephrine use (4·06 [2·41–6·63]), and emergency department steroid use (2·67 [1·54–4·65]) were associated with a higher risk of receiving repeat epinephrine.

Emergency department revisit was reported for 21 (1·1%) of 1931 patients with lengths of stay of less than 4 h and for 62 (1·7%) of 3710 patients with lengths of stay of 4 h or more (p=0·10; appendix p 9). When using multiple imputation for the entire cohort, the less than 2% incidence threshold was 107 min (95% CI 97–115; appendix p 13; the multiple imputation analyses stratified by respiratory and cardiovascular involvement is in the appendix [pp 14–16]). The less than 2% threshold for the first age quartile (<3·3 years; n=1410) was 109 min (95% CI 82–123), 118 min (109–168) for the second and third quartiles (3·3 years to <13·1 years; n=2819), and 117 min (98–122) for the fourth quartile (≥13·1 years; n=1412; appendix pp 17–19). The less than 2% threshold for patients who fulfilled NIAID/FAAN criteria was 117 min (95% CI 109–124; appendix p 20). There was a small difference in the less than 2% threshold for 1426 patients with less severe versus 3008 patients with severe respiratory involvement (110 min [95% CI 85–142] *vs* 117 min [109–124]; appendix pp 21–22), in contrast to 156 patients with less severe cardiovascular involvement versus 258 patients with severe cardiovascular involvement (105 min [95% CI 42–177] *vs* 186 min [136–258]; appendix pp 23–24). Observation periods based only on initial emergency department symptoms and examination findings are in the appendix (pp 25–27). The estimated medians and 95% CIs using cluster bootstrapping analysis were consistent with those from the primary analysis (106 min *vs* 107 min; appendix p 10). The Forest plot depicting the impact of each centre on the overall results showed minimal variation among sites (appendix p 28).

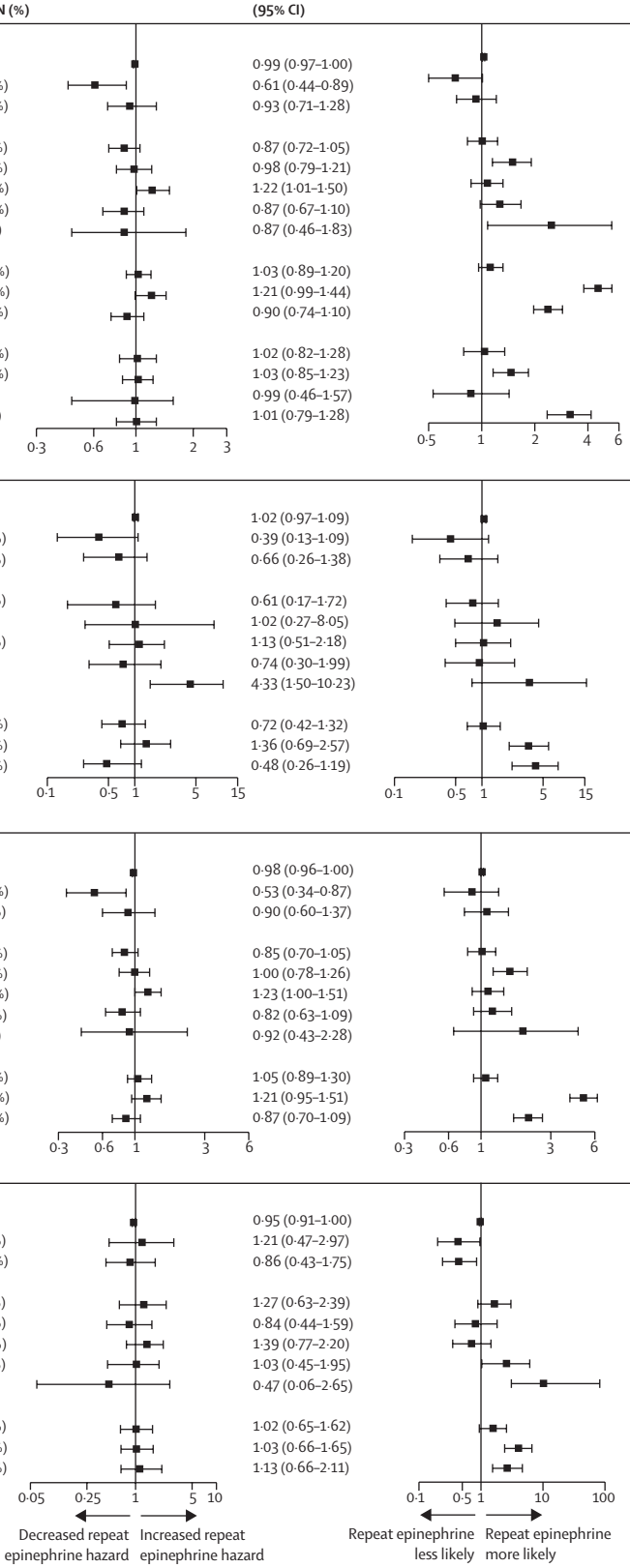
Discussion

In this large multicentre cohort of children with anaphylaxis, we established the cumulative incidence and timing of repeat epinephrine dosing based on initial reaction severity. Our data suggest that a 2-h observation period post-epinephrine is probably safe for most children without cardiovascular involvement. Although patients with cardiovascular involvement require a longer observation period, the risk of repeat epinephrine beyond 4 h is low. Although extending emergency department observation beyond the a priori less than 2% incidence threshold captures more patients who received a repeat dose of epinephrine, the incidence curves become flat, with diminishing returns seen with longer observation periods. Clinicians can incorporate these findings to inform observation periods based on reaction severity, provider and patient or caregiver risk tolerance, and access to epinephrine autoinjectors (EAIs). Applying

Figure 3: **Predictors of repeat epinephrine administration based on pre-emergency department and initial emergency department symptoms using multivariable cure models**

The cure mixture model models both cure rate and time to last dose of epinephrine. Odds ratios were estimated from logit part. Hazard ratios were estimated from time-to-event part. Age was included in the cure models as a continuous variable. We did not report the number and percentage of patients with and without repeat dosing stratified by age. *Respiratory was defined as any of the following: wheezing, stridor, cough, increased work of breathing, dyspnoea, rhinorrhoea, or throat symptoms. †Cardiovascular was defined as any of the following: hypotension, syncope, dizziness, incontinence, or altered mental status.

A All patients (n=5641)	Repeat dosing with characteristic, n/N (%)	No repeat dosing with characteristic, n/N (%)	Hazard ratio (95% CI)	Odds ratio (95% CI)
Patient and reaction characteristics				
Age, years	..	..	0·99 (0·97–1·00)	1·03 (1·01–1·04)
Unknown trigger	95/803 (11·8%)	906/4838 (18·7%)	0·61 (0·44–0·89)	0·71 (0·50–1·01)
Food trigger	620/803 (77·2%)	3462/4838 (71·6%)	0·93 (0·71–1·28)	0·93 (0·72–1·21)
Past medical history				
Asthma	341/803 (42·5%)	1603/4838 (33·1%)	0·87 (0·72–1·05)	1·01 (0·83–1·23)
Asthma controller medication use	164/803 (20·4%)	591/4838 (12·2%)	0·98 (0·79–1·21)	1·50 (1·15–1·91)
Anaphylaxis	306/803 (38·1%)	1255/4838 (25·9%)	1·22 (1·01–1·50)	1·08 (0·87–1·32)
Anaphylaxis to current trigger	157/803 (19·6%)	528/4838 (10·9%)	0·87 (0·67–1·10)	1·27 (0·98–1·67)
Severe anaphylaxis	12/803 (1·5%)	20/4838 (0·4%)	0·87 (0·46–1·83)	2·49 (1·08–5·46)
Medications				
Pre-emergency department antihistamine use	513/803 (63·9%)	2631/4838 (54·4%)	1·03 (0·89–1·20)	1·12 (0·96–1·32)
Pre-emergency department epinephrine use	607/803 (75·6%)	1955/4838 (40·4%)	1·21 (0·99–1·44)	4·58 (3·79–5·47)
Emergency department steroid use	627/803 (78·1%)	3246/4838 (67·1%)	0·90 (0·74–1·10)	2·38 (1·97–2·87)
Initial reaction severity				
Less severe respiratory reaction	178/803 (22·2%)	1248/4838 (25·8%)	1·02 (0·82–1·28)	1·04 (0·79–1·35)
Severe respiratory reaction	503/803 (62·6%)	2505/4838 (51·8%)	1·03 (0·85–1·23)	1·47 (1·16–1·84)
Less severe cardiovascular reaction	23/803 (2·9%)	133/4838 (2·7%)	0·99 (0·46–1·57)	0·87 (0·53–1·43)
Severe cardiovascular reaction	83/803 (10·3%)	175/4838 (3·6%)	1·01 (0·79–1·28)	3·18 (2·35–4·17)
B Patients without respiratory or cardiovascular involvement (n=1070)				
Patient and reaction characteristics				
Age, years	..	..	1·02 (0·97–1·09)	1·06 (1·00–1·11)
Unknown trigger	12/95 (12·6%)	180/975 (18·5%)	0·39 (0·13–1·09)	0·44 (0·16–1·19)
Food trigger	70/95 (73·7%)	712/975 (73·0%)	0·66 (0·26–1·38)	0·70 (0·33–1·52)
Past medical history				
Asthma	22/95 (23·2%)	172/975 (17·6%)	0·61 (0·17–1·72)	0·79 (0·39–1·54)
Asthma controller medication use	9/95 (9·5%)	57/975 (5·8%)	1·02 (0·27–8·05)	1·50 (0·49–4·45)
Anaphylaxis	31/95 (32·6%)	227/975 (23·3%)	1·13 (0·51–2·18)	1·05 (0·50–2·13)
Anaphylaxis to current trigger	15/95 (15·8%)	93/975 (9·5%)	0·74 (0·30–1·99)	0·94 (0·38–2·36)
Severe anaphylaxis	2/95 (2·1%)	4/975 (0·4%)	4·33 (1·50–10·23)	3·51 (0·77–15·68)
Medications				
Pre-emergency department antihistamine use	54/95 (56·8%)	468/975 (48·0%)	0·72 (0·42–1·32)	1·04 (0·68–1·62)
Pre-emergency department epinephrine use	63/95 (66·3%)	379/975 (38·9%)	1·36 (0·69–2·57)	3·43 (2·05–5·78)
Emergency department steroid use	81/95 (85·3%)	627/975 (64·3%)	0·48 (0·26–1·19)	4·13 (2·21–7·43)
C Patients with respiratory involvement* but no cardiovascular involvement (n=4076)				
Patient and reaction characteristics				
Age, years	..	..	0·98 (0·96–1·00)	1·02 (1·00–1·04)
Unknown trigger	68/586 (11·6%)	657/3490 (18·8%)	0·53 (0·34–0·87)	0·87 (0·56–1·32)
Food trigger	468/586 (79·9%)	2501/3490 (71·7%)	0·90 (0·60–1·37)	1·10 (0·77–1·54)
Past medical history				
Asthma	269/586 (45·9%)	1307/3490 (37·4%)	0·85 (0·70–1·05)	1·02 (0·81–1·26)
Asthma controller medication use	131/586 (22·4%)	475/3490 (13·6%)	1·00 (0·78–1·26)	1·58 (1·21–2·07)
Anaphylaxis	230/586 (39·2%)	923/3490 (26·4%)	1·23 (1·00–1·51)	1·12 (0·87–1·43)
Anaphylaxis to current trigger	115/586 (19·6%)	397/3490 (11·4%)	0·82 (0·63–1·09)	1·20 (0·89–1·62)
Severe anaphylaxis	8/586 (1·4%)	15/3490 (0·4%)	0·92 (0·43–2·28)	1·94 (0·65–4·61)
Medications				
Pre-emergency department antihistamine use	377/586 (64·3%)	1962/3490 (56·2%)	1·05 (0·89–1·30)	1·08 (0·89–1·30)
Pre-emergency department epinephrine use	453/586 (77·3%)	1417/3490 (40·6%)	1·21 (0·95–1·51)	5·03 (4·05–6·24)
Emergency department steroid use	453/586 (77·3%)	2384/3490 (68·3%)	0·87 (0·70–1·09)	2·12 (1·67–2·63)
D Patients with cardiovascular involvement† (n=495)				
Patient and reaction characteristics				
Age, years	..	..	0·95 (0·91–1·00)	0·98 (0·94–1·02)
Unknown trigger	15/122 (12·3%)	69/373 (18·5%)	1·21 (0·47–2·97)	0·43 (0·20–0·96)
Food trigger	82/122 (67·2%)	249/373 (66·8%)	0·86 (0·43–1·75)	0·44 (0·24–0·85)
Past medical history				
Asthma	50/122 (41·0%)	124/373 (33·2%)	1·27 (0·63–2·39)	1·66 (0·89–3·04)
Asthma controller medication use	24/122 (19·7%)	59/373 (15·8%)	0·84 (0·44–1·59)	0·82 (0·38–1·82)
Anaphylaxis	45/122 (36·9%)	105/373 (28·2%)	1·39 (0·77–2·20)	0·71 (0·35–1·45)
Anaphylaxis to current trigger	27/122 (22·1%)	38/373 (10·2%)	1·03 (0·45–1·95)	2·60 (1·03–6·12)
Severe anaphylaxis	2/122 (1·6%)	1/373 (0·3%)	0·47 (0·06–2·65)	10·27 (3·09–82·37)
Medications				
Pre-emergency department antihistamine use	82/122 (67·2%)	201/373 (53·9%)	1·02 (0·65–1·62)	1·58 (0·94–2·58)
Pre-emergency department epinephrine use	91/122 (74·6%)	159/373 (42·6%)	1·03 (0·66–1·65)	4·06 (2·41–6·63)
Emergency department steroid use	93/122 (76·2%)	235/373 (63·0%)	1·13 (0·66–2·11)	2·67 (1·54–4·65)



our findings has the potential to reduce anaphylaxis observation periods and hospitalisations.

Guidelines from the US Joint Task Force on Practice Parameters, the Resuscitation Council UK (RCUK), and the National Institute for Health and Clinical Excellence (NICE) state that there is a lack of evidence for how long patients with anaphylaxis should be observed.[3–5] The NICE guidelines recommend observing patients aged 16 years or older for 6 h to 12 h and hospitalising patients younger than 16 years.[3] Applying the NICE recommendations would have increased the proportion of participants hospitalised in our cohort from 16·6% (n=935) to 90·0% (n=5078). In contrast, the RCUK recommends risk-stratified observation periods (2 h *vs* ≥6 h *vs* ≥12 h) because 6 h to 12 h observation periods might miss over 50% of biphasic reactions,[5] which is likely too long in light of our results. Given the rate of biphasic reactions is so low, it would subject a lot of patients to long observation periods to capture these rare events.

The preponderance of anaphylaxis literature has centred on detecting biphasic reactions, which are estimated to occur in less than 5% of reactions.[16,23] Although it is important to identify biphasic anaphylaxis, clinical decision making and guidelines must also consider the 95% of patients who do not have these reactions. Our analytic approach using the time from the first to last dose of epinephrine captures patients with biphasic (1·5%) and persistent (10·7%) anaphylaxis, biphasic (4·2%) and persistent (24·8%) non-anaphylactic allergic reactions, refractory anaphylaxis (2·1%), and patients who did not have these outcomes (61·3% of the cohort). Additionally, our data is consistent with other large cohorts, showing that biphasic reactions are not fatal. As such, accepting a non-zero percent risk of receiving epinephrine after emergency department discharge is reasonable, especially if patients have access to EAIs or live in locations with rapid emergency medical service response times.[23]

Previous research identified cardiovascular involvement as a risk factor for biphasic or refractory anaphylaxis.[16–18] Our data reinforces this point because the less than 2% time threshold for patients with cardiovascular involvement was 161 min compared with patients without cardiovascular involvement who did or did not have respiratory involvement (109 min *vs* 105 min). Patients with more severe respiratory and cardiovascular involvement were at increased risk of receiving repeat epinephrine in the cure model. Thus, these patients might need to be observed longer than patients with less severe symptoms.

Consistent with previous research, our data reinforce that it is challenging to identify patients at risk of receiving repeat epinephrine.[6,15,24] Delayed epinephrine administration has been found to be a risk factor for biphasic anaphylaxis.[25,26] Thus, it was surprising that receipt of pre-emergency department epinephrine was a risk factor for repeat dosing. However, pre-emergency department epinephrine use might be a surrogate measure of reaction severity because patients with more severe reactions are more likely to receive epinephrine than those with less severe reactions. Confounding by severity might also explain why emergency department steroid use was a risk factor for repeat epinephrine.[27] Although previous research has shown conflicting data about whether asthma history is a risk factor for severe anaphylactic reactions, we found that patients on an asthma controller medication were at risk of repeat epinephrine,[28] reinforcing the complex interplay between patient attributes and reaction characteristics on clinical outcomes.

Our findings should not be used to identify patients at risk of biphasic, persistent, or refractory anaphylaxis, or how long patients should be observed to capture these outcomes, given that we did not account for the timing of clinical courses in relation to initial epinephrine administration. Because we could not account for the timing of symptom resolution and because there was the potential for not capturing all post-discharge epinephrine doses, our findings should not be interpreted as prescriptive management recommendations. If applied in clinical practice, our findings can reduce emergency department observation periods for children without cardiovascular involvement (91% of encounters) and might reduce hospitalisations for children with cardiovascular involvement whose symptoms resolve promptly, completely, and durably. Furthermore, our findings can help clinicians assess risk to inform management, which should also be informed by clinical experience, patient or caregiver preferences, access to EAIs, and knowledge or comfort using them.[13,31,32]

Our findings should only inform observation periods for children treated with epinephrine in the pre-emergency department or emergency department settings, as we excluded reactions not treated with epinephrine.[33] Additionally, 84·2% of patients treated with pre-emergency department epinephrine in our study did not receive epinephrine after emergency department arrival. Thus our data are supportive of new recommendations in the 2023 US Joint Task Force on Practice Parameters that not all children treated with epinephrine in the community require emergency department care.[29] However, our findings show that patients with cardiovascular involvement and severe respiratory findings should be evaluated in the emergency department. The 2% risk threshold was almost 60 min longer for patients with than without cardiovascular involvement, and patients with severe respiratory and cardiovascular involvement were more likely to receive repeat epinephrine. In contrast, patients without these clinical findings could remain at home if their symptoms resolve completely after epinephrine administration, they have access to a second EAI, and a caregiver is present to administer the EAI.[29]

Our study has limitations. First, our findings might not be generalisable to community emergency departments that care for different patient populations and have staff with variable paediatric training and experience. Second, there is potential for information bias owing to the retrospective study design. We controlled for this bias by using strict data extraction guidelines, performing routine data queries, and evaluating interrater reliability. Although we used imputation for 3·5% of participants, it was done using a conservative approach to generate conservative risk thresholds to limit the likelihood of post-observation epinephrine use. Furthermore, we performed a sensitivity analysis using multiple imputations, which resulted in a shorter less than 2% risk threshold (107 min *vs* 115 min). Although multiple imputation might be more accurate than single imputation, we sought to generate conservative risk thresholds to limit the likelihood of post-observation epinephrine use.

Third, there was the potential for loss to follow-up, including patients who re-presented to a different emergency department. However, this was likely an uncommon event because of the overall low emergency department revisit rate and the fact that participating hospitals represent large referral centres and are trusted for the care they provide to children.[30] Fourth, there is the potential for epinephrine underuse and overuse. Thus, prospective research is necessary to evaluate the timing of symptom resolution or recurrence in relation to the timing of epinephrine. Fifth, although 12% of our study cohort did not fulfil NIAID/FAAN criteria, clinicians must determine the length of observation irrespective of whether patients fulfil anaphylaxis criteria. The NIAID/FAAN criteria are not diagnostic criteria, they are clinical criteria to help clinicians determine whether patients are likely having an anaphylactic reaction.[10] In our cohort, we found that the less than 2% threshold was 117 min for patients who fulfilled NIAID/FAAN criteria, compared with 115 min for the entire cohort. Thus, these patients likely represent similar phenotypes.

In summary, in this large multicentre anaphylaxis cohort, we found that a 2-h observation period post-epinephrine is safe for most children without cardiovascular involvement. Patients with cardiovascular involvement might require a longer period of observation, but the risk of repeat epinephrine beyond 4 h is low. Incorporating our findings into clinical care might reduce anaphylaxis observation periods and limit unnecessary hospitalisations.

Contributors

Conceptualisation: TED, HAS, YZ, SB, NZ, KAM, MIN, DCB, RDM, and DS. Data curation : TED (secondary), KAM (secondary), SBF (secondary), PLA (primary), KRB (primary), BB (primary), SSC (primary), W-JC (primary), ARC (primary), JSC (primary), AD (primary), JRD (primary), JFF (primary), KK (primary), CLK (primary), KYK (primary), CDL (primary), JL (primary), TRL (primary), AMM (primary), MMM (primary), J-AON (primary), TLN (primary), CDP (primary), CJR (primary), NVS (primary), GS (primary), JS (primary), VT (primary), CVW (primary), PSW (primary), and YW (primary). Formal analysis: TED, YZ, SB and NZ. Funding acquisition: TED, HAS, and DS. Investigation: TED, HAS, YZ, SB, NZ, KAM, PLA, KRB, BB, SSC, W-JC, ARC, JSC, AD, JRD, JFF, KK, CLK, KYK, CDL, JL, TRL, AMM, MMM, J-AON, TLN, CDP, CJR, NVS, GS, JS, VT, CVW, PSW, and YW. Methodology: TED, HAS, YZ, SB, NZ, KAM, MIN, DCB, RDM, and DS. Project administration: TED and SB. Resources: SBF, PLA, KRB, BB, SSC, W-JC, ARC, JSC, AD, JRD, JFF, KK, CLK, KYK, CDL, JL, TRL, AMM, MMM, J-AON, TLN, CDP, CJR, NVS, GS, JS, VT, CVW, PSW, YW, and DS. Software: YZ, SB, and NZ. Supervision: HAS, NZ, KAM, MIN, DCB, RDM, SBF, and DS. Validation: YZ, SB, and NZ. Visualisation: YZ. Writing–original draft: TED, HAS, YZ, NZ, KAM, MIN, DCB, RDM, SBF, and DS. Writing–review and editing: TED, HAS, YZ, SB, NZ, KAM, MIN, DCB, RDM, SBF, PLA, KRB; BB, SSC, W-JC, ARC, JSC, AD, JRD, JFF, KK, CLK, KYK, CDL, JL, TRL, AMM, MMM, TLN, CDP, CJR, NVS, GS, JS, VT, CVW, PSW, YW, and DS. YZ and NZ accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

HAS reports advisory board or consulting fees from DBV Technologies, N-Fold, and Siolta Therapeutics; received stock options from N-Fold and DBV Technologies; receives funding to his institution (Icahn School of Medicine) from the National Institutes of Health–National Institute of Allergy and Infectious Diseases and the Food Allergy Research & Education; and royalties from Elsevier. DCB did consulting for CSL Behring Consultancy. All other authors declare no conflicts of interest.

Data sharing

De-identified individual data that support the results will be shared from 9 months to 36 months after publication, provided the investigator who proposes to use the data has approval from an Institutional Review Board and executes a data use or sharing agreement with Cincinnati Children's Hospital Medical Center. Data can be accessed by contacting the corresponding author.

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