

Epinephrine Autoinjectors: New Data, New Problems



Susan Waserman, MSc, MDCM, FRCPC^a, Ernie Avilla, MBA(c)^a, Moshe Ben-Shoshan, MD, MSc^b, Lana Rosenfield, MD^c, Andrea Burke Adcock, MD^c, and Matthew Greenhawt, MD, MBA, MSc^d *Hamilton, Ontario and Montreal, Québec, Canada; Aurora, Colo*

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List of Design Committee Members: Susan Waserman, MSc, MDCM, FRCPC, Ernie Avilla, MBA(c), Moshe Ben-Shoshan, MD, MSc, Lana

Rosenfield, MD, Andrea Burke Adcock, MD, and Matthew Greenhawt, MD, MBA, MSc (authors); Scott H. Sicherer, MD (editor)

Learning objectives:

1. To understand the features and functionality of epinephrine autoinjectors (EAI).
2. To illustrate the current gaps in anaphylaxis management by health care professionals.
3. To illustrate the current utilization of EAI by patients and caregivers in schools or camps.

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Epinephrine is the first-line treatment for anaphylaxis. Despite this, there have been identified gaps in the management of anaphylaxis including infrequent or delayed use of epinephrine

for acute allergic reactions, as well as inadequate epinephrine autoinjector (EAI) training, and prescription rates of these devices for patients at risk. This paper reviews new data, and new

^aDepartment of Medicine, Clinical Immunology and Allergy, McMaster University, Hamilton, Ontario, Canada

^bDivision of Pediatric Allergy and Clinical Immunology, Department of Pediatrics, McGill University Health Center, Montreal, Québec, Canada

^cClinical Immunology and Allergy PGY-5, McMaster University, Hamilton, Ontario, Canada

^dDepartment of Pediatrics, Allergy Section, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, Colo

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Corresponding author: Susan Waserman, MSc, MDCM, FRCPC, Division of Clinical Immunology and Allergy, McMaster University, 1280 Main St West, HSC 3V49, Hamilton, Ontario L8S 4K1, Canada. E-mail: waserman@mcmaster.ca. 2213-2198

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Abbreviations used

BMI- Body mass index
CI- Confidence interval
EAI- Epinephrine autoinjector
ED- Emergency department
EPS- Epinephrine prefilled syringe
IM- Intramuscular
IV- Intravenous
OR- Odds ratio
RCT- Randomized control trial
STMD- Skin-to-muscle depth

problems in recently published literature on EAI. A database search was conducted for publications between January 2015 and February 2017 using keywords related to EAI including their functionality and features, carriage, prescription rates, barriers, and side effects. Eligibility criteria included patients at risk for anaphylaxis, caregivers, and health care professionals. Experimental studies and observational studies were included. Of 1,737 potentially relevant articles, 19 were used for analysis. These articles addressed specific aspects of an EAI, including (1) information on features and functionality; (2) prescriptions; (3) training on their use; and (4) carriage and use at the time of reaction by patients, schools, camps, emergency departments, and paramedics. Our review highlights that existing gaps in anaphylaxis management remain unaddressed. Patient needs are largely unmet, and very few studies are being designed to clarify and instill best practice, and to determine how to increase adherence to existing anaphylaxis guidelines through integrated knowledge translation strategies. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:1180-91)

Key words: Anaphylaxis; Epinephrine autoinjector use/carriage; Prescription rates; Treatment guidelines

Anaphylaxis is a serious allergic reaction that is rapid in onset and may be associated with fatality.¹ Current guidelines recommend prompt use of intramuscular (IM) epinephrine as first-line treatment.¹⁻⁴ Currently, anaphylaxis has been defined by multiple guidelines, all of which emphasize cardiorespiratory symptoms or involvement of 2 or more organ systems as key identifying features. Administration via the IM route is known to provide faster and higher peaks of plasma concentration compared with the subcutaneous route.⁵

Despite its pivotal role, utilization of epinephrine in the management of anaphylaxis remains suboptimal. Previous studies have identified gaps in anaphylaxis management by health care professionals, patients, and their caregivers (including schools and other key stakeholders in the community). Findings included infrequent use of epinephrine in the treatment of acute allergic reactions^{6,7}; significant delay in the timing of epinephrine administration after the occurrence of a reaction^{6,7}; low prescription rates for epinephrine autoinjectors (EAI) across different settings including hospital, outpatient clinics, or emergency departments (EDs); and inappropriate prescription of antihistamines and corticosteroids during and in the aftermath of treated reactions.^{6,8} Findings also revealed inadequate training of patients and/or caregivers (including school teachers) on when

and how to use an EAI correctly.^{6,9} It has been previously noted that many patients do not carry an EAI or did not have one available at the time of a reaction, particularly in cases of documented fatal anaphylaxis^{6-8,10,11} an outcome that many view as almost entirely preventable.

The objective of this paper is to present a succinct review of the evidence from recently published literature (January 1, 2015, to February 6, 2017) focused on new data and new challenges related to EAI.

INCLUDED STUDIES

A database search (Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE, and Versions(R)) for articles (up to February 6, 2017) was conducted using the following key words: “epinephrine,” AND-ed “hypersensitivity or food hypersensitivity or anaphylaxis or epinephrine autoinjectors or self administration” AND-ed “features or functionality or needle length or injection pressure or rapid onset of activity or doses or IM or subcutaneous or storage or expiry date or carriage or prescription or dispensing rates, accidental injections, barriers, fear, side effects or stock epinephrine or preparedness or anaphylaxis action plan or training, laws or epinephrine tablets or needle-less devices.” Search terms were generated using known terms and synonyms suggested by allergy specialists.

Eligibility criteria

For article inclusion, the following eligibility criteria were used:

Population: Included were patients at risk for anaphylaxis and their caregivers (including schools and other community settings) and health care professionals involved in their care.

Intervention: Included were any approaches or protocols that incorporated a strategy for EAI use.

Comparator: Included were any studies for inclusion irrespective of whether there was a comparator included in the study design.

Outcomes: Included were any related to treatments, prescription rates, EAI training/education, and carriage.

Study design: Included were experimental studies (eg, randomized controlled trials [RCTs]), other experimental designs (eg, nonrandomized methods of assignment, controlled before-after studies, and interrupted time series), and observational studies (eg, prospective or retrospective cohort studies, cross-sectional studies, and case-control studies). Per an agreed on *a priori* decision of the authors, we excluded case reports, opinion-based reports (ie, editorials, letters, and nonsystematic or narrative reviews), as well as basic science or animal (non-human) studies. All included studies were agreed on by author consensus after review in an iterative process.

Data synthesis

The analysis involved summarizing the data, and presenting results in a narrative synthesis. We prepared descriptive tables to give an overview of the included study characteristics. This manuscript was not designed to carry out quantitative analysis, meta-analysis, or assess risk of bias.

RECENT EVIDENCE

Of 1,737 potentially relevant articles identified by our search, 1,412 did not meet the inclusion/exclusion criteria or were

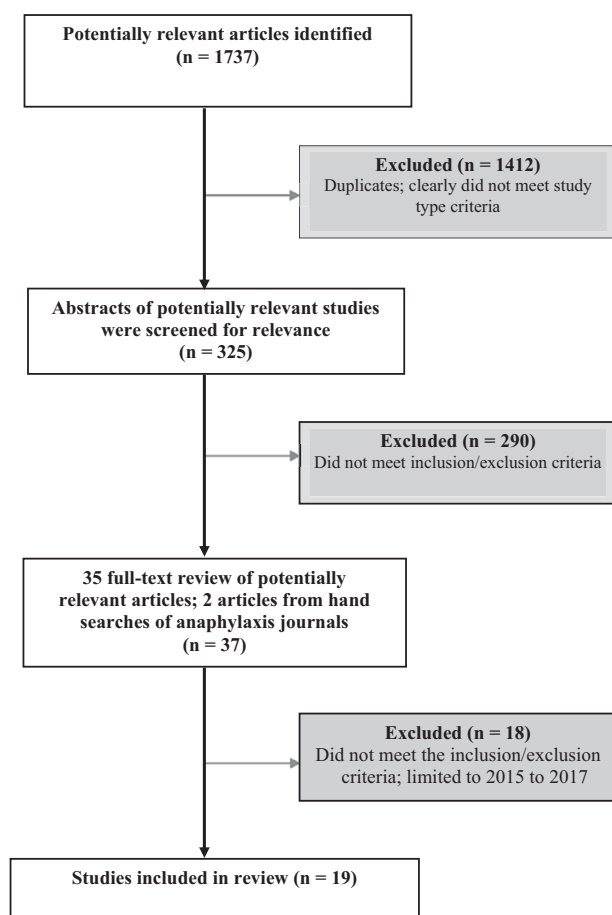


FIGURE 1. Study identification flowchart. Of 1,737 potentially relevant articles identified by our search, 1,412 did not meet the inclusion/exclusion criteria or were duplicates and removed from the review. Of 325 citations that were screened for relevance, 37 were selected for full-text review (including 2 articles identified by experts in the field) and 32 met the inclusion criteria. Of the 32 full-text articles, 19 were included in the analysis.

duplicates and removed from the review. Of 325 citations that were screened for relevance, 37 were selected for full-text review (including 2 articles identified by experts in the field) and 32 met the inclusion criteria. Of the 32 full-text articles, 19 were included in the analysis (Fig 1).

The majority of the studies (Table I) were epidemiological in nature, consisting of retrospective cohort studies ($n = 6$); cross-sectional surveys ($n = 5$); prospective studies ($n = 5$); case-control study ($n = 1$); pretest/posttest ($n = 1$); and retrospective chart review ($n = 1$). More than 80% of the studies involved hospital- or clinic-based populations ($n = 12$) or community settings ($n = 4$), and these populations varied widely across studies with respect to participant age and gender. No controlled studies of any type were identified in the literature search.

An analysis of the studies revealed 4 major themes addressing aspects of an EAI (Table IIA-D), including (1) information on features and functionality; (2) prescriptions; (3) training on their use; and (4) carriage and use at the time of reaction by patients, schools, camps, EDs, and paramedics.

Features and functionality of EAls

Of the 6 studies that described the features and functionality of EAls (Table IIA), 3 studies examined the use of IM injection. A cross-sectional survey of 43 pediatric intensivists across 5 pediatric intensive care units (Sao Paulo, Brazil) correctly identified epinephrine as the treatment of choice for anaphylaxis (83.8%) and 41.9% administered via the IM route.¹⁵ A web-based survey completed by health care providers ($N = 172$) at an academic ED (Mayo Clinic Hospital, Rochester, Minn) assessed provider perceptions and preferences of 2 methods of IM epinephrine administration (autoinjector and manual injection). The EAI was rated more favorably for time required for training, ease of use, convenience, satisfaction with weight-based dosing, risk of dosing errors, and speed of administration ($P < .001$), whereas manual IM injection (eg, non-autoinjector use involving an ampule of epinephrine drawn with a needle and syringe, then subsequently injected) was associated with lower risk of finger stick injury (2% reported finger stick injury with an EAI) and lower out-of-pocket costs to patients ($P < .001$).¹³ A retrospective cohort study, conducted in EDs between April 2007 and March 2012, described the differences in epinephrine administration among older (aged >50 years) and younger patients with anaphylaxis and subsequent cardiovascular complications after epinephrine administration. Fewer older patients with anaphylaxis received epinephrine (36% vs 61%; unadjusted odds ratio [OR], 0.3; 95% confidence interval [CI], 0.2-0.5) and were more likely to receive intravenous (IV) epinephrine versus younger patients (4% vs 0.5%). Patients who received IV epinephrine (42.9%) were more likely to have cardiac complications (sinus tachycardia, atrial fibrillation, ST-segment depression) due to excessive dosing, than those who received IM epinephrine (0.9%) (unadjusted OR, 99.6; 95% CI, 7.4- ∞). Among patients treated with IM epinephrine, 3.5% of older patients experienced cardiovascular complications versus 0.5% younger patients (unadjusted OR, 1.09; 95% CI, 0.65- ∞). Neither involved excessive epinephrine dosing with IM administration. The authors postulated that potential for cardiovascular complications in older adults may be the cause for clinician reluctance to administer epinephrine, yet the IV route was more often used in the older age group that they recommended to be avoided because of the potential for cardiac complications.¹⁹ These findings demonstrate that older patients with anaphylaxis may be at additional risk in the ED.

One study specifically studied the issue of the needle length of an EAI, comparing children weighing 15 to 30 kg with those weighing >30 kg, and determined that variation in the EAI needle length in children of different weights is associated with: (1) a risk of epinephrine delivery into an inappropriate tissue compartment, leading to unpredictable serum levels; and (2) a risk of injection into bone.¹⁶ Children 15 to 30 kg had an 11% risk of intraosseous injection with EpiPen Jr and Auvi Q, and 38% with Jext, compared with 3% with Jext in children weighing >30 kg. There was also a 1% risk of subcutaneous injection in children 15 to 30 kg, compared with 9% in children >30 kg with currently available EAls. It should be noted that these risks were based on measurements of skin-to-muscle depth (STMD) and skin-to-bone depth using maximal applied pressure and ultrasound.

One study explored the critical issue of epinephrine degradation from storage at temperature extremes. EAls were stored

TABLE I. Characteristics of included studies

Study	Study objective	Setting/duration	Population	Design
Bardou et al 2017 ¹²	To evaluate the functional performance of the Zeno device in the setting of IM delivery to the lateral thigh	Clinic center, France June and December 2015	Adult healthy volunteers aged between 18 and 60 y and body mass index (BMI) 20-30 kg/m ² N = 37 subjects with evaluable MRI scans included analysis	Prospective cohort study
Campbell et al 2016 ¹³	To examine health care providers' preferences and perceptions about the optimal mode of epinephrine delivery (safety, effectiveness, ease of administration, convenience, and cost)	Emergency department, Mayo Clinic Hospital April and June 2011	Emergency department personnel N = 172	Cross-sectional survey
Civelek et al 2016 ¹⁴	To determine etiology and clinical features of anaphylaxis patients prescribed adrenaline autoinjectors within a certain period	Pediatric allergy clinic January 2008 and December 2011	N = 843 anaphylaxis patients	Cross-sectional survey
Colleti et al 2016 ¹⁵	To assess the knowledge of pediatric intensivists regarding the first-line drug and the route of administration for the treatment of anaphylaxis	Pediatric ICUs, Sao Paulo State, Brazil March to June 2015	N = 43 pediatric intensivists	Cross-sectional survey
Dreborg et al 2016 ¹⁶	To evaluate whether children and adolescents who are at risk of anaphylaxis from food allergy weighing 15-30 kg and >30 kg would receive epinephrine into the intramuscular space, the bone, or subcutaneous space	Western University, London, Ontario, Canada July 2012 to June 2014	Patients less than 18 y of age, with diagnosed food allergy N = 202 (102 weighed 5-30 kg; 100 weighed >30 kg)	Prospective cohort study
Foster et al 2015 ¹⁷	To assess anaphylaxis preparedness among preschool staff members before and after an educational intervention	Preschools September 2011 and May 2012	N = 10 preschools N = 171 staff members	Pre/posttest in a convenience sample
Hogue et al 2016 ¹⁸	To describe the occurrence of anaphylactic reactions and the training and personnel resources available to manage these events	Schools, USA May 2014 and July 2014	N = 6,019 schools	Cross-sectional survey
Kawano et al 2017 ¹⁹	To compare the frequency of epi nephrine administration and the subsequent documented cardiovascular complications in patients with anaphylaxis	Emergency department, Vancouver, British Columbia, Canada April 2007 to March 2012	N = 492 patients with anaphylaxis	Retrospective cohort study
Kimchi et al 2015 ²⁰	To assess anaphylaxis cases managed by paramedics	Emergency medical services/paramedics May 2013 and May 2014	N = 104 anaphylaxis cases	Prospective cohort study

(continued)

TABLE I. (Continued)

Study	Study objective	Setting/duration	Population	Design
Ko et al 2016 ²¹	To investigate whether adrenaline use in hemodynamically stable patients can prevent the in-hospital occurrence of hypotension in hemodynamically stable patients with anaphylaxis	Emergency department, Tertiary Care, Seoul, Korea January 2004 and December 2013	Adult (≥ 16 y) patients with anaphylaxis N = 340 hemodynamically stable patients; 300 no hypotension; 40 hypotension	Retrospective cohort study
Lee et al 2016 ²²	To compare the percentage, triggers, and management of anaphylaxis between 2 Canadian tertiary hospitals	Emergency department, British Columbia and Montreal 2014 and 2016	N = 977 children with anaphylaxis	Prospective cohort study
Lee et al 2016 ²³	To determine the trends of epinephrine autoinjector prescriptions in Olmsted County residents	Olmsted County residents over a 7-y period, 2004-2010	All Olmsted County residents identified by REP census	Retrospective cohort study
Pourang et al 2016 ²⁴	To quantify the accuracy of anaphylaxis-related ICD-9 codes in the Southern California Permanente Medical Group	HMO—Kaiser Permanente, Southern California January 2008 and December 2012	N = 2,531,563 patients were included in the analysis	Retrospective cohort study
Rachid et al 2016 ²⁵	To simulate the effects of constant or cyclic thermal heat stress greatly exceeding the recommendations of the manufacturer for optimal EAI storage on the epinephrine doses delivered from the EAI	University of Manitoba	N = 25 EpiPens 0.3 mg, lot number 3GU006, labeled to deliver 0.3 mL of epinephrine USP 1:1000	Case-control study
Ridolo et al 2015 ²⁶	To verify the proper use of the device, the correct administration of drug, and to identify possible misuse by patients at risk of anaphylaxis	Allergy clinics, Italy July and December 2013	N = 242 patients who had been prescribed an adrenaline autoinjector for at least 1 y	Prospective cohort study
Saleh-Langenberg et al 2015 ²⁷	To describe and evaluate practice in EAI prescriptions by GPs to food-allergic patients	General practice, the Netherlands From 2001 to 2012	N = 148 patients aged 12-23 y who consulted their GP for allergic symptoms due to food from 2001 to 2012	Retrospective cohort study
Schellpfeffer et al 2016 ²⁸	To estimate the prevalence of food allergies among otherwise healthy campers in a large number of summer camps throughout the United States and Canada	Summer camps, USA and Canada October 2011	N = 3,055 campers	Retrospective cohort study
Sheikh et al 2015 ²⁹	To examine the circumstances, features, and management of anaphylaxis in children and adults	Anaphylaxis campaign, UK-wide patient charity May 2001-September 2013	N = 243 unique subjects	Cross-sectional survey
Sidhu et al 2016 ³⁰	To assess the adherence to the guidelines in the ED	Emergency department, Arkansas Children's Hospital January 2004 and January 2006 (preguideline period) and those from July 2007 and July 2011 (postguideline period)	N = 187 patients presenting with anaphylaxis	Retrospective chart review

EAI, Epinephrine autoinjector; ED, emergency department; GP, general practitioner; HMO, Health Maintenance Organization; ICD-9, International Classification of Diseases, Ninth Revision; ICU, intensive care unit; IM, intramuscular; MRI, magnetic resonance imaging; REP, Rochester Epidemiology Project.

TABLE II. Summary of themes

Theme	Subtheme	Description	Study
(A) Features and functionality of an EAI	New mode of epinephrine delivery	• Prefilled, needle-free gas propulsion drug delivery through micronozzles • Of 37 subjects, 35 had MRI scans that demonstrated that IM penetration represents a success rate of 94.6% • Resulted in mean injectate penetration depths of 30.1 mm (range, 20.2-45.6 mm) with no differences between male and female subjects • BMI showed little impact on injection depth • Device pressure Pmax (maximum pressure after 2 ms) had the greatest impact on increasing injection depth	Bardou et al 2017 ¹²
	IM vs manual injection	• ED health care providers (n = 172) rated the autoinjector more favorably with regard to ease of use, convenience, satisfaction with weight-based dosing, risk of dosing errors, and speed of administration ($P < .001$ for all comparisons) • Manual injection was rated more favorably with regard to the risk of provider self-injury and patient cost ($P < .001$ for both comparisons)	Campbell et al 2016 ¹³
		• N = 43 pediatric intensivists across 5 PICUs • 83.7% use epinephrine as the first-line drug for anaphylaxis. 41.9% described the IM as the preferred route of administration	Colleti et al 2016 ¹⁵
	Needle length	• In ED, older patients were more likely to receive intravenous epi • N = 202 children and adolescents who are at risk of anaphylaxis from food allergy weighing 15-30 kg (n = 102) and >30 kg (n = 100) • Children weighing 15-30 kg would be at 11% risk of the EAI needle reaching the femur with the Epipen Jr or Auvi-Q 0.15 mg and 38% with Jext • Children weighing >30 kg, 3% of children were at risk injection into bone using a low-pressure EAI, Emerade • 1% of children weighing 15-30 kg and 9% of those weighing >30 kg using Epipen Jr, Auvi-Q/Allerject, or Jext may receive the epinephrine subcutaneously • No children at 15-30 kg and 2% of those weighing >30 kg would have a subcutaneous injection using the low-pressure EAI, Emerade	Kawano et al 2017 ¹⁹ Dreborg et al 2016 ¹⁶
	Storage	• N = 25 in-date EAIs were stored constantly or cyclically at 70°C (excessive heat) or 25°C (controls) for 5 or 10 d. • Constant heat exposure had a greater effect than cyclic heat exposure on the degradation of epinephrine • EAI storage at excessively high temperatures accelerates degradation of epinephrine in a 1 mg/mL solution and should be strictly avoided	Rachid et al 2016 ²⁵
		• N = 843 patients with a history of anaphylaxis (91.1%) were treated in an emergency setting during the first anaphylaxis episode • 10.7% of the anaphylaxis cases prescribed an EAI on discharge from the ED	Civelek et al 2016 ¹⁴
(B) Prescription patterns of an EAI	Low prescription of EAI—ED setting	• N = 52,405 patients identified to have anaphylaxis • 16.1% prescribed an EAI within 60 d of the initial anaphylaxis encounter ◦ Once epinephrine was prescribed, the medication was dispensed 95.9% of the time	Pourang et al 2016 ²⁴
	Low prescription of EAI—HMO setting		

(continued)

TABLE II. (Continued)

Theme	Subtheme	Description	Study
	Low prescription of EAI—general practitioners	• N = 1,015 subjects with allergic symptoms to food consulted GP; 34 identified as food allergic • 37 % prescribed an EAI ◦ Of these, 5 patients experienced a previous anaphylactic reaction to food; 2 had been prescribed an EAI	Saleh-Langenberg et al 2015 ²⁷
	Increase prescription of EAI—outpatients (Olmsted)	• N = 3,801 patients from 2004 to 2010 were identified in Olmsted County • Total of 7,991 prescriptions • 8% increase in prescription rates each year over the 7-y study period • First-time prescriptions per patient during the study period remained stable • Rates of EAI prescriptions were higher in women overall compared with men • Highest rates were observed among patients aged 0-9 y during which boys received more prescriptions than girls • Women received more prescriptions than men in the older age groups	Lee et al 2016 ²³
	(C) Training on the use of an EAI	• N = 171 preschool staff members participated in the educational seminar and postintervention survey • Comfort level with recognizing anaphylaxis significantly increased after the education session (mean [SD], 5.2 [2.4] vs 8.7 [1.2]; $P < .001$) • Comfort level with administering an EAI significantly increased after the intervention (mean [SD] increase, 3.7 [2.3]; $P < .001$)	Foster et al 2015 ¹⁷
(D) Carriage or use of an EAI at the time of reaction		• 5,613 of 6,019 schools (93%) provided information regarding staff members who were trained to recognize anaphylaxis • Less than a third of schools trained all staff • 29% trained most staff in anaphylaxis recognition	Hogue et al 2016 ¹⁸
	Schools	• 5,578 schools provided information on the types of staff who were permitted to administer epinephrine via an EAI (EAI). 54% permitted the school nurse and select staff to administer epinephrine • All or most staff were permitted to administer epinephrine in 38% of schools • 3% of schools limited EAI use to the school nurse • 3% percent allowed both students and staff to administer epinephrine	Hogue et al 2016 ¹⁸
	Camps	• N = 3,055 campers from 167 US and 3 Canadian summer camps had documented food allergies (median age of 11 y) • 22% had multiple food allergies of which 44.3% also had asthma • Overall, 39.6% brought a prescribed EAI to the camp ◦ Sample population with food allergies and asthma, 48.6% had EAI. ◦ Sample with food allergies only and without a diagnosis of asthma, 32.5% had EAI • Stratifying data by camp type (overnight), campers, 41.5% had EAI; among day campers, 23.9% had an EAI	Schellpfeffer et al 2016 ²⁸
	Patients with EAI prescription	• N = 242 patients with a prescribed EAI for at least 1 y • At follow-up visit asked to demonstrate the correct use of the autoinjector; 39 % used correctly, whereas the majority committed at least 1 error; 6% failed	Ridolo et al 2015 ²⁶

	• N = 243 patients (mean age, 19.1 y; SD, 16.6) • 64% children; 36% adults (ie, aged 16-72 y). • Self-injectable epinephrine was available in 79% of the cases only used in 38% of episodes • Usage of self-injected adrenaline was lower in children (30%) than in adults (54%) • 82% of children had adrenaline available at the time of the reaction compared with 74% of adults	Sheikh et al 2015 ²⁹
Emergency department	• N = 492 patients, 54.7% received epinephrine • 36.1% older patients • 60.8% younger patients	Kawano et al 2017 ¹⁹
	• N = 761 adult patients with anaphylaxis • N = 340 hemodynamically stable patients; 300 no hypotension; 40 hypotension • Adrenaline use in hemodynamically stable patients with anaphylaxis was less frequent in the hypotensive group ($P = .010$). • Adrenaline use in hemodynamically stable patients with anaphylaxis was associated with a reduced risk of developing hypotension (OR, 0.254; 95% CI, 0.091-0.706)	Ko et al 2016 ²¹
	• N = 187 patients; median (range) age was 7 (1-18) y • N = 61 patient cases preguideline period • N = 126 cases were included from the postguideline period • 93% postguideline and 92% preguideline received treatment with an antihistamine • 75% postguideline and 73% preguideline received corticosteroid • 15% overall received self-injectable epinephrine before arrival at ED • ED overall usage of epinephrine was 47% • On discharge, 61% received a self-injectable epinephrine • Postguideline patients were 15% more likely to receive a self-injectable epinephrine prescription • Postguideline patients—increase in the usage of the IM route (46% postguideline vs 6% preguideline; $P < .001$)	Sidhu et al 2016 ³⁰
	• N = 104 anaphylaxis cases managed by paramedics • Epinephrine was administered in 64.4% • Epinephrine was not administered in 28.6% of moderate or severe cases • Cases of known food allergy, 50% used EAI before ambulance arrival • Antihistamines and steroids were taken before ambulance arrival in 40% and in 3.8% of the cases	Kimchi et al 2015 ²⁰

(continued)

TABLE II. (Continued)

Theme	Subtheme	Description	Study
		• Epinephrine administration after arrival to ED 59.2% (BC) vs 42.2 (MTL) • Antihistamines administration after arrival to ED 59.8 (BC) vs 36.2 (MTL) • Steroids after ED arrival 60.1 (BC) vs 11.9 (MTL) • Epinephrine was used more often at the BCCH. This difference was mainly related to higher percentages of epinephrine use in the BCCH ED during mild and moderate reactions • Steroids were used almost 5 times more often in the BCCH ED • Patients at BCCH ED and MCH received self-injectable epinephrine (27.7% and 33.1%, respectively) before arrival at ED	Lee et al 2016 ²²

BC, British Columbia; BCCH, British Columbia Children's Hospital; BMI, body mass index; EAI, epinephrine autoinjector; ED, emergency department; GP, general practitioner; HMO, Health Maintenance Organization; MCH, Montreal Children's Hospital; MRI, magnetic resonance imaging; MTL, Montreal; OR, odds ratio; PICU, pediatric intensive care unit.

for 5 days at 70 °C and cycled back to room temperature for 4 hours out of every 24 hours to simulate the effect of temperature fluctuations to which an EAI might be exposed. When compared with controls (EAIs stored for 5 days at 25 °C for 24 hours), results showed that storage of EAIs at excessively high temperatures (70 °C) accelerated degradation of epinephrine (measured using reverse-phase high-performance liquid chromatography with UV detection), and recommended that EAIs not be used if they had been stored in this state.²⁵ Conversely, the same authors examined the effects of extreme cold on EAIs and found that freezing EAIs at -25 °C (cycled back to room temperature for 4 hours out of every 24 hours for 5-10 days) did not affect activation, dose, and the epinephrine content of the doses.³¹

One study explored an alternative delivery system of an EAI. It investigated a new mode of epinephrine delivery using a pre-filled, needle-free delivery system (via gas propulsion of the drug through micronozzles [250-300 µm diameter; triggered by pushing the device onto skin]), and found this to result in the mean depth of the injectate (saline) within the muscle to be 30.1 ± 5.8 mm (range, 20.2-45.6 mm) with no differences in mean depth with gender or body mass index (BMI).¹² The study also revealed that device pressure Pmax (the maximum injection pressure after 2 milliseconds) had the greatest impact on increasing injection depth versus STMD, dermal and subcutis thickness at injection site, BMI, and thigh circumference.³¹

These mean maximum injection depths are comparable to a similar European study investigating the 3 currently available EAIs (Jext, EpiPen, and Anapen).³²

Prescribing EAIs

Three studies investigated health care service utilization related to the actual rate of EAI prescription. These three studies all indicated that the rate of EAI prescription is low across different health care settings including EDs, health care maintenance organizations, and within general practice (Table IIB).^{14,24,27} The under prescription of an EAI may be a sign of ongoing difficulty by clinicians in diagnosing anaphylaxis and could potentially result in the suboptimal treatment of future reactions. One study of the general population in Olmsted county Minnesota (a well-characterized area involved in prior anaphylaxis studies with well-validated methodology to accurately sample the patient lives of the area) found an increase of 8% in prescription rates over a 7-year period,²³ suggesting either an increased prevalence or awareness of anaphylaxis at the population level in the United States.

Training regarding identifying anaphylaxis and the proper use of EAIs

Inadequate training on the proper use of EAIs in US schools was a major gap identified in one study (EpiPen4Schools Study; sponsored by EpiPen device maker Mylan Pharmaceutical [Basking Ridge, NJ]). Of 5,578 schools surveyed, only 31% were reported to have trained all staff at their facility on anaphylaxis recognition.¹⁸ One study described the effects of an educational seminar on proper EAI use to 172 preschool staff members. Pre- to posttest assessment revealed significant increases in reported comfort levels with anaphylaxis recognition ($P < .001$) and EAI administration ($P < .001$) (Table IIC).¹⁷

Carriage or use of EAIs at the time of reaction

Nine studies described EAI carriage and use in 3 different settings: (1) community settings (schools and camps), (2)

patients with EAI prescriptions, and (3) EDs and paramedics (Table IID).

Schools and camps. Of 5578 US schools surveyed (EpiPen4Schools Study; Mylan), 54% of schools allowed the school nurse and/or select staff to administer an EAI. Only 3% of schools surveyed allowed both students and staff to administer an EAI.¹⁸ The EpiPen4Schools program also assessed anaphylactic events and EAI use during 2013-2014. Of 919 anaphylactic events reported (N = 607 schools), 851 events had data on EAI use: 74.7% were treated with EAIs (48.7% school's stock EAI; 45.4% personal EAI; 5.6% other EAI); 8.5% received a second epinephrine injection.³³ Of the 204 individuals not treated with an EAI, 77% received antihistamines, 12.7% received another treatment, and 8.3% received no treatment.³³ Of those individuals who had an anaphylactic event, 69.0% had a known allergy, 21.9% had no preexisting allergy and 8.8% were unknown to have a history of preexisting allergies. Anaphylaxis was triggered by food (62.5%), venom (9.6%), environmental/medication/health related (6.6%), latex (1.1%), and unknown causes (20.3%). This demonstrates the potential usefulness of stock epinephrine in the school setting. Another study revealed that of 3055 food allergic individuals who attended summer camp (167 camps within the USA and Canada), 32.5% brought an EAI to the camp (either day or overnight camp). Among those respondents who reported attending overnight camp, only 41.5% had an EAI, in comparison to only 23.9% of day campers, highlighting a very low rate of carriage and increased risk for food allergic children at camp, almost half of whom also reported concurrent asthma.²⁸

Patients. One study identified that even when patients with a reported episode of anaphylaxis carried an EAI, many did not use it at the time of their reaction.²⁹ Another study asked 242 patients (mean age 42.6 ± 17.7 ; who had been prescribed an EAI for at least 1 year) to demonstrate how to self-administer an EAI, using a trainer device. The patients were evaluated by demonstrating 4 steps correctly, including (1) removing the safety cap, (2) properly handling the autoinjector, (3) selecting the mid-anterolateral thigh as the site of injection, and (4) holding the autoinjector in place for at least 10 seconds. Of the 242 patients, 54% were not able to recall all the steps for correct EAI use or completely failed to activate the device. Selecting the correct injection site and holding the EAI in place for 10 seconds were steps that were most often incorrect.²⁶ Tissue injury in young children due to holding the needle in the leg for 10 seconds has been reported. EpiPen instructions indicate that the device should be held firmly against the thigh for 10 seconds. However, during this time, the needle remains fully extended, increasing the probability for needle-related injuries, particularly in young children. Hence it was recently suggested that the holding time should be reduced to 3 seconds.³⁴

EDs and paramedics. Studies conducted within EDs revealed substantial disparities in the management of patients presenting with anaphylaxis.²² In one study, epinephrine was administered to 15% of patients who had physician diagnosed anaphylaxis, and only 61% were prescribed an EAI on discharge³⁰; furthermore, despite physician diagnosed anaphylaxis, antihistamines (93%) and steroids (73%) were administered more often than IM epinephrine in the acute setting (46%).³⁰ A study of anaphylaxis cases managed by paramedics

reported that a substantial proportion (36%) of patients were not treated with epinephrine before ambulance arrival, and in 40% of these cases, the patients had self-administered antihistamines.²⁰ An ED study investigated whether epinephrine use in hemodynamically stable (defined as systolic blood pressure ≥ 90 mm Hg) patients can prevent the in-hospital occurrence of hypotension with anaphylaxis (N = 340). Patients who developed hypotension during an ED stay were compared with those who did not. A total of 40 of 340 patients (11.8%) developed hypotension. In-hospital epinephrine use in hemodynamically stable patients with anaphylaxis was associated with a reduced risk of developing hypotension (OR, 0.254; 95% CI, 0.091-0.706).²¹

DISCUSSION

Our review of recently published studies (January 1, 2015, to February 6, 2017) revealed a number of themes, the most common of which was inadequate utilization of an EAI by health care providers, patients, and caregivers across multiple settings. This included suboptimal rates of EAI prescriptions for patients at risk, as well as general reluctance to administer epinephrine for acute reactions by providers, paramedics, and most importantly, by patients themselves. The first line use of antihistamines and steroids rather than epinephrine by caregivers in circumstances of clear anaphylaxis is worrisome, given that anaphylaxis may progress to fatality in less than 1 hour,³⁵ and because the peak effect of antihistamines and steroids is at least 1 hour after administration. This is compounded by the fact that although many anaphylaxis action plans have criteria for giving antihistamines before epinephrine based on severity, the recognition and/or interpretation of these symptoms and what constitutes anaphylaxis is less clear for patients and caregivers.

These themes have been relatively consistent over the years, suggesting 2 things:

- (1) Better guidance may be required on when EAIs should be prescribed and used, and under what conditions/circumstances it should be administered. This is especially important given the increasing prevalence of anaphylaxis, especially in young children, and a growing trend toward stock epinephrine in various settings.
- (2) Better knowledge translation strategies are required for the identification and management of anaphylaxis, as well as identification of barriers to implementation of best-practice guidelines for the care of patients with anaphylaxis.

Our review of the recent literature highlights that these needs are still largely unmet, and that few studies are being designed to clarify and instill best practice, or to determine how to increase adherence to existing guidelines. These remain critical issues to address.

An emerging and potentially important issue is that of needle length, supported by several studies identified in this review. These studies question whether the available needle lengths for EAIs are appropriate for all children, to both maximize IM administration and avoid intraosseous administration and injury.

A recent Cochrane Systematic Review³⁶ of 5 RCTs assessed if using needles of different lengths and gauges for administering vaccines to children (N = 1135; aged 2-6 months) and adolescents (N = 215 aged 14-24 years) had any effect on (1) immune response; (2) pain experienced during the vaccination procedure;

and (3) adverse reactions (swelling, tenderness, and redness at the injection site, fever) after vaccination. The review found moderate quality evidence that infants (aged 2-6 months) vaccinated in the thigh with 25-mm needles either 23 G or 25 G, using the World Health Organization injection technique, had a reduced occurrence of local reactions and achieved a comparable immune response to 25 G, 16-mm needles. It should be noted that needles in these studies were not autoinjectors and not used with the same high injection pressure as would be for EAI; hence findings regarding adverse reactions at the injection site may not be directly comparable. Further research is needed to assess whether findings related to EAI needle length, suggesting risks at either end of the weight spectrum, are clinically relevant in the context of acute allergic reactions and treatment outcomes.

In addition, our review highlights that there may be immediate benefits to training school staff on the recognition of anaphylaxis symptoms and administration of EAIs. These are not new arguments per se, but arguments that now have significance given the number of states and provinces allowing or mandating that schools stock EAI, as well as allowing any able bodied individual on the premises to inject the student (protected by Good Samaritan Laws in North America). Although such training is paramount to ensuring good outcomes for school-based treatment, there may be limited reach and use of these training resources in certain jurisdictions, and no clarity on how such training can best be implemented. Furthermore, these abilities may be further limited by state or provincial regulations and/or resources. It is important to note that these data emphasize the need to continue to improve both caregiver and school staff education to better support patients at risk.

Another emerging area of research identified in the review is that of specific device preference. Over the past decade, new EAI devices have entered the marketplace offering differing features and functions (eg, size, esthetics, consumer preference). However, our review reveals that new devices likely face the same obstacles as their predecessors, namely, appropriate needle length for children and adults of varying weight, optimal storage of EAIs, and when to use. One study offered a new approach to address "needle-phobia" by testing the injection depth of a needle-less prefilled syringe device. Additional studies are needed to evaluate new device designs and their impact on patient adherence including EAI carriage and use. Undoubtedly, there may be favorable economic (lower retail prices for EAIs) and patient-reported outcomes related to increasing the number of available devices especially if more data can substantiate that tailored preference in device choice increases overall compliance. It will be important, however, to consider how variation in the features and functionality of EAI may affect the education of patients and caregivers, and whether variety may undermine the confidence of those administering epinephrine with possibly unfamiliar devices. With recent well-publicized device pricing dynamics and a potential trend that pharmacy benefit managers, Medicaid plans, and large chain suppliers have exerted leverage through exclusive contracting or forced substitution to a particular device, it will also be important to cross-train individuals on a multitude of available devices given consumer and/or provider preference for a specific (and potentially more familiar) device may no longer be feasible.

In the United States, there is evidence that suggests that EAI prescriptions have increased by 70% between 2003 and 2010. With high cost of EAIs, access by individuals who do not have

insurance plans may be costly and potentially difficult. In response to demands for affordable EAIs, the US Food and Drug Administration authorized a generic EAI (named USP auto-injector), though the wholesale price remains high. An additional branded generic device by Mylan is also now available. An alternative choice to EAIs is the epinephrine prefilled syringe (EPS). The EPS contains 0.3 mg in a single dose syringe and is currently under review by the US FDA; however, physicians have the option to prefill syringes in clinic or ask pharmacists to fill syringes with the appropriate amount of epinephrine. Although evidence suggests that patients can be trained to self-inject medication for home treatment (such as immunoglobulin for immunodeficiency, methotrexate for rheumatoid arthritis, or insulin for diabetics), there are no studies examining the safety and efficacy of self-administered EPS.³⁷

Study limitations

Our review did not limit our search to study designs engineered to assess the best quality of evidence such as RCTs—none which exist. Given ethical considerations it is unlikely that RCTs assessing the use of epinephrine in anaphylaxis will be conducted. However, our broad objective of highlighting current evidence on EAIs including challenges is addressed in prospective, retrospective, and epidemiological evaluations (cross-sectional and cohort studies) that assess risk factors and long-term outcomes. In addition, we did not address potential sources of variability between the studies by conducting quality assessment and critical appraisal. Lastly, we used a very short timeframe for evidence review that may have limited these conclusions. We are aware that additional potentially eligible manuscripts may have been published during the review period for this manuscript. However, we have elected not to include these, so that our literature search process remains systematic.

CONCLUSIONS

Our current review of the literature on "new data and new challenges" regarding EAIs has identified many themes consistent with previous reviews, including a low prescription rate of EAIs for patients at risk of anaphylaxis, low EAI carriage, and inadequate use in acute allergic reactions in patients of all ages by health care professionals, parents and caregivers, and patients themselves. Unfortunately, our review highlights that little progress has been made.

New challenges have emerged regarding EAI needle length and unpredictable delivery in higher weight individuals versus trauma and delivery to bone in lower weight children. The clinical significance of these findings in the context of acute treatment requires further study.

Lastly, this review highlights the importance of anaphylaxis education and EAI training for patients and their caregivers, health care professionals, and the greater community. Hopefully these efforts will improve or even reverse these enduring themes that continue to be identified as gaps in anaphylaxis management.

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