

Epinephrine auto-injector needle lengths Can both subcutaneous and periosteal/intraosseous injection be avoided?

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ABSTRACT

Background: Epinephrine should be administered intramuscularly in the anterolateral aspect of the thigh. The length of the epinephrine auto-injector (EAI) needle should ensure intramuscular injection.

Objective: To discuss suitable EAI needle lengths based on ultrasound measurements related to weight.

Methods: The skin-to-muscle distance (STMD) and skin-to-bone distance (STBD) were measured by ultrasound in the mid-third of the anterolateral area of the right thigh when applying high pressure (8 lb; high-pressure EAI [HPEAI]) or low pressure (low-pressure EAI [LPEAI]) on the ultrasound probe. The study included 302 children and adolescents and 99 adults. The maximum and minimum STMD and the maximum and minimum STBD were estimated.

Results: Using HPEAIs, the risk of periosteal or intraosseous penetration was 32% in children weighing less than 15 kg. The risk of subcutaneous injection was 12% in adolescents and 33% in adults. With LPEAIs, there was no risk of periosteal or intraosseous injection and the risk of subcutaneous injections in adolescents and adults was lower at 2% and 10%, respectively. A new EAI for injection in small children would have no risk of periosteal or intraosseous injection but would have 71% chance of subcutaneous deposit of epinephrine.

Conclusion: Common HPEAIs have a high risk of periosteal or intraosseous penetration in children and subcutaneous injections in overweight and obese adults. LPEAIs have some risk of subcutaneous injection in adults. HPEAIs with 0.1 mg of epinephrine and shorter needles have no risk of periosteal or intraosseous injection but have a high risk of subcutaneous deposit. For adult or overweight or obese patients, HPEAIs and LPEAIs should have longer needles. Future studies should focus on triggering pressures and variations in needle length.

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Introduction

Currently, prompt administration of intramuscular epinephrine is recommended treatment for anaphylaxis.^{1,2} Outside the hospital setting, epinephrine auto-injectors (EAIs) are the standard method of administering epinephrine in patients with food allergy and patients receiving immunotherapy at home who are at risk of general reactions. In Europe and North America, the high-pressure EAIs (HPEAIs) EpiPen and EpiPen Jr (Meridian Medical Technologies, St Louis, Missouri),³ Auvi-Q (Bridgewater, New Jersey) and Allerject (Laval, Québec, Canada),^{4,5} and Jext (ALK-Abelló, Hørsholm, Denmark) are currently the most commonly prescribed EAIs. To avoid the risk of periosteal or intraosseous injection, the Auvi-Q 0.1 mg, with a shorter needle than other HPEAIs (7.5 vs 15 mm), has recently been introduced. Recently, a low-pressure EAI

(LPEAI), Emerade (MEDECA Pharma, Uppsala, Sweden), has been introduced.^{6,7} For proper injection, it requires low pressure. The LPEAIs have longer needles than HPEAIs and a higher dose (0.5 mg; Table 1).

The dose of epinephrine recommended for treatment of anaphylaxis is 0.01 mg/kg.^{9–13} However, the recommended doses have been determined empirically (Table 1). The recommended doses vary among countries and academic societies. Proposed dosage recommendations are listed in Table 2.

There is a risk for injecting epinephrine into subcutaneous tissue instead of the muscular compartment or periosteal or intraosseous deposition. Computed tomography,¹⁴ injection in pigs,^{15–17} ballistic gel,⁸ and ultrasound of the human mid-antrolateral aspect of the right thigh^{8,18–23} have been used to estimate the risk of subcutaneous and periosteal or intraosseous injection.^{8,18–20,24}

The recently introduced Auvi-Q 0.1-mg HPEAI is intended for use in small children to avoid periosteal or intraosseous injection of epinephrine. The needle length, 7.5 mm, is half as long as that of other HPEAIs.

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Based on data on the distance from skin to muscle (STMD) and skin to bone (STBD) obtained by ultrasound of the middle anterolateral aspect of the right thigh,^{18–20} the possible risk of subcutaneous and periosteal or intraosseous injection of epinephrine using EAI is discussed.

Methods

Patients

Patients with food allergy assessed at a referral-only allergy clinic were consecutively included based on an appropriate history and positive skin prick test reactions.

Three groups of children and adolescents participated: children younger than 12 years weighing less than 15 kg ($n = 100$; group 1),¹⁹ children younger than 12 years weighing 15 to 30 kg ($n = 102$; group 2), and adolescents 12 to 18 years of age weighing more than 30 kg ($n = 100$; group 3).²⁰ In total, 302 children and adolescents were

Table 1
Auto-Injectors Commonly Used in Europe and/or North America in 2017^a

Epinephrine auto-injector	Needle length (mm)		Pressure
	Penetrating needle length	Distance from skin surface to within muscle (~ 2 mm) ⁸	
EpiPen Jr 0.15 mg ^b , Jext 0.15 mg ^b	13	11	thrusted or pressed hard
EpiPen 0.3 mg ^b , Jext 0.3 mg ^b	15	13	
Auvi-Q 0.1 mg ^b	7.5	5.5	
Emerade 0.15 mg ^c	16	14	slight pressure
Emerade 0.3 mg ^c	23	21	
Emerade 0.5 mg ^c	23	21	

^aThe mean needle lengths of the high-pressure epinephrine auto-injectors EpiPen, EpiPenJr, and Jext differ by less than 1 mm. Therefore, we use 13 mm (skin-to-muscle distance) and 15 mm (skin-to-bone distance) for the high-pressure epinephrine auto-injectors. The recently introduced Auvi-Q 0.1 mg has a substantially shorter needle.

^bThese devices are high-pressure epinephrine auto-injectors.

^cThis device is a low-pressure epinephrine auto-injector.

Table 2
Epinephrine Dose as Recommended by Different Authorities and Academic Societies

A. Dosing of intramuscular epinephrine according to 0.01-mg/kg rule ^{9–13}		
Dose by EAI	kg	Dose/kg
0.5 mg	50	0.01
0.3 mg	30	0.01
0.15 mg	15	0.01
B. According to EAACI guidelines ¹²		
Weight	Dose	mg/kg
7.5–25 kg	0.15 mg	0.02–0.006
25–30 kg ^a	0.3 mg	0.012–0.01
C. According to AAAAI practice parameter 2015 ³⁵		
<15 kg	0.15 mg	>0.01
15–30 kg	0.3 mg	0.01–0.005
D. According to Swedish anaphylaxis document ¹¹		
10 ^b –20 kg	0.15 mg	>0.015–0.008
20–60 kg	0.3 mg	0.016–0.005
>60 kg ^c	0.5 mg	0.008– < 0.008

Abbreviations: AAAAI, American Academy of Allergy, Asthma and Immunology; EAACI, European Academy of Allergy and Clinical Immunology; EAI, epinephrine auto-injector.

^aNo dose recommended for adolescents weighing more than 30 kg.

^bEven lower.

^cTentative.

included (125 girls and 177 boys). Furthermore, 99 adults (range 18–72 years), 69 of whom were women, were included in the study.¹⁸ Data on these patients have been published previously.^{18–20} Further patient characteristics are presented in eTables 1 and 2. The subjects were assessed from July 2012 to June 2014.

Ultrasound Estimation of STMD and STBD

An ultrasound of the mid-antrolateral aspect of the mid-antrolateral right thigh (ie, the recommended location for injecting an EAI) was completed for all subjects when applying high pressure and low pressure. The estimated pressure to mimic the pressure applied to HPEAIs was approximately 8 lb. Low pressure was applied to mimic the pressure applied to LPEAIs.

Four ultrasound measurements were collected from each patient: STMD with low pressure (STMD_{min}), STMD with high pressure (STMD_{max}), STBD with low pressure (STBD_{min}), and STBD with high pressure (STBD_{max}). Figure 1 shows the principle of measurement. The STMD was measured from the skin surface to the inner aspect of the fascia of the vastus lateralis muscle and the bone depth was measured at the outer aspect of the periosteum of the femur as illustrated in Figure 1. The ultrasound measurements were performed by 1 investigator.

Analysis

Data from all included children and adults were analyzed in various weight groups.

Song et al¹⁵ reported on the potential effect of propulsion of the injection bolus spreading 94% beyond the tip of the needle in pig subcutaneous tissue. However, Diacono et al¹⁷ found the fascia to be an impermeable barrier to fluids injected by EAIs. Furthermore, the entire needle orifice must pass completely into the muscle for proper administration of an intramuscular injection. The injection

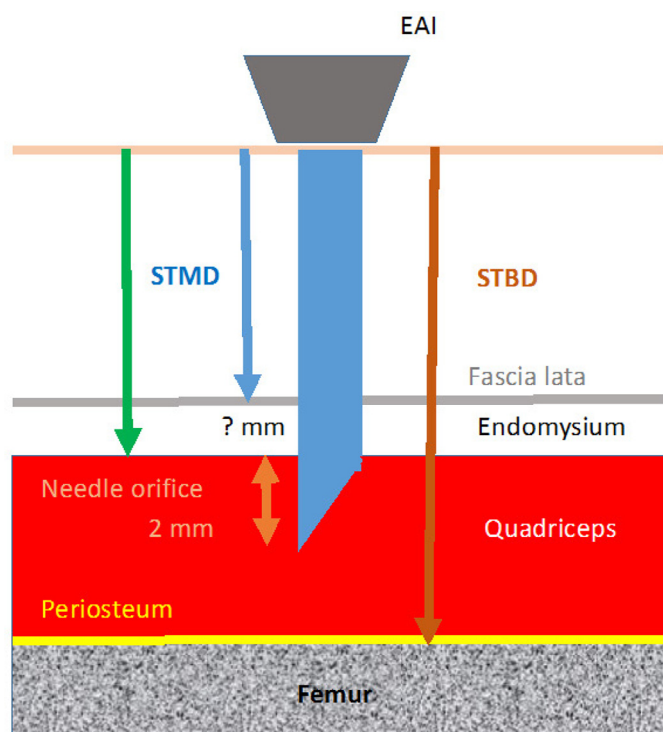


Figure 1. Schematic drawing showing an epinephrine auto-injector (EAI) penetrating the skin, subcutaneous tissue, fascia lata, endomysium, and muscle.¹ STBD, skin-to-bone distance; STMD, skin-to-muscle distance.

must pass the epimysium. If part of the orifice is within the epimysium during the injection, then epinephrine spreads within the loose epimysium tissue.¹⁷

The needle lengths used in this study are those provided by the EAI manufacturers.^{3–7} Because the difference in mean needle length of several HPEAIs is with fractions of a millimeter, we regarded all HPEAIs as having the same needle length (Table 1).

The length of the needle's eye of the EpiPen and EpiPen Jr was estimated to be 2 mm and that of the LPEAI was reported by the manufacturer to be 1.7 mm.²⁵ Because specifications allow some variation, we considered all needle orifices to be 2 mm. Therefore, considering the findings by Diacono et al,¹⁷ we used the needle length minus 2 mm for estimation of the STMD threshold. For estimation of the STBD, the full length of the needles was used (Table 1).

We present different dosages: (1) the recommended dose based on weight using 0.01 mg/kg⁹; (2) the dose used by the manufacturers based on weight; (3) the dosing recommended by the European Academy of Allergy and Clinical Immunology guidelines; and (4) the recent Swedish recommendations¹¹ (Table 2). Results are presented in relation to weight limits for children weighing less than 15 and 15 to 30 kg, adolescents weighing more than 30 kg, and adults.

Outcome Variables

We used 2 primary outcome variables: the proportion of children with (1) STBD shorter than the total needle length and (2) STMD longer than the needle length minus 2 mm (Table 1).

Statistics

We estimated the proportion (number and percentage) of subjects who would likely receive epinephrine intramuscularly and subcutaneously, respectively, using HPEAIs and LPEAIs. Because the technique of measuring distance by ultrasound is not precise and differences in estimated distances are small, the number of patients at risk of subcutaneous or periosteal or intraosseous injection is graded semi-quantitatively in classes (Table 3).

- No patients would have a subcutaneous or periosteal or intraosseous injection
- 1% to 3% of patients would have a subcutaneous or periosteal or intraosseous injection

- **4% to 14%** of patients would have a subcutaneous or periosteal or intraosseous injection
- **≥ 15%** of patients would have a subcutaneous or periosteal or intraosseous injection

Results

Patient Sample

Basic data and statistics of the samples investigated have been published separately elsewhere.^{18–20} The age and weight distribution of children is presented in eTable 1. Patient characteristics are presented in eTables 1 and 2. Because children, adolescents, and adults from all weight groups were included, age varied from 0.2 to 72 years and weight varied from 5 to 149 kg.

Most patients (73%) had at least 1 allergic disease in addition to food allergy. Many children (38%) were sensitized to cow's milk, hen's egg, soy and wheat, peanut (61%), and tree nuts (25%). Furthermore, 34% had pollen-induced allergic rhinitis and/or sensitization to fruits and 41% were sensitized to indoor allergens, mainly house dust mite, cat, and dog. Adults were sensitized mainly to indoor allergens (79%) and pollens (77%; eTable 2).

The mean compression with the application of high pressure was 14.1 mm (range 3.7–31.0 mm). The compression was mainly of the muscle. Using all data, the mean compression of the muscle was 90.2% of the total compression. Thus, increased pressure on the EAI induces only a slight decrease of the STMD_{max}, mainly influencing the STBD_{max}.

EAI Needle Length in Relation to Weight

Because the needle length of the EAIs varies with the dose of epinephrine, differences in dose related to weight influence the risk for subcutaneous and periosteal or intraosseous injection. The chance of subcutaneous or periosteal or intraosseous injections using the HPEAI and LPEAI are presented in Figures 2 to 5 and Table 3.

Skin-to-bone distance

The full needle length of the EAI was used in the calculations. The different proposed weight limits (ie, 15, 30, and 60 kg; Table 1) are presented in Figure 2 for HPEAI data and in Figure 3 for LPEAI data.

Using our ultrasound-based STBD, HPEAIs with a needle length of 13 mm could cause a periosteal or intraosseous injection in 32%

Table 3
STMD and STBD in Relation to Weight

	n	Auvi-Q	EpiPen, EpiPen Jr, Jext		Emerade	
		HPEAI 5.5 mm	HPEAI 11 mm	HPEAI 13 mm	LPEAI 14 mm	LPEAI 21 mm
STMD, n						
Children <15 kg	103	71 ^d	0 ^a		1 ^b	
Children 15–30 kg	99	53 ^d	0 ^a		0 ^a	
Adolescents >30 kg	100			12 ^c		2 ^b
Adults (>18 y)	99			33 ^d		10 ^c
		HPEAI 7.5 mm	HPEAI 13 mm	HPEAI 15 mm	LPEAI 16 mm	LPEAI 23 mm
STBD, n						
Children <15 kg	103	0 ^a	33 ^d		0 ^a	
Children 15–30 kg	99	0 ^a	10 ^c		0 ^a	
Adolescents >30 kg	100			3 ^b		0 ^a
Adults (>18 y)	99			0 ^a		0 ^a

Abbreviations: EAI, epinephrine auto-injector; HPEAI, high-pressure epinephrine auto-injector; LPEAI, low-pressure epinephrine auto-injector; STBD, skin-to-bone distance; STMD, skin-to-muscle distance.

^aNo patients would have a subcutaneous or periosteal or intraosseous injection.

^bOne percent to 3% of patients would have a subcutaneous or periosteal or intraosseous injection.

^cFour percent to 14% of patients would have a subcutaneous or periosteal or intraosseous injection.

^dAt least 15% of patients would have a subcutaneous or periosteal or intraosseous injection.

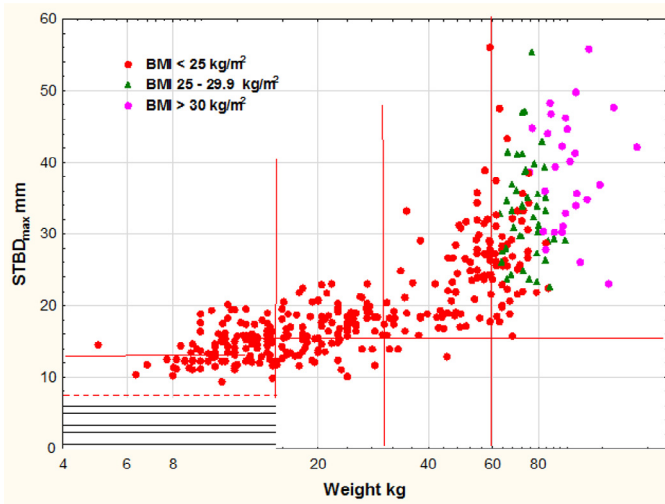


Figure 2. High-pressure skin-to-bone distance (STBD_{max}) against weight. The 2 horizontal solid lines indicate the needle lengths of high-pressure epinephrine auto-injectors. The broken line indicates the needle length of the new epinephrine auto-injector for small children (Auvi-Q 0.1 mg). The solid vertical lines indicate 15, 30, and 60 kg.² Red areas indicate STBD_{max} data with a risk of periosteal or intraosseous injection. As indicated by the area with black horizontal lines, there is no risk of periosteal or intraosseous injection using the short-needle high-pressure epinephrine auto-injector Auvi-Q 0.1 mg. BMI, body mass index.

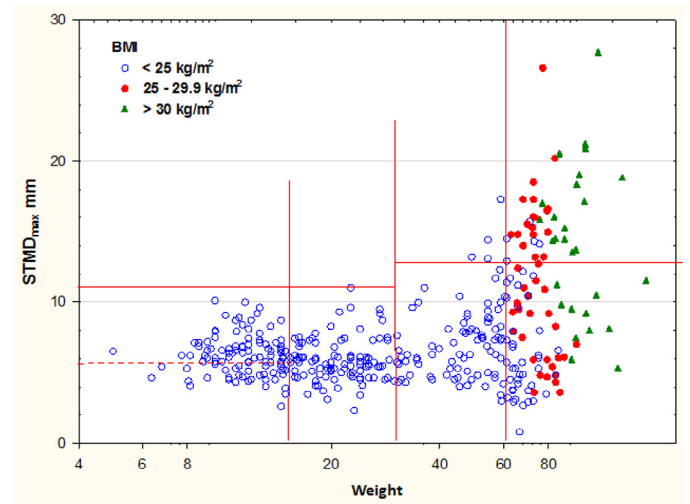


Figure 4. High-pressure skin-to-muscle distance (STMD_{max}) against weight. The 2 horizontal solid lines indicate the needle lengths of high-pressure epinephrine auto-injectors minus 2 mm. The short broken line indicates the needle length of the new high-pressure epinephrine auto-injector for small children (Auvi-Q 0.1 mg). The solid vertical lines indicate 15, 30, and 60 kg.² The red area to the right indicates STMD_{max} data with a risk of subcutaneous injection. The red area to the left indicates STMD_{max} data with a risk of subcutaneous injection using the new short-needle high-pressure epinephrine auto-injector Auvi-Q 0.1 mg. BMI, body mass index.

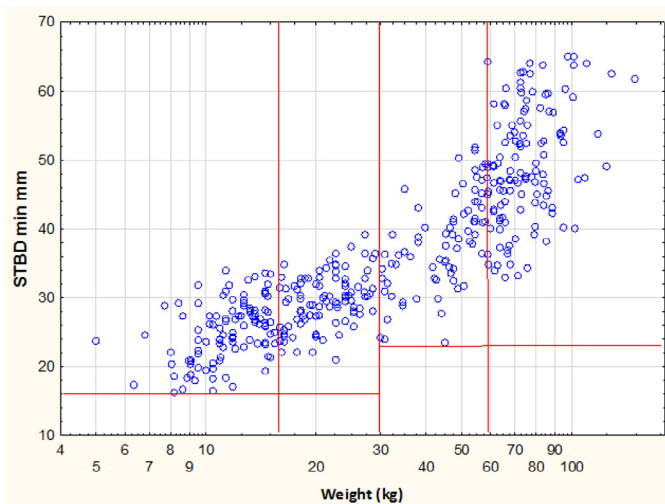


Figure 3. Low pressure skin-to-muscle distance (STBD_{min}) against weight. The 2 horizontal solid lines indicate the needle lengths of low-pressure epinephrine auto-injectors. The solid vertical lines indicate 15, 30, and 60 kg.²

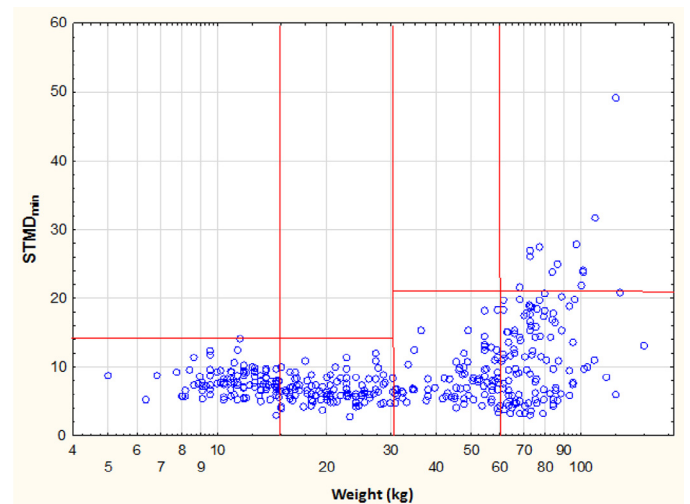


Figure 5. Low-pressure skin-to-muscle distance (STMD_{min}) against weight. The 2 horizontal solid lines indicate the needle lengths of low-pressure epinephrine auto-injectors minus 2 mm. The solid vertical lines indicate 15, 30, and 60 kg.² The red area indicates STMD_{min} with a risk of subcutaneous injection.

of children weighing less than 15 kg and in 10% of those weighing 15 to 30 kg. A few adolescents weighing more than 30 kg and no adults had a STBD_{max} less than 15 mm and could receive a periosteal or intraosseous injection when using an HPEAI. The new HPEAI 0.1 mg has no risk of hitting the bone when used in children weighing less than 30 kg.

When using an LPEAI, no children, adolescents, or adults would have a periosteal or intraosseous injection (Table 3).

Skin-to-muscle distance

The STMD was measured and compared with the length of the needles minus 2 mm (needle orifice; Table 1).

When using an HPEAI in children weighing less than 30 kg, there was no risk of subcutaneous injection. However, 12% of adolescents

weighing more than 30 kg and 33% of adults would probably receive a subcutaneous injection (Table 3).

One percent of children weighing less than 15 kg, 2% of those weighing more than 30 kg, and 10% of adults were at risk for subcutaneous injection when using an LPEAI.

Discussion

In recent years the possibility of subcutaneous or periosteal or intraosseous injection of epinephrine using EAI has been widely discussed. There are several studies on the subject using computed tomography,¹⁴ injection into ballistic gel,⁸ pig subcutaneous tissue,^{15–17} or ultrasound in humans.^{18–23} This study is the most extensive in investigating the relations between the STMD and STBD

as estimated by ultrasound within the mid-anterolateral aspect of the right thigh, the recommended area for intramuscular injection of epinephrine using EAI^s.^{18–20}

We studied 401 patients 0.2 to 72 years of age at risk of anaphylaxis from food allergy with data originating from 3 reports performed with the same design and equipment.^{18–20} Patients referred to the clinic were consecutively included. Thus, the sample represents children and adults with true food allergy from Ontario, Canada.

In this study, we analyzed all patients together correlating STMD and STBD with weight.

Although this is the most extensive study on STMD and STBD, there were relatively few numbers of patients per age group. Therefore, we graded the possible risk of subcutaneous and periosteal or intraosseous injection semi-quantitatively using classes as identified in the data presented in our results. Table 3 presents the risks of subcutaneous and bony injections based on the different age and weight classes.

The general epinephrine dosage recommendation of 0.01 mg/kg body weight has not been adequately studied but is generally used in health care for the treatment of anaphylaxis.^{26,27} However, these recommendations are not fully used by EAI manufacturers and academic societies (Table 2). Most recommendations suggest 0.3 mg for all patients weighing more than 20, 25, or 30 kg, including heavy adults. The proposed empiric dose, 0.01 up to 0.5 mg/kg, would result in doses of 0.15 mg to children weighing 15 kg (7.5–30 kg), 0.3 mg to adolescents weighing 30 kg (15–60 kg), and 0.5 mg to those weighing more than 60 kg (25–> 100 kg). The limits within parentheses are proposed doses for weight groups.

The high-pressure ultrasound technique applied in our study was approximately 8 lb, corresponding to approximately 35 N. Schwirtz and Seeger²⁸ investigated the pressure needed to release the needles of the EpiPen and Jext EAI^s. The range of force needed for activation of the EpiPen and Jext varied from 36 to 57 N (extracted from imprecise figures). According to the manufacturer, the Auvi-Q EAI requires 10 lb for activation (ie, ~45 N). Thus, the approximate pressure applied in our study is within the range needed for the activation of HPEAI^s.

The true STMD and STBD during the delivery of an EAI will vary with the pressure applied to release the EAI. In our study, we found that EAI^s applied with high pressure (8 lb), with the proper footprint to the skin, compressed mainly the muscle (>90% of compression). Therefore, there was some decrease of the STMD and more pronounced decrease of the STBD when comparing high- and low-pressure distances. It is unlikely an LPEAI applied with high pressure would deposit the drug deeply, because the needle is released and injected with 1 spring and the drug is injected using another spring.

We did not have exact data from all manufacturers on the pressure that is required to trigger their respective EAI^s. We recommend that manufacturers of all EAI^s declare the pressure needed to release the EAI needle and document the STBD and STMD in appropriate samples of patients of similar numbers as those used in this study.

We conclude that subcutaneous injection using an HPEAI is most common in adults and children and adolescents weighing more than 30 kg. Ten percent and 33% are at risk of a subcutaneous injection when using LPEAI^s and HPEAI^s, respectively. In this study, we found subcutaneous injection uncommon in children.

It has been argued that injection in living or dead mammalian tissue or the use of computed tomography¹⁴ would mimic the in vivo clinical situation better than measuring the STMD and STBD by ultrasound.^{8,18–23} In vivo mammalian studies cannot be performed in humans for ethical reasons. However, these studies have been completed in pigs¹⁵ and other animals that have skin and fascia that are different from those of humans. Therefore, future studies of EAI^s should be based on ultrasound assessments to confirm

intramuscular injections. We suggest that measurements of serum epinephrine levels be completed with new EAI^s.^{26,27} In such studies, the time from injection to serum peak determines whether the injection has been intramuscular (~10 minutes) or subcutaneous (>30 minutes). However, the use of this method is limited because it cannot be used in large samples, elderly patients with possible cardiac problems, or small children.

According to our data, periosteal or intraosseous injection is most common in children weighing less than 15 kg using HPEAI^s (32%), whereas no children are at risk of receiving a periosteal or intraosseous injection when using an LPEAI device. If the injection hits the bone, the device might not deliver epinephrine from plugging with cortical bone. Moreover, if the injection is delivered into the periosteal space, there is a risk of rapid absorption of epinephrine. This could lead to serious side effects including cardiac arrhythmias and death.

The Auvi-Q 0.1 mg was introduced to lower the risk of periosteal or intraosseous injection. As noted earlier, this is a major drawback of other HPEAI^s intended for use in children. Our data confirm that the new Auvi-Q 0.1-mg product does not have a risk of hitting the bone. However, there is a high risk of subcutaneous injection that increased from 0% to 71% when using our method of estimating the likelihood of injection of the full dose of epinephrine into the intramuscular compartment.

Recently, Greenberger et al²⁹ discussed contemporary issues regarding EAI^s. They discussed several points of interest that are addressed in our study. Greenberger et al²⁹ claimed penetrating the fascia might not be a problem, provided the force of the injection is strong enough. To achieve such a potent force, we believe the devices must be modified. The HPEAI uses 1 spring for penetration of the skin and another for injection of epinephrine, whereas the LPEAI uses 2 separate springs that makes it easier to increase the pressure on the injection fluid without increased injection force. Furthermore, our data show the needle length and the pressure on the skin (ie, the degree of compression of the tissues) are essential for decreasing the number of adults receiving a subcutaneous injection. Moreover, Greenberger et al²⁹ proposed the LPEAI with a longer needle might increase the risk for periosteal or intraosseous injection. However, our data showed the risk of periosteal or intraosseous injection was decreased using the LPEAI. This is achieved by requiring less pressure to trigger the device, leading to less compression of the muscle. We believe there is minimal risk of periosteal or intraosseous injection in patients using LPEAI^s with higher than required pressure. Although this is a theoretical risk, this adverse effect has not been reported. The study by Greenberger et al²⁹ brings up the possibility of a needle-free injection device. That subject has recently been reviewed by Ravi et al.³⁰ This type of device could be useful. However, the depth of an injection would rely on the force applied on the injection fluid. Therefore, further documentation on the possibility to apply a pressure suitable for penetration of the muscle in overweight and thin patients is required before this technique can be endorsed.

Future investigations of the influence of needle length of EAI^s using ultrasound should apply a precise pressure.³¹ The pressure should be defined according to the specification limits approved by authorities (ie, ensuring precise correct pressure on the device). Furthermore, the variation in needle length according to the manufacturers' authority-approved variation should be taken into account. Thus, we recommend manufacturers document the ability of the shortest and longest needles that might pass the quality control to deliver epinephrine in the muscle and not risk penetrating the periosteum or bone. Another point that should be considered is the influence of winter clothing. Thick clothes can increase the risk of subcutaneous injection but decrease the risk of periosteal penetration.

Other complications to the use of EAI^s should be considered. Brown et al³² recently published a case series of lacerations and

embedded needles after use of EAI in children. Broken and embedded needles could occur from the needle hitting the bone. There also have been several case reports of fatal gas gangrene after injection of epinephrine into the subcutaneous or intramuscular space.^{33,34} Furthermore, there have been cases reported to authorities of deep, longstanding pain after the use of auto-injectors that might have been caused by needles injuring the periosteum or bone. However, there are no prospective data on this possible adverse reaction.

In summary, the currently most commonly used HPEAI and LPEAI might not deliver epinephrine intramuscularly in a significant number of patients. There is a risk of subcutaneous injection in patients with high weight that is most pronounced in adults when using HPEAI and to a lesser extent when using LPEAI in adults. The new Auvi-Q 0.1-mg EAI has a high risk of subcutaneous injection when used in small children using our method of predicting subcutaneous injection. The risk of periosteal or intraosseous penetration is highest in young children using HPEAI. There was no risk for periosteal or intraosseous injection in adults in our study or when using LPEAI or the new Auvi-Q 0.1-mg EAI in small children.

We suggest that new and marketed EAI should document the possible risk of subcutaneous and periosteum or intraosseous injection. We propose using ultrasound probes of the same footprint as the respective EAI and analyzing the influence of various needle lengths and the variation in pressure specified in the product monograph. Clinicians should be aware that currently available EAI are not appropriate for all their patients.

Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.janai.2018.02.028>.

References

- [1] Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAAI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy*. 2014; 69:1008–1025.
- [2] Simons FE, Arduzzo LR, Bilo MB, et al. International consensus on (ICON) anaphylaxis. *World Allergy Organ J*. 2014;7:9.
- [3] EpiPen®/EpiPen® Jr. Prescribing information. St Louis, Missouri: Dey Pharmaceuticals; 2014.
- [4] Allerject® 0.15 mg/Allerject® 0.30 mg prescribing information. Laval, QC, Canada: Sanofi-Aventis; 2013.
- [5] AuviQ prescribing information. Bridgewater, NJ: Sanofi-Aventis US; 2012.
- [6] Product resume. Emerade. MEDECA Pharma AB; FASS; 2017. <https://docetp.mpa.se/LMF/Emerade%20solution%20for%20injection%20ENG%20SmPC.doc>.
- [7] Emerade®. An adrenaline auto-injector for emergency treatment of anaphylaxis. Valeant Pharmaceuticals; 2018. <http://www.emerade.com/hcp/adrenaline-auto-injector>.
- [8] Stecher D, Bulloch B, Sales J, et al. Epinephrine auto-injectors: is needle length adequate for delivery of epinephrine intramuscularly? *Pediatrics*. 2009;124: 65–70.
- [9] Simons FE, Gu X, Silver NA, et al. EpiPen Jr versus EpiPen in young children weighing 15 to 30 kg at risk for anaphylaxis. *J Allergy Clin Immunol*. 2002;109: 171–175.
- [10] Emergency medical treatment of anaphylactic reactions. *Resuscitation*. 1999; 41:92–99.
- [11] Gottberg L, ed. Anafylaxi. Rekommendationer för omhändertagande och behandling. 2015 [Anaphylaxis. Recommendations for care and treatment, 2015]; Svenska Föreningen för Allergologi, SFFA (Swedish Association for Allergology). October 15, 2015. http://www.sffa.nu/wp-content/uploads/2015/07/2014_SFFA_Anafylaxi.pdf.
- [12] Muraro A, Roberts G, Worm M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy*. 2014;69:1026–1045.
- [13] Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol*. 2014;133:291–307, quiz 308.
- [14] Song TT, Nelson MR, Chang JH, et al. Adequacy of the epinephrine autoinjector needle length in delivering epinephrine to the intramuscular tissues. *Ann Allergy Asthma Immunol*. 2005;94:539–542.
- [15] Song TT, Merrill NL, Cole JW. Delivery depth of epinephrine by auto-injector into the subcutaneous tissue of pig. *Ann Allergy Asthma Immunol*. 2013;111: 143–145.
- [16] Song TT. Epinephrine autoinjectors: compression and propulsion do have a role in delivery depth. *J Allergy Clin Immunol Pract*. 2015;3:827–828.
- [17] Diacono D, Pumphrey RS, Sharma V, et al. The deep fascia of the thigh forms an impenetrable barrier to fluid injected subcutaneously by autoinjectors. *J Allergy Clin Immunol Pract*. 2015;3:297–299.
- [18] Tsai G, Kim L, Nevis IF, et al. Auto-injector needle length may be inadequate to deliver epinephrine intramuscularly in women with confirmed food allergy. *Allergy Asthma Clin Immunol*. 2014;10:39.
- [19] Kim L, Nevis IF, Tsai G, et al. Children under 15 kg with food allergy may be at risk of having epinephrine auto-injectors administered into bone. *Allergy Asthma Clin Immunol*. 2014;10:40.
- [20] Dreborg S, Wen X, Kim L, et al. Do epinephrine auto-injectors have an unsuitable needle length in children and adolescents at risk for anaphylaxis from food allergy? *Allergy Asthma Clin Immunol*. 2016;12:11.
- [21] Johnstone J, Hobbins S, Parekh D, et al. Excess subcutaneous tissue may preclude intramuscular delivery when using adrenaline autoinjectors in patients with anaphylaxis. *Allergy*. 2015;70:703–706.
- [22] Bhalla MC, Gable BD, Frey JA, et al. Predictors of epinephrine autoinjector needle length inadequacy. *Am J Emerg Med*. 2013;31:1671–1676.
- [23] Kim H, Dinakar C, McInnis P, et al. Inadequacy of current pediatric epinephrine autoinjector needle length for use in infants and toddlers. *Ann Allergy Asthma Immunol*. 2017;118:719–725, e1.
- [24] Song TT. Predictors of epinephrine autoinjector needle length inadequacy. *Am J Emerg Med*. 2014;32:473–474.
- [25] Emerade® epinephrine autoinjector, orifice and needle specification. Uppsala, Sweden: Medeca Pharma; 2015.
- [26] Simons FE, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol*. 1998;101:33–37.
- [27] Simons FE, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *J Allergy Clin Immunol*. 2001;108:871–873.
- [28] Schwirtz A, Seeger H. Comparison of the robustness and functionality of three adrenaline auto-injectors. *J Asthma Allergy*. 2012;5:39–49.
- [29] Greenberger PA, Wallace DV, Lieberman PL, et al. Contemporary issues in anaphylaxis and the evolution of epinephrine autoinjectors: what will the future bring? *Ann Allergy Asthma Immunol*. 2017;119:333–338.
- [30] Ravi AD, Sadhna D, Nagpaal D, et al. Needle free injection technology: a complete insight. *Int J Pharm Investig*. 2015;5:192–199.
- [31] Andersen HH, Lundgaard AC, Petersen AS, et al. The lancet weight determines wheal diameter in response to skin prick testing with histamine. *PLoS ONE*. 2016;11:e0156211.
- [32] Brown JC, Tuuri RE, Akhter S, et al. Lacerations and embedded needles caused by epinephrine autoinjector use in children. *Ann Emerg Med*. 2016;67:307–315, e8.
- [33] Van Hook R, Vandeveld AG. Letter: Gas gangrene after intramuscular injection of epinephrine: report of fatal case. *Ann Intern Med*. 1975;83:669–670.
- [34] Stuart Hannah RC, Heddle R, Smith W. Fatal gas gangrene related to self-injection treatment of anaphylaxis. *Ann Allergy Asthma Immunol*. 2011;106: 538.
- [35] Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis—a practice parameter update 2015. *Ann Allergy Asthma Immunol*. 2015;115:341–384.

Supplementary Data

eTable 1

Summary Data on 302 Children and Adolescents Requiring Emergency Epinephrine Auto-Injector Treatment in the Community

	Median	Mean	Max	Min	Percentile	
					5	95
Children 0–18 y (n = 302)						
Age (y)	6	6.9	18	0.7	1.0	16.0
Girls (n = 125, 41%)						
Height (cm)	114.3	120.5	190.5	52.1	73.7	177.8
Weight (kg)	20.6	29.0	88.9	5.0	9.1	72.6
BMI (kg/m ²)	16.8	17.8	33.0	6.0 ^a	11.5	27.0
Adults >18 y						
Age (y)	35.0	37.2	72	18	25.0	47.8
Women (n = 68)						
Height (cm)	167.6	168.3	195.6	142.2	162.6	175.3
Weight (kg)	72.6	76.0	149.2	45.4	63.5	83.9
BMI, 60% > 25 kg/m ² ; 25% > 30 kg/m ²	26.0	26.8	50.2	17.9	22.3	30.0

Abbreviations: BMI, body mass index; Max, maximum; Min, minimum.

^aA 3-year-old boy (weight 5 kg, height 91.4 cm).

eTable 2

Basic Data on 302 Children and Adolescents and 99 Adults Requiring Emergency EAI Treatment in the Community^a

	Children + adolescents (n = 302)		Adults (n = 99)	
	n	%	n	%
Sensitization by SPT or allergy				
Milk, egg, soy, wheat	116	38	10	10
Lentils, beans, peas	18	6	9	9
Shrimp, fish, shell-fish	23	8	32	32
Peanut	186	61	29	29
Tree nut	77	25	33	33
Pollen, fruits, vegetables	104	34	76	77
In-door allergens	123	41	78	79
Allergic diseases				
Rhinitis	122	40	73	74
Asthma	113	37	52	53
Eczema	107	35	10	10
Urticaria	30	10	6	6
Any	220	73	86	88
Medication				
EAI ± β_2 -agonist	155	51.2	52	53
Asthma without EAI or β_2 -agonist	9	3	13	13
EAI			46	46
EAI + β_2 agonist + inhaled steroids			5	5

Abbreviations: EAI, epinephrine auto-injector; SPT, skin prick test.

^aBecause the number of adults was close to 100, percentages are not listed.