American Journal of Emergency Medicine 99 (2026) 270–275

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Retrospective comparison between 0.3 mg and 0.5 mg dosing of intramuscular epinephrine for anaphylaxis

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ARTICLE INFO

Article history:
Received 27 August 2025
Received in revised form 7 October 2025
Accepted 8 October 2025
Available online xxxx

Keywords:
Intramuscular
Injections
Epinephrine
Anaphylaxis

ABSTRACT

Background: Anaphylaxis is an acute and life-threatening reaction. Intramuscular (IM) epinephrine is the first line agent for management. The World Allergy Organization recommends IM epinephrine 0.01 mg/kg, with a maximum dose of 0.5 mg. However, 0.3 mg is commonly used which may increase the risk of poor outcomes in adults greater than 50 kg. This study aims to investigate the incidence of escalating care after initial epinephrine dosing in management of anaphylaxis.
Methods: This retrospective study included patients who received IM epinephrine 0.3 or 0.5 mg for anaphylaxis within a single health system. The primary outcome was the incidence of escalating care after an initial dose of IM epinephrine, defined as an additional dose of IM epinephrine, epinephrine infusion initiation, or intubation. Secondary outcomes, including adverse effects, were compared between groups.
Results: Of 338 meeting inclusion criteria, 254 and 84 patients were in the 0.3 mg and 0.5 mg groups, respectively. The primary composite outcome was significantly higher in the 0.3 mg group compared to the 0.5 mg group (29.5 % vs. 7.1 %, $p < 0.001$). Individual outcomes of an additional IM dose and infusion initiation were significantly higher in the 0.3 mg group. A multivariate logistic regression confirmed an initial dose of 0.5 mg epinephrine was independently associated with a lower incidence of the primary outcome.
Conclusion: Significantly fewer patients receiving an initial 0.5 mg IM epinephrine dose required escalation of care compared to those who received 0.3 mg. Future prospective studies are needed to confirm the results of this study.

1. Introduction

Anaphylaxis, an acute and life-threatening hypersensitivity reaction, occurs through both immunologic and non-immunologic mechanisms after exposure to patient-specific allergens [1]. In the United States, the risk of anaphylaxis from medications, food, insect venom, radiocontrast, occupational allergens, and idiopathic anaphylaxis in a lifetime is estimated to be between 1.6 % and 5.1 % [2,3]. In recent years, the incidence has continued to rise and peaks between the ages of 50 and 69 years [1,2,4]. Despite rising rates, it continues to be under-diagnosed and under-treated with first-line agents due to similarities in the definition of anaphylactic and non-anaphylactic hypersensitivity reactions [5]. Due to the risk of suboptimal treatment, guidance recommends that patients presenting with systemic hypersensitivity that do not meet full diagnostic criteria of anaphylaxis may also be candidates for treatment with intramuscular (IM) epinephrine due to the risk of worsening hypersensitivity and progression of reaction [5].

Intramuscular epinephrine is the first line agent for the acute management of anaphylaxis, requiring prompt administration for optimal clinical outcomes [1,2,4-8]. Epinephrine was first noted to be effective and recommended for the treatment of anaphylaxis when used as a deep IM injection at a dose of 0.3 mg in a pharmacology guide published in 1918 and has remained the standard of care for over a century [8]. Currently, guidance from the World Allergy Organization and American College of Allergy, Asthma, and Immunology and American Academy of Allergy, Asthma, and Immunology recommend dosing IM epinephrine at 0.01 mg/kg of body weight, with the maximum dose of 0.3 mg for children aged 6 to 12 years and 0.5 mg for teenagers and adults [2,5,10]. Despite these recommendations, utilizing the weight-based maximum dose of 0.5 mg may not be a widespread practice. This could be due to a lack of strong efficacy data, perceived risk of

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https://doi.org/10.1016/j.ajem.2025.10.020

increased adverse events, and practitioner comfortability with the 0.3 mg dose, likely related to the availability of 0.3 mg epinephrine autoinjectors [2,10,11].

Although epinephrine bares the concern for cardiotoxicities, including fatal arrhythmias and myocardial infarction, these adverse effects are most commonly associated with intravenous (IV) boluses of epinephrine rather than IM epinephrine [2,5,8]. Specifically, the use of IM epinephrine is safer than IV epinephrine due to fewer dosing errors and adverse effects [2,7,8,12]. At the current recommended doses for the treatment of anaphylaxis, IM epinephrine has been noted to be safe [2,5,10,13,14]. However, there is not currently data comparing the two different doses of IM epinephrine in an adult population being treated for emergency allergic reactions. Despite the possible risks of adverse effects, it is important for all clinicians who treat patients with anaphylaxis to understand that suboptimal dosing of IM epinephrine may result in escalation of care and unnecessary resource utilization [11].

At our enterprise, composed of a large academic medical center in a metropolitan area and three regional hospitals, there is considerable variability for the initial dosing of epinephrine for the treatment of anaphylaxis. This study aims to describe the outcomes associated with epinephrine dosing for anaphylaxis through assessment of escalation of care and adverse effects after different initial doses of IM epinephrine.

2. Methods

2.1. Study design, setting, and population

This retrospective cohort analysis evaluated patients that received IM epinephrine for anaphylaxis from January 1, 2018 to November 17, 2024. The study was approved by the local Institutional Review Board (#241776). Patients who were at least 18 years of age and had received at least one dose of IM epinephrine for anaphylaxis were considered for inclusion in the study. Patients were considered to have anaphylaxis based on the World Allergy Organization definition of anaphylaxis or by clinical suspicion of anaphylaxis by the treating physician based on documentation in electronic medical record note [2]. The World Allergy Organization defines anaphylaxis as being highly likely when a patient experiences an acute onset of illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (generalized hives, pruritis or flushing, swollen lips-tongue-uvula), acute onset of hypotension or bronchospasm or laryngeal involvement after exposure to a known or highly probable allergen for that patient even in the absence of typical skin involvement, and at least one of the following: respiratory compromise, reduced blood pressure or associated symptoms of end-organ damage, or severe gastrointestinal symptoms. Patients were excluded if they received a dose of IM epinephrine from Emergency Medical Services, the patient administered their own epinephrine autoinjector, or the patient weighed less than 50 kg. Eligibility for inclusion was confirmed through manual medical record review.

2.2. Study protocol

The initial manual chart review, including inclusion and exclusion of patient charts, was performed by a pharmacy resident training in critical care. A random number generator was used for all patients within the specified time frame that received a dose of either 0.3 mg or 0.5 mg of IM epinephrine to determine which patient charts would be assessed for inclusion in the analysis. All patient charts that were selected for assessment by the random number generator and met criteria for inclusion were included in the analysis until the number of included patients met the prespecified number of patients needed to meet power. The inclusion of patient charts was followed by data collection of baseline patient demographics, presenting symptoms, receipt of medications, as well as outcome data. Safety outcome data including interpretation of electrocardiogram (EKG) for ischemic changes or presence of arrhythmia (atrial or ventricular) was performed by a board-certified emergency medicine physician. All data collection methods were in accordance with retrospective chart review guidance by Kaji et al. [15]. Missing data points were managed based on the specific missing variable. The absence of documented presenting symptoms or resolution of symptoms was considered to have a negative status for the variable while patients without documentation of heart rate, systolic blood pressure, troponin levels or EKGs within the defined timeframe were excluded from assessment of the specified safety outcome. A board-certified emergency-medicine clinical pharmacist reviewed a random 10 % sample of included patients included in the analysis to assess systematic bias. To evaluate interrater reliability, Cohen's kappa was calculated for primary outcome data to examine interobserver agreement, with levels above 0.80 being considered almost perfect agreement [15,16]. Study data were collected and managed using Redcap© electronic data capture tools hosted by the associated medical center [17,18].

2.3. Key outcome measures

The primary composite outcome of the study was the incidence of escalation of care for anaphylaxis after the receipt of an initial dose of IM epinephrine. This composite outcome was defined by the occurrence of any of the following events within 6 h of the initial dose of IM epinephrine: administration of an additional dose of IM epinephrine, initiation of an epinephrine infusion, or intubation deemed to be a result of anaphylaxis progression. Secondary efficacy outcomes included the individual components of the composite outcome, resolution of symptoms (determined by physician discretion of change in symptoms after receiving the initial dose of epinephrine), and length of stay in the emergency department (ED) for the cohort of patients that presented with the chief complaint of anaphylaxis. Safety outcomes included peak change in heart rate and systolic blood pressure greater than 200 mmHg within 6 h of epinephrine administration, ischemic changes noted on EKG within 6 h of epinephrine administration per ED physician interpretation (defined as new ST-elevation or ST-depression), atrial or ventricular arrhythmia within 6 h of epinephrine administration, and elevated troponin after epinephrine (defined as greater than or equal to 0.04 ng/mL) within 12 h of epinephrine administration [6].

2.4. Data analysis

Based on prior studies, we assumed a 13 % baseline risk of escalation of care among patients who received 0.3 mg of IM epinephrine for the initial treatment of anaphylaxis [19-21]. Therefore, we determined that total sample size of 332 patients in a ratio of 1:3 (0.5 mg:0.3 mg) would achieve an 80 % power assuming an absolute difference of 10 % in the primary outcome and a two-sided type I error of 0.05.

Descriptive statistics were used to compare baseline characteristics, expressed as numbers and percentages or medians and interquartile ranges. Statistical analysis testing was performed using IBM SPSS Statistics Version 29© (Armonk, NY) and RedCap © [17,18]. Categorical variables, including the primary and secondary efficacy and safety outcomes, were analyzed with a chi-square test or a Fischer's Exact Test when less than 5 values were present. Continuous variables were analyzed using the Mann-Whitney *U* Test. A multivariate logistic regression model was used to assess factors independently associated with the primary outcome including initial dose of IM epinephrine, age, weight in kg, anaphylaxis as the primary reason for presentation, receipt of other medications for anaphylaxis, and severe symptoms on presentation. The Hosmer and Lemeshow Test was utilized to assess the goodness-of-fit of the regression model with a *p*-value above 0.05 indicating the model and data fit well together while the Omnibus Tests of Model Coefficients was used to evaluate if the independent variables used in the regression models were able to predict the outcome

variable. A p-value less than 0.05 on the Omnibus Tests of Model Coefficients suggests that the independent variables significantly improve the regression model. Additionally, the variance inflation factor and tolerance values were collected for factors undergoing logistic regression to test for collinearity. We considered a variance inflation factor of 1 to signify no correlation, factors between 1 and 5 to suggest moderate correlation, and factors greater than 5 to suggest problematic collinearity. A tolerance value close to 1 suggested minimal collinearity and a value close to 0 suggested high multicollinearity.

Severity of presenting symptoms for the multivariate logistic regression model were considered based on information from both the World Allergy Organization's systemic allergic reaction grading system and the population-based study by Manivannan and colleagues [2,19]. The World Allergy Organization guidelines break down symptoms of allergic reaction and anaphylaxis on a grading scale ranging from 1 (least severe) to 5 (most severe) [2]. Symptoms of laryngeal edema, severe bronchospasm without response, respiratory failure, syncope, hypotension, and loss of consciousness are characterized as Grades 4 or 5 on the severity scale [2]. Manivannan and colleagues found that patients presenting with wheezing, arrhythmias, hypotension and shock, stridor, laryngeal edema, cough, and nausea or vomiting were more likely to receive a repeated dose of epinephrine for the indication of anaphylaxis [19]. Therefore, we defined mild to moderate presenting symptoms as urticaria, dizziness or lightheadedness without syncope, mouth swelling, shortness of breath, wheezing, gastrointestinal pain or cramping, cough, and nausea or vomiting while severe symptoms as hypotension and/or shock, syncope, laryngeal edema, and tachycardia.

3. Results

3.1. Study population

Out of the 433 patients that were assessed for eligibility, 338 patients met the inclusion criteria with 254 patients and 84 patients in the 0.3 mg and 0.5 mg groups, respectively. As depicted in Fig. 1, patients were most commonly excluded due to receiving epinephrine for an indication other than anaphylaxis or receiving their initial IM epinephrine dose from Emergency Medical Services or a self-administered epinephrine autoinjector.

Baseline characteristics between groups were similar (Table 1). Included patients had a median age of 44 years (IQR: 29 to 57), were predominantly female (61 %), and had a median weight of 82 kg (IQR:71 to 98). The primary reason for hospital presentation was anaphylaxis in 73 % of patients, which slightly favored the 0.5 mg group compared to 0.3 mg group. The remaining 27 % of patients were already in the emergency department or admitted to the hospital at the time of the patient's initial anaphylaxis symptoms. The most common initial symptoms of anaphylaxis were urticaria (78 %), shortness of breath (57 %), facial or mouth swelling (38 %), and nausea and/or vomiting (23 %). At presentation, 38 % of patients were classified as having at least one severe symptom. Additionally, 95 % percent of patients in the study also received at least one adjunctive agent for anaphylaxis. The most common adjunct was an antihistamine followed by steroids and albuterol, respectively.

3.2. Outcomes

The primary composite outcome was significantly more common in the epinephrine 0.3 mg group compared to the epinephrine 0.5 mg group (30 % vs. 7 %, $p < 0.001$) (Table 2). This finding was primarily driven by the 0.3 mg group receiving additional doses of IM epinephrine. Overall, the most common escalation of anaphylaxis treatment was an additional dose of IM epinephrine, occurring in 23 % of the included patients, followed by the initiation of an epinephrine infusion in 6 % and intubation in 2 %. Cohen's kappa for the composite and individual primary efficacy outcomes were each 1.00, indicating perfect agreement between the data collection of the primary and secondary reviewer.

The secondary efficacy outcome of resolution of symptoms after the first IM epinephrine dose was more common in the 0.5 mg group compared to the 0.3 mg group. However, in patients requiring an escalation of care, the median time from the initial IM epinephrine dose to first escalation of care outcome was not different between the groups. Notably, of the patients that presented to the ED for treatment of anaphylaxis, patients receiving an initial dose of 0.3 mg had a longer length of stay in the ED and a higher likelihood of hospital admission compared to the patients receiving an initial dose of 0.5 mg.

Safety outcomes of this study are depicted in Table 3. There was no major difference between the groups for the outcomes of peak increase in heart rate, systolic blood pressure > 200 mmHg, ischemic changes on EKG, and atrial or ventricular arrhythmia within 6 h of initial IM epinephrine or elevated troponin within 12 h of initial epinephrine dose.

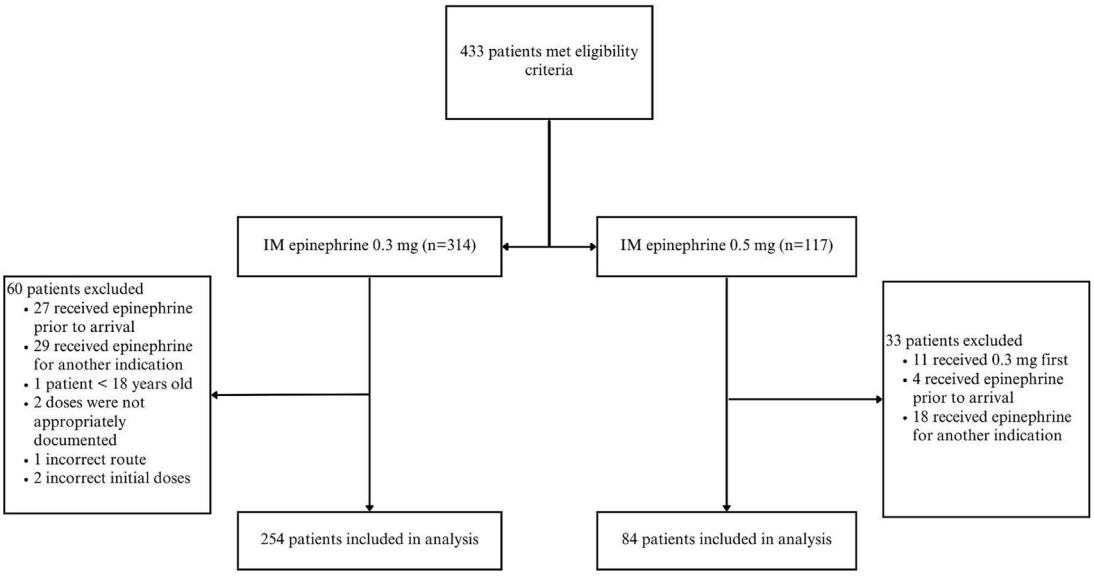

Fig. 1. Selection of patients for inclusion and exclusion.

Table 1
Baseline characteristics.

	IM epinephrine 0.3 mg ($n = 254$)	IM epinephrine 0.5 mg ($n = 84$)	*P* value
Age (yr) - median [IQR]	42 [28–56]	49.5 [33.8–61.0]	0.340
Male – n. (%)	93 (36.6)	38 (45.2)	0.160
Race – n. (%)			
White (Non-Hispanic)	187 (73.6)	70 (83.3)	
Black	41 (16.1)	11 (13.1)	0.281
Hispanic	18 (7.1)	3 (3.6)	
Asian	2 (0.8)	0 (0)	
Other	6 (2.4)	0 (0)	
Height (cm) - median [IQR]	167.6 [160.0–175.3]	167.6 [160.0–176.5]	0.729
Weight (kg) - median [IQR]	81.8 [70.5–95.2]	86.2 [69.2–100.1]	0.302
Anaphylaxis was reason for presentation – n. (%)	178 (70.1)	69 (82.1)	0.031
Initial Symptoms – n. (%)			
Urticaria	196 (74.2)	67 (79.7)	0.620
Facial or mouth swelling	89 (35.0)	40 (47.6)	0.040
Shortness of breath	143 (56.3)	49 (58.3)	0.744
Wheezing	36 (14.2)	14 (16.6)	0.577
Hypotension and/or shock	34 (13.4)	8 (9.5)	0.352
Dizziness without syncope	27 (10.6)	3 (3.5)	0.149
Syncope	2 (0.8)	2 (2.4)	1.000
GI pain or diarrhea	24 (9.4)	9 (10.7)	0.735
Laryngeal edema	37 (14.6)	12 (14.3)	0.949
Cough	12 (4.7)	1 (1.2)	0.198
Nausea and/or vomiting	61 (24.0)	15 (17.9)	0.241
Tachycardia	43 (16.9)	14 (16.7)	0.956
At least one severe symptom – n. (%)	99 (40.0)	30 (35.7)	0.594
Receipt of other anaphylaxis medications – n. (%)	241 (95.3)	79 (94.0)	0.661
Steroids	227 (91.2)	77 (92.8)	0.544
Antihistamines	239 (96.0)	81 (97.6)	0.409
Albuterol	50 (20.1)	13 (15.7)	0.391

IQR, interquartile range.

However, safety data was not documented in many patients included in the analysis. Specifically, 26 % of patients had a documented increase in heart rate, 43 % had a documented systolic blood pressure, and 18 % had a documented EKG within 6 h after epinephrine administration. Only 14 % had documented troponin within 12 h after IM epinephrine administration. Overall, this analysis was not powered to detect a difference in safety outcomes, and findings are difficult to interpret due to the insufficient number of patients with documented safety data.

A multivariate logistic regression model for escalation of care after the initial dose of IM epinephrine was conducted to determine factors independently associated with the primary outcome (Table 4). After considering factors including initial IM epinephrine dose, age, weight, anaphylaxis as the indication for hospital presentation, receipt of other anaphylactic medications, and presentation with severe symptoms of anaphylaxis, we found that increased age, an initial dose of epinephrine 0.3 mg, and use of other anaphylactic medications were found to be associated with an increased risk of requiring an escalation of care after the initial dose of IM epinephrine. Based on collinearity statistics for the variables included, there was minimal to no correlation based on variance inflation factor variables ranging from 1.0 to 1.1 and tolerance variable ranging from 0.88 to 0.98. The model was statistically significant based on the Omnibus Tests of Model Coefficients ($p < 0.001$) and this binary logistic regression model had a satisfactory goodness of fit with a *P* value of 0.589 based on the Hosmer and Lemeshow Test.

4. Discussion

In this study evaluating 338 patients treated with IM epinephrine for anaphylaxis, 254 patients were initially treated with IM epinephrine 0.3 mg and 84 patients initially treated with IM epinephrine 0.5 mg. Patients receiving an initial dose of 0.3 mg were significantly more likely to require an escalation of care and were less likely to have a resolution of symptoms after the first IM epinephrine dose compared to an initial dose of 0.5 mg. The individual primary outcomes of an additional IM epinephrine dose and initiation of epinephrine infusion were more likely to occur in the 0.3 mg group, which was also statistically significant. Additionally, initial doses of 0.3 mg of epinephrine, older age, and requirement of other anaphylaxis medications were each individually associated with escalation of care.

Epinephrine has been used as the first-line agent for anaphylaxis since the early 1900s [9]. Original pharmacology guides for that era

Table 2
Efficacy outcomes.

	IM epinephrine 0.3 mg (n = 254)	IM epinephrine 0.5 mg (n = 84)	P value
Escalation of care – n. (%)	75 (29.5)	6 (7.1)	<0.001
Additional IM epinephrine dose	71 (28.0)	5 (6.0)	<0.001
Epinephrine infusion	20 (7.8)	1 (1.2)	0.034
Intubation	7 (2.8)	0 (0.0)	0.199
Time from first IM epinephrine dose to first escalation of care (min) – median [IQR]	26 [9.5–78.5]	29 [16.5–39.3]	0.928
Resolution of symptoms after first epinephrine dose – n. (%)	184 (72.4)	80 (95.2)	<0.001
Requirement of hospital admission – n./total no. (%)*	51/178 (28.7)	10/69 (14.5)	0.010
ED Length of Stay (hrs) - median [IQR]*	5.0 [3.9–6.9]	4.1 [2.8–5.4]	<0.001

IM, intramuscular; *ED*, Emergency Department; *IQR*, interquartile range.
* In patients that presented to the Emergency Department for the indication of anaphylaxis.

Table 3
Safety outcomes.

	IM epinephrine 0.3 mg	IM epinephrine 0.5 mg	*P* value
Peak increased change in HR (bpm) - median [IQR]	19.5 [10.0–30.0]	29.0 [21.0–38.5]	0.077
SBP > 200 mmHg after epinephrine – n./total no. (%)	4/108 (3.7)	1/38 (2.6)	1.000
Elevated troponin – n./total no. (%)	8/40 (20.0)	3/6 (50.0)	0.065
Peak troponin after epinephrine – median [IQR]	0.01 [0.00–0.02]	0.08 [0.01–0.18]	0.115
Ischemic changes on 12-lead EKG – n./total no. (%)	8/49 (16.3)	2/11 (18.2)	0.881
Atrial fibrillation or atrial flutter on 12-lead EKG – n./total no. (%)	3/49 (6.1)	1/11 (9.1)	0.566

HR, heart rate; *BPM*, beats per minute; *SBP*, systolic blood pressure; *EKG*, electrocardiogram; *IQR*, interquartile range.

recommend the use of 0.3 mg of epinephrine for anaphylaxis. However, by the 1930s, epinephrine doses ranging from 0.5 mg to 1.0 mg were considered the ideal treatment with the maximum efficacy [9]. Importantly, these recommendations were not based off clinical trials, but from the observations of clinicians that treated anaphylaxis [9]. The Food Drug Administration (FDA) first approved epinephrine IM autoinjector for marketing for the treatment of anaphylaxis in adults at a dose of 0.3 mg in 1987 [9]. However, even guidelines for the treatment of anaphylaxis published after epinephrine's FDA approval continued to recommend initial doses up to 0.5 mg for adult patients [9,21].

Currently, the World Allergy Organization Anaphylaxis Guidance and American College of Allergy, Asthma, and Immunology and American Academy of Allergy, Asthma, and Immunology guidance for the treatment of anaphylaxis recommends using a weight-based dose of 0.01 mg/kg of body weight for a maximum total dose of 0.5 mg IM epinephrine [2,5,9,10]. Therefore, most patients over 12 years of age are recommended to receive the maximum dose of 0.5 mg [2,5,10]. Guidance by the American College of Allergy, Asthma, and Immunology and American Academy of Allergy, Asthma, and Immunology in 2015 also suggests that the higher recommended dose of 0.5 mg should be considered in patients whose symptoms of anaphylaxis are severe [9,11]. Although World Allergy Organization states that IM epinephrine treatment remains suboptimal, it does not address the possibility of adult patients commonly receiving a lower than recommended dose of 0.3 mg [2]. While the higher dose of 0.5 mg IM has been referenced in anaphylaxis treatment guidance throughout history, there is little information explaining the preference for and frequent use of the 0.3 mg dose. This may be related to the widespread awareness of the epinephrine autoinjector's 0.3 mg dose and practitioner comfortability with that dose.

To our knowledge, this is the first study to compare IM epinephrine 0.3 mg and IM epinephrine 0.5 mg for the treatment of anaphylaxis in the adult acute care setting. Although our analysis assessed safety, the interpretation of data is difficult due to a significant portion of patients without documented safety data. Prior literature includes two randomized cross-over trials by Duvauchelle et al. (2018) and Patel et al. (2020) in healthy adult males and teenagers at risk for food-induced anaphylaxis, respectively [14,22]. These pharmacokinetic analyses monitored the safety and absorption of IM epinephrine at doses of 0.3 mg and 0.5 mg [14,22]. Investigators of both studies found that participants tolerated epinephrine without adverse effects, regardless of the dose provided, but the 0.5 mg dose resulted in higher plasma epinephrine levels versus the 0.3 mg dose [14,22]. A multicenter efficacy analysis investigating the impact of IM epinephrine for the treatment of immunotherapy-induced anaphylaxis in 38 patients by Correa et al. (2021) found that after an initial dose of IM epinephrine 0.5 mg, an additional dose of IM epinephrine was necessary in only 29 % of patients, but 42 % of patients did require transfer to the emergency department due to continued symptoms of anaphylaxis [13]. A population-based study by Manivannan et al. (2009) found that repeat dosing of epinephrine was required in 13 % of patients after receiving an initial average dose of 0.27 mg [19]. Repeat dosing was found to be more common in young patients presenting with more severe symptoms including wheezing, hypotension or shock, laryngeal edema, and nausea or emesis [19]. None of these studies directly compared 0.3 mg to 0.5 mg but did provide some convincing evidence that not only is 0.3 mg potentially inadequate, but that it also may require repeat doses and further escalations of care. This is consistent with the results of our study.

Regarding the safety of epinephrine in the treatment of anaphylaxis, a retrospective observational study evaluating risks of cardiotoxicity after treatment of anaphylaxis with IM epinephrine was conducted by Pauw and colleagues in 2023. The authors reviewed the incidence of ischemic EKG changes, elevations in systolic blood pressure, elevated troponin, cardiac arrest, or percutaneous coronary intervention. Overall, the investigators found low rates of cardiotoxicity (4.7 %). Of the toxicity found, most were related to findings of new ischemic changes on EKG (2.4 %), elevated troponin (1.8 %), and arrythmias (1.8 %) [6]. Our analysis found higher rates of ischemic changes on EKG (17 %) and elevated troponins (24 %), which is likely due to the extent of missing data safety data. This is an area where future prospective studies should be thoroughly evaluated.

Table 4
Logistic regression model.

	Odds ratio (OR)	Confidence interval (95 %)	P value
Initial epinephrine dose*	0.17	0.07–0.41	<0.001
Age	1.02	1.00–1.03	0.027
Weight	1.00	0.99–1.00	0.610
Anaphylaxis as reason for presentation	0.70	0.39–1.25	0.224
Receipt of other anaphylaxis medications	0.24	0.08–0.72	0.011
Severe symptoms of anaphylaxis	1.18	0.68–2.0	0.557

* Initial IM epinephrine dose, 0.3 or 0.5 mg.

4.1. Study limitations

There are limitations to this study. This is a retrospective study that relied on chart review for patient inclusion and data collection which is prone to systematic bias [15]. To reduce this risk, a secondary reviewer collected data on a 10 % random sample of patients and a Cohen's kappa was used to quantify agreement between the reviewers. Based on the retrospective nature of the analysis, patient characteristics and select secondary and safety outcomes had missing data. Inclusion of patients was dependent on adequate charting of symptoms and diagnosis of anaphylaxis by clinical provider based on electronic medical record note. Additionally, the site of IM epinephrine injection was not well documented. Therefore, some patients may have received the medication in their deltoid opposed to the anterolateral aspect of the thigh, which has more rapid and complete absorption. Furthermore, the secondary efficacy outcome of resolution of symptoms after the first dose of epinephrine was subjective information based on provider's discretion and if not documented led to a negative status for the variable. This could have led to improper classification of the patient. Additionally, this was a single-health system analysis which could limit generalizability. However, this study included all adult hospitals within the system

including rural community hospitals as well as a large academic hospital within a metropolitan area and all patients who received epinephrine for anaphylaxis, not only patients who presented to the emergency department with it as a primary complaint. Fewer patients were included in the epinephrine 0.5 mg group, making its sample size smaller than the 0.3 mg group. This was expected due to 0.3 mg more commonly being used to treat anaphylaxis at the study institution, and enrollment was adjusted to ensure adequate statistical power. Lastly, there was a significant portion of safety data endpoints that were absent in the electronic medical record of patients included in our analysis. Therefore, we are unable to make conclusions regarding safety due to our sample size not meeting power. Further studies are needed to determine the impact of the two doses of IM epinephrine on safety outcomes in anaphylaxis. Overall, our study adds valuable information to the available literature and should provide adequate rationale for future confirmatory studies.

5. Conclusion

Our study found that an initial dose of 0.3 mg of IM epinephrine for the treatment of anaphylaxis was associated with an increased need for an additional IM epinephrine dose, initiation of epinephrine infusion, or intubation compared to using an initial dose of 0.5 mg. These findings support the World Allergy Organization weight-based recommendation for adult patients experiencing anaphylaxis. Our analysis is unable to make conclusions on the safety between the two doses of IM epinephrine due to insufficient data. Larger, prospective studies are needed to confirm the use of an initial IM epinephrine dose of 0.5 mg leads to less escalation of care and to determine the impact of the two doses on safety outcomes in patients with anaphylaxis. Our study provides justification for following the recommended guideline dosing of epinephrine in the treatment of anaphylaxis.

Authors' contribution

All authors made a significant contribution to the work reported and gave final approval of the version to be published.

CRediT authorship contribution statement

Caroline A. Jackson: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Ryan C. Dillon:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **L. Montana Fleenor:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Emily K. Pauw:** Writing – review & editing, Supervision, Formal analysis, Data curation. **Mary M. O'Keefe:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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