Children under 15 kg with food allergy may be at risk of having epinephrine auto-injectors administered into bone

Laura Kim1, Immaculate FP Nevis2,3, Gina Tsai3, Arunmozhi Dominic3, Ryan Potts4, Jack Chiu3 and Harold L Kim2,3,5*

Abstract

Background: The Epipen® Jr and Allerject® 0.15 mg are currently the most commonly prescribed epinephrine auto-injectors (EAIs) for the management of anaphylaxis in pediatric patients in North America and Canada. To ensure rapid absorption, it should be administered intramuscularly into the anterolateral aspect of the thigh. We examined whether the 12.7-mm needle length of the Epipen® Jr and Allerject® 0.15 mg is adequate for delivering epinephrine intramuscularly in pediatric patients who weighed <15 kg.

Methods: Consecutive pediatric patients with food allergy weighing <15 kg who required an EAI were included. Ultrasounds of the mid-anterolateral thigh were performed under minimal (min) and maximal (max) pressure. Skin-to-muscle depth (STMD) and skin-to-bone depth (STBD) measurements were completed. Baseline characteristics were compared between patients with a STBDmax <12.7 mm vs. ≥12.7 mm. Linear regression including variables such as age, sex, body mass index (BMI) and race was performed. The proportion of patients with a STBDmax <12.7 mm was compared in those weighing <10 kg vs. 10–14.9 kg.

Results: One hundred patients were included; 29 (29%) had STBDmax <12.7 mm. Height (p = 0.02) and weight (p = 0.0002) differed significantly between the two groups. Approximately 19% of those weighing 10–14.9 kg and 60% of those <10 kg had a STBDmax <12.7 mm. In the multivariable regression analysis, BMI was found to be a significant predictor of STBDmax.

Conclusions: A large proportion of children <15 kg prescribed an EAI is at risk of having the auto-injector administered into bone. Since alternative EAIs with shorter needle lengths are not currently available, EAIs should be prescribed with appropriate counselling in this population.

Keywords: Food allergy, Anaphylaxis, Skin-to-bone depth, Epinephrine, Auto-injector, Pediatric, Needle length

Background

Anaphylaxis has been identified as an important cause of morbidity and mortality [1]. Although epidemiological data on anaphylaxis are limited, a study from Spain revealed an incidence of 103 episodes per 100,000 person years [2]. A significant number of hospital admissions are due to anaphylaxis and, although less common, death from anaphylaxis can also occur. A recent analysis of fatalities in Brazil suggests that the accuracy of diagnostic codes using International Classification of Diseases-10 (ICD-10) may miss a significant number of fatal anaphylaxis cases [3,4]. A major risk factor for death from anaphylaxis is the delayed use or failure to use epinephrine [5]. One study found that in infants with anaphylaxis, only 30% received epinephrine injections [6].

Currently, it is recommended that epinephrine be administered intramuscularly (to allow for rapid absorption) since subcutaneous delivery has been shown to result in slower absorption [7,8]. For the outpatient management of anaphylaxis, EAIs are generally recommended. The Epipen® Jr and Allerject® 0.15 mg, for example, are widely prescribed for pediatric patients with anaphylaxis. These EAIs have a needle length of 12.7 mm and are indicated for at-risk patients weighing between 15 and 30 kg [9,10]. In clinical practice, however, these EAIs...
pressure (STBDmax) is less than the needle length of the bone since their skin-to-bone depth at maximal pressure following adjustment for age, sex and BMI did not differ between the two groups (p = 0.36). The mean STMD and STBD without pressure also differed significantly between the two groups (p < 0.05) (see Table 1). There were no patients with STMDmax >12.7 mm.

Multivariable linear regression analysis showed BMI (p = 0.02; Figure 3) to be significantly associated with STBDmax pressure following adjustment for age, sex and

Methods
All of the patients’ parents or guardians provided written, informed consent prior to participating in this study. The Lawson Health Research Institute Research Ethics Board at Western University in London, Ontario, Canada approved the study.

Consecutive pediatric patients with confirmed food allergy weighing less than 15 kg who would benefit from EAI prescriptions in an allergist’s office were included in this trial. The subjects were assessed from July 2012 to November 2013. All subjects’ parents/guardians agreed to participate in the study. An ultrasound on the anterolateral aspect of the right mid thigh (the recommended site for injections with EAs) was performed to measure four distances of tissue depths: skin-to-muscle depth with minimal pressure (STMDmin), skin-to-muscle depth with maximal pressure (STMDmax), skin-to-bone depth with minimal pressure (STBDmin) and skin-to-bone depth with maximal pressure (STBDmax) (see Figure 1). The investigator applied the pressure while performing the ultrasound measurements on each subject. The estimated maximal force was 2–8 lbs. All ultrasounds were completed by a single physician using a Sonosite Titan ultrasound machine.

The primary outcome variable was the proportion of subjects with a STBDmax less than 12.7 mm. These subjects may be at risk of injecting epinephrine completely through the muscle and into the femur. Baseline characteristics between patients with a STBDmax <12.7 mm and those with a STBDmax ≥12.7 mm were analyzed and compared using the Student’s t-test/Mann Whitney U test for continuous variables and Chi-square/Fischer’s exact test for categorical variables. Linear regression analysis was performed including variables such as age, sex, race, and body mass index (BMI). The likelihood of the STBDmax being <12.7 mm was also calculated for the patient cohorts weighing <10 kg and 10–14.9 kg.

Results
A total of 100 participants weighing <15 kg were included in this study; 29 subjects (29%) had a STBDmax <12.7 mm (see Figure 2). Baseline characteristics of patients with a STBDmax <12.7 mm vs. ≥12.7 mm are compared in Table 1. Weight (p = 0.0002) and height (p = 0.02) were significantly different between the two groups. Interestingly, mean BMI did not differ between the two comparison groups (p = 0.36). The mean STMD and STBD without pressure also differed significantly between the two groups (p < 0.05) (see Table 1). There were no patients with STMDmax >12.7 mm.

Multivariable linear regression analysis showed BMI (p = 0.02; Figure 3) to be significantly associated with STBDmax pressure following adjustment for age, sex and
Since mean weight of the participants was significantly different between the two groups, multivariable linear regression analysis was repeated using age, sex, race and weight as independent variables. Weight (kg) was found to be the strongest predictor of STBDmax (p = 0.001; Figure 4).

Table 2 and Figure 5 show the proportion of patients with a STBDmax <12.7 mm or ≥12.7 mm according to different weight groupings. Approximately 19% of patients between 10 and 14.9 kg had a STBDmax <12.7 mm compared with 60% of those weighing under 10 kg (p = 0.0008).

**Discussion**

This prospective study examined whether the length of the EAI needles are adequate for delivering epinephrine intramuscularly in pediatric patients at risk of anaphylaxis who weighed <15 kg. Importantly, although the Epipen® Jr and the Allerject® 0.15 mg are officially indicated for children between 15 and 30 kg in Canada, they are often prescribed in children <15 kg as there is no clinically available EAI that delivers a lower dose of epinephrine. Ultrasound measurements of the mid anterolateral thigh were performed with pressure application to simulate the pressure required to inject an auto-injector. Although we originally believed that a significant proportion of these children was at risk of receiving the auto-injector subcutaneously (rather than intramuscularly) due to obesity, we found that a significant proportion of these children were at risk of receiving the auto-injectors into the bone. Physicians should be aware of this potential risk.

Currently, there are no published clinical studies assessing whether the 12.7-mm length of the EAI needles are adequate for delivering epinephrine intramuscularly in pediatric patients weighing <15 kg at risk of anaphylaxis. All of our subjects had a STMDmax <12.7 mm, suggesting that none of these children were at risk of having the auto-injector administered into the subcutaneous space. Our findings contrast those reported by Stecher et al. [12] who identified 12% of children weighing <30 kg that were at risk of receiving the EAI into the subcutaneous space. Age and BMI correlated with STMD in these children. It is important to note that this study enrolled children (1–12 years of age) presenting to the radiology or emergency departments of a tertiary-care hospital in a non-consecutive fashion. Subjects were not at risk of anaphylaxis, and ultrasounds with pressure and measurements to the femur were not completed. Almost half of the study population was Hispanic and children who weighed <15 kg were not analyzed separately. Our study, on the other hand, assessed primarily Caucasian children <15 kg who were at risk of anaphylaxis. Also, ultrasounds with pressure were performed to simulate how auto-injectors are given in the “real-life” setting.

Our study found that almost 30% of children < 15 kg had a STBDmax <12.7 mm and were therefore at risk of receiving epinephrine into the bone. Patients weighing <10 kg were at even greater risk since 60% of these subjects had a STBDmax <12.7 mm. We believe these findings are clinically important, particularly since there are currently no randomized controlled trials evaluating or comparing

**Table 1 Baseline characteristics of the patient cohort**

| Characteristic                  | Total (n = 100) | Patients with STBDmax ≥12.7 mm (n = 71) | Patients with STBDmax <12.7 mm (n = 29) | P value |
|--------------------------------|----------------|------------------------------------------|-----------------------------------------|---------|
| Age (months), median (IQR)     | 17 (45)        | 18 (45)                                  | 16 (31)                                 | 0.19    |
| Males, n (%)                   | 55 (55)        | 39 (55)                                  | 16 (55)                                 | 0.98    |
| White race, n (%)              | 78 (78)        | 57 (80)                                  | 21 (72)                                 | 0.38    |
| Weight (kg), mean (SD)         | 11.5 (2.2)     | 12.1 (1.9)                               | 10.2 (2.3)                              | 0.002   |
| Height (m), mean (SD)          | 0.84 (0.1)     | 0.85 (0.1)                               | 0.79 (0.1)                              | 0.02    |
| BMI (kg/m²), mean (SD)         | 16.4 (1.9)     | 16.5 (1.9)                               | 16.1 (1.3)                              | 0.36    |
| STMDmax (mm), mean (SD)        | 6.4 (1.4)      | 6.7 (1.4)                                | 5.5 (0.9)                               | 0.0003  |
| STMDmax (mm), mean (SD)        | 7.8 (1.8)      | 8.1 (1.8)                                | 7.1 (1.6)                               | 0.02    |
| STBDmax (mm), mean (SD)        | 25.1 (4.3)     | 26.2 (3.8)                               | 22.3 (4.0)                              | 0.0001  |

IQR: interquartile range; SD: standard deviation; BMI: body mass index; STMDmax: skin-to-muscle depth with minimal pressure; STMDmax: skin-to-muscle depth with maximal pressure; STBDmax: skin-to-bone depth with minimal pressure; STBDmax: skin-to-bone depth with maximal pressure.
subcutaneous, intramuscular, periosteal, cortical, intraoss- 
eous or intravenous epinephrine administration in patients 
with anaphylaxis. However, the ethical considerations in 
completing studies of this nature may be prohibitive. In 
children with a history of anaphylaxis, epinephrine injected 
intramuscularly compared to subcutaneously has been 
shown to lead to higher serum epinephrine levels more 
rapidly [13,14]. This more rapid peak in epinephrine levels 
has been the basis for recommending intramuscular epi-
nephrine administration as the standard of care for 
anaphylaxis. Intravenous or intraosseous epinephrine 
is reserved for severe, life-threatening anaphylaxis with as-
sociated hypotension, airway swelling, severe bronchospasm 
or inadequate response to intramuscular epinephrine. Intra-
venous epinephrine should be given at a 1/100,000 strength 
at a maximum infusion rate of 10 mcg/min [1,11,15]. The 
EpiPen® Jr and Allerject® 0.15 mg provide a total dose of epi-
nephrine of 0.15 mg at 1/2,000 and 1/1,000 strengths re-
spectively [9,10]. These strengths are 50 and 100 times the 
concentration suggested for intraosseous infusion respect-
ively. Importantly, there are no studies to confirm that the 
auto-injectors would penetrate through the femur of chil-
dren. But we believe the auto-injector needle would pene-
trate the bone as supported by a case report of an adult 
female experiencing an accidental injection that went com-
pletely through the bone of a distal phalanx [16]. Also, the 
thickness of the cortical bone of the femur has not been for-
mally studied in young children. Animal studies confirm 
that intraosseous epinephrine administration leads to similar 
serum epinephrine levels as intravenous administration 
[17,18]. Although the intravenous or intraosseous route of 
administration should be used in the appropriate clinical set-
ting, there have been reports of severe side effects with 
intravenous epinephrine administration. For example, 
a 29-year-old woman had a myocardial infarction after 
receiving 0.1 mL of 1/10,000 intravenous epinephrine 
[19]. Sullivan reported two patients who had ventricu-
lar tachycardia after receiving a 5-mL intravenous in-
jection of 1/10,000 epinephrine [20]. There is also a 
report of a 5-month-old child weighing 7 kg who pre-
sented with an allergic reaction to an emergency de-
partment and received 0.7 mL of 1/1,000 subcutaneous 
epinephrine twice and then 0.7 mL of 1/1,000 epineph-
rine intravenously [21]. The infant had a cardiac arrest 
and could not be resuscitated. Although these reports 
involve cases where epinephrine was given at higher 
doses or concentrations than currently recommended, 
they illustrate the potential risks of intravenous and 
intraosseous epinephrine.

Children weighing <15 kg with a STBD_{max} <12.7 mm 
who are prescribed an EAI are at risk of injecting a more 
concentrated and higher-than-recommended dose of 
epinephrine into the intraosseous space. There are vari-
ous strategies that might be considered to help the clin-
ician to deal with this issue. Ideally, all children requiring 
an EAI should have a STBD_{max} measurement with ultra-
sound to identify those who may be at risk of intraosseous 
admnistration. In at-risk children, other forms of inject-
able epinephrine could be considered, such as the 
provision of separate syringes (with variable needle 
lengths) and vials of epinephrine. However, one study 
suggests that the parents of these children may not be 
able to draw up the proper doses of epinephrine reli-
ably in a reasonable timeframe to manage anaphylaxis 
[13]. Another strategy would be to instruct the child’s 
parent or care provider to squeeze the leg and muscle 
at the site of injection so that the EAI does not com-
press the muscle. In most patients, we believe this 
would lead to intramuscular injection. If using this 
strategy, persons injecting must be cautious not to in-
ject the device into their own hand. Manufacturers 
should also consider developing auto-injectors with 
variable needle lengths (and doses) and/or devices that
require less pressure for administration, as this would increase the likelihood of intramuscular injection. More thorough studies assessing the pharmacokinetics and pharmacodynamics of injecting epinephrine into the periosteum, cortical bone or intraosseous space are also required.

The main strengths of this study were that the patient cohort included children at risk of anaphylaxis who weighed <15 kg, the STBD\textsubscript{max} was used as the primary variable, and ultrasound measurements were taken in the proper location for EAI application. The findings of this research reveal a potential shortcoming in our current approach to anaphylaxis.

One limitation of this study was that it was performed in only one clinic. It is possible that the findings may differ if utilizing a multicentre study design. Therefore, we suggest that a similar study be replicated in other centres. A second limitation was that one physician performed all of the ultrasound measurements in an unblinded fashion. Nonetheless, we feel the data collected were accurate since measurements were simple to perform and easily reproducible. The ultrasound machine included an easy-to-use tool to accurately determine the measurements for each variable assessed in our study. A third limitation is that the physician applied the maximum pressure to the thigh without using any method of formally quantifying the pressure applied with the ultrasound probe. We believe that, in many children, “real-life” use of the auto-injector may actually lead to more muscle compression and/or an increased risk of injecting into the bone than was noted in our study. This may occur because greater force may be applied by parents injecting the auto-injectors, the surface area of the currently available auto-injectors are less than that of the ultrasound probe and/or the device may be given in an area where muscle thickness is less than that in the mid anterolateral thigh. In future studies, we suggest that the pressures required to trigger the various types of auto-injectors be measured and that these pressures be applied for ultrasound measurements. The pressure required and the depth of muscle compression may vary for each device and, possibly, for each individual patient. A final limitation of this study is that the data were not analyzed to address other EAls aside from the Epipen\textsuperscript{®} Jr and the Allerject\textsuperscript{®} 0.15 mg. The risk is likely similar for injection into the bone with the Epipen\textsuperscript{®} Jr and the Allerject\textsuperscript{®} 0.15 mg. But the surface

### Table 2 Proportion of subjects with STBD\textsubscript{max} less than or ≥12.7 mm according to weight

| Weight (kg) | No. of patients with STBD\textsubscript{max} ≥12.7 mm | Number of patients with STBD\textsubscript{max} <12.7 mm | P value | P value |
|-------------|-----------------------------------------------------|------------------------------------------------------|---------|---------|
| <10         | 10 (40)                                             | 15 (60)                                              | 0.0002  | 0.0008  |
| 10 to 14.9  | 61 (81)                                             | 14 (19)                                              | 0.0002  |         |

STBD\textsubscript{max}: skin-to-bone depth with maximal pressure.

**Figure 5** Box plots of different weight groups among the two comparison groups.

P=0.0008
area and pressure required to inject these devices may affect the depth of injection. These products as well as products that become available later should be compared in future studies.

Conclusions
A significant proportion of children weighing under 15 kg who require a prescription for an EAI is at risk of receiving epinephrine injections into the bone. Given this risk, EAs should be prescribed with caution in this patient population. At this time, there are no alternative EAs with needle lengths shorter than 12.7 mm. We recommend further research in this area using larger patient cohorts and multicentre study designs.

Abbreviations
EAI: Epinephrine auto-injector; STMD: Skin-to-muscle depth; STMDmin: Skin-to-muscle depth with minimal pressure; STMDmax: Skin-to-muscle depth with maximal pressure; STBD: Skin-to-bone depth; STBDmax: Skin-to-bone depth with minimal pressure; STBDmin: Skin-to-bone depth with maximal pressure; BMI: Body mass index.

Competing interests
HK has been on an advisory board for Sanofi Canada and the speakers’ bureau for Pfizer Canada. GT, IN, RP, JC, and AD declare that they have no competing interests.

Authors’ contributions
LK, GT, RP, JC, and HK were responsible for data analysis. LK and IN drafted the manuscript. All of LK, GT, RP, JC, and HK were responsible for the conception and design of the study. LK and RP were responsible for the acquisition of the data. IN and AD were responsible for data analysis. LK and IN drafted the manuscript. All of the authors contributed substantially to the interpretation of the data, critically revised the manuscript for important intellectual content, approved the final version submitted for publication and agree to act as guarantors of the work.

Acknowledgements
The authors would like to thank Julie Tasso and Dr. David Fischer for their thoughtful review and commentary on the manuscript.

Funding
This research was investigator-initiated and received no funding.

Author details
1Department of Anatomy and Cell Biology, McGill University, Montreal, Quebec, Canada.
2Michael D. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada.
3Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada.
4Department of Biology, University of Waterloo, Waterloo, Ontario, Canada.
5S25 Belmont Avenue West, Suite 205, Kitchener N2M 5E2, Ontario, Canada.

Received: 12 June 2014 Accepted: 16 July 2014
Published: 1 August 2014

References
1. Kim HL, Fischer D. Anaphylaxis. Allergy Asthma Clin Immunol 2011, 7(Suppl 1):S6-S8.
2. Tejedor Alonso MA, Moro Moro M, Mugica Garcia MV, Estebane Hernandez J, Rosado Inglemo A, Vila Albeda C, Gomez Traeira C, Cardenas Contreras R, Sanz Sacristan J, Hernandez Merino A: Incidence of anaphylaxis in the city of Alcorcon (Spain): a population-based study. Clin Exp Allergy 2012, 42:576-589.
3. Gibbison B, Sheikh A, McShane P, Haddow C, Scarl A: Anaphylaxis admissions to UK critical care units between 2005 and 2009. Anesthesiology 2012, 67:833-839.
4. Tanno LK, Ganem F, Demoly P, Toscan CM, Bienenbach AL: Undernotification of anaphylaxis deaths in Brazil due to difficult coding under the ICD-10. Allergy 2012, 67:763-769.
5. Levy MB, Goldberg MR, Nachshon I, Tabachnick E, Katz Y: Lessons from cases of mortality due to food allergy in Israel: cow's milk protein should be considered a potentially fatal allergen. J Allergy Clin Immunol 2012, 129:9-33.
6. Fleisher DM, Perry TT, Atkins D, Wood RA, Burks AW, Jones SW, Henning AK, Stabilein D, Sampson HA, Sicherer SH: Allergic reactions to foods in preschool-aged children in a prospective observational food allergy study. Pediatrics 2012, 130:e25-e32.
7. Simons FE, Arduoso RF, Dimov V, Ebsiawa M, El-Gamal YM, Lockey RF, Sanchez-Borges M, Senna GE, Sheikh A, Thong BY, Worm M: World Allergy Organization Anaphylaxis Guidelines: 2013 update of the evidence base. Int Arch Allergy Immunol 2013, 162:193-204.
8. Watersen S, Watson W: Food allergy. Allergy Asthma Clin Immunol 2011, 7(Suppl 1):S7.
9. EpiPen®/EpiPen® Jr Prescribing Information. Napa, California: Dey Pharma. March 13, 2012. Available at: https://www.epipen.ca/sites/default/files/pdf/hcp/en/English_PiPd.pdf. Accessed April 22, 2014.
10. Allerject® 0.15 mg/ Allerject® 0.30 mg Prescribing Information. Laval, Quebec: Sanofi-Aventis Canada Inc. May 28, 2013. Available at: http://products.sanofi.ca/en/allerject.pdf. Accessed July 15, 2014.
11. Cheng A: Emergency treatment of anaphylaxis in infants and children. Paediatr Child Health 2011, 16:35-40.
12. Stecher D, Bullboch B, Sales J, Schafer C, Keayey L: Epinephrine auto-injectors: is needle length adequate for delivery of epinephrine intramuscularly? Pediatrics 2009, 124:65-70.
13. Simons FER, Chan ES, Gu X, Simons KJ: Epinephrine for the out-of-hospital (first-aid) treatment of anaphylaxis in infants: is the ampule/syringe/needle method practical? J Allergy Clin Immunol 2001, 108:1040-1044.
14. Simons FER, Roberts JR, Gu X, Simons KJ: Epinephrine absorption in children with a history of anaphylaxis. J Allergy Clin Immunol 1998, 101:33-37.
15. Brown AFT: Therapeutic controversies in the management of acute anaphylaxis. J Accid Emerg Med 1999, 15:89-95.
16. Schintler MV, Arbab E, Abeer W, Spedel S, Schramagl E: Accidental perforating bone injury using the EpiPen® autoinjection device. Allergy 2005, 60:259-260.
17. Sapien R, Stein H, Padbury JF, Lockrem JD, VanLente F: Comparison study of intraosseous, central intravenous, and peripheral intravenous infusions of emergency drugs. Ann J Dis Child 1990, 144:112-117.
18. Shaver KJ, Adams C, Weiss SJ: Acute myocardial infarction after administration of low-dose intravenous epinephrine for anaphylaxis. CEM 2005, 8:290-294.
19. Sullivan TJ: Cardiac disorders in penicillin-induced anaphylaxis. Association with intravenous epinephrine therapy. JAMA 1982, 248:2161-2162.
20. Canadian Medical Protective Association Newsletter. March 2010.

Cite this article as: Kim et al. Children under 15 kg with food allergy may be at risk of having epinephrine auto-injectors administered into bone. Allergy. Asthma Clinical Immunology 2014; 10:40.

Submit your next manuscript to BioMed Central and take full advantage of:
- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

dox10.1186/1710-1492-10-40