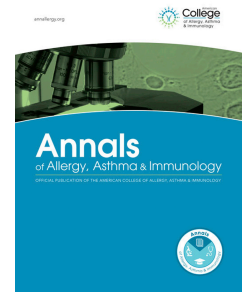


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Point of care ultrasonography in the allergy and immunology clinic

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Abbreviations:

POC – point of care

CT – computed tomography

EAI - epinephrine autoinjector

IM – intramuscular

SC – subcutaneous

STMD - skin to muscle depth

STBD - skin to bone depth

SCIT - subcutaneous immunotherapy

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Introduction

Point of care (POC) clinical ultrasonography is used across multiple medical specialties to guide diagnosis and treatment, and to enhance the safety of invasive procedures. POC clinical ultrasonography is defined as a focused ultrasonographic examination, performed and interpreted by the treating clinician, to answer a specific question or to guide a procedure.¹ Emergency department physicians were early adopters of POC ultrasonography in the late 1990's; since then, technological advances have resulted in enhanced portability, improved image quality, and user-friendly interfaces, expanding the use of POC ultrasonography at the bedside.² Subsequently, this method has been validated by multiple studies as a safe, rapid, and cost-effective clinical tool which improves patient care.^{3, 4, 5, 6, 7} For example, a recent meta-analysis showed sensitivities and specificities in the high 90s when emergency medicine physicians used POC ultrasonography for diagnosing deep vein thrombosis.⁸ Renal ultrasonography is increasingly used to help diagnose and manage nephrolithiasis, especially when recurrent, when cumulative radiation from CT is a concern.³ POC ultrasonography can be used to investigate lung pathology, including pulmonary edema or pneumothorax, and it is more sensitive and specific than physical examination for soft tissue infections.⁹ Real time visualization of critical and pathological anatomy increases the safety of many procedures which have historically been performed without ultrasound imaging guidance. This includes removal of retained foreign bodies, incision and drainage, regional anesthesia, fracture and joint dislocation reduction, and needle placement and cannulation.

In Allergy and Immunology, a role for POC ultrasonography was highlighted by multiple studies demonstrating that the standard epinephrine autoinjector (EAI) needle length was inadequate for intramuscular delivery of epinephrine, particularly for women, at risk of anaphylaxis.^{10, 11, 12}

24 Conversely, for pediatric patients (weighing under 15 kg), commercially available EAI needle
25 lengths may be too long, risking inadvertent intraosseous injection and resultant cardiovascular
26 complications.^{13, 14} Other promising venues for the use of ultrasonography in Allergy and
27 Immunology entail needle guidance for subcutaneous allergen immunotherapy injections, to
28 reduce the chance of inadvertent intramuscular injection and systemic side effects. As well,
29 ultrasonography is an integral component of intralymphatic allergen immunotherapy, which
30 consists of three ultrasound guided inguinal node injections over a period of two months.^{15, 16}

31
32 The following review summarizes evidence supporting the use of POC ultrasonography as an
33 adjunct clinical tool for Allergists and Immunologists. We discuss the utility of ultrasound in an
34 Allergy clinic in ensuring adequate epinephrine injection in the setting of anaphylaxis. We also
35 discuss how POC ultrasonography can be routinely used in the Allergy clinic to help minimize
36 the risk of intramuscular subcutaneous immunotherapy injections and adverse systemic side
37 effects. Lastly, we discuss novel uses of POC ultrasonography in Allergy and Immunology,
38 including its role in intralymphatic immunotherapy.

Role of ultrasonography in enhancing safe delivery of epinephrine in anaphylaxis

In the setting of anaphylaxis, epinephrine has long been established as the initial choice of treatment.^{17, 18, 19} Once anaphylaxis is recognized, rapid administration of epinephrine can be life-saving. Recommendations regarding route and site of epinephrine injection were solidified in landmark randomized controlled trials of children and adults at risk for anaphylaxis. These studies demonstrated that peak plasma epinephrine concentrations were achieved significantly faster after intramuscular (IM) injection by means of an epinephrine auto-injector (EAI) into the vastus lateralis than after subcutaneous (SC) injection into the deltoid muscle. Greater absorption of epinephrine from the vastus lateralis muscle in comparison with the deltoid muscle is thought to be due to greater blood flow in the highly vascularized vastus lateralis. In contrast, delayed peak plasma concentration of subcutaneous epinephrine is related to its vasoconstrictive effects; in fact, this property is exploited in medical procedures, where concomitant administration of subcutaneous epinephrine delays local absorption of local anesthetics. Ensuring prompt intramuscular delivery of epinephrine is therefore paramount in the safe and timely management of anaphylaxis.

The recommended dose of epinephrine for anaphylaxis is 0.01 mg/kg (maximum 0.5 mg) administered intramuscularly every 5–15 min as necessary. Given the time and training needed to ensure proper dosing, EAI are the standard tools of administering epinephrine outside of the hospital setting. In North America, the Epipen® and Auvi-Q® (previously available as Allerject® in Canada) are the most commonly prescribed EAI. Different EAI are available in Europe with distinct physical characteristics, including pressure required for delivery of the medication and needle lengths [Table 1].^{17, 18}

Given the differences in needle lengths, a significant number of patients may receive epinephrine subcutaneously with the currently available EAI.^{10, 20, 21, 22} A 2009-2011 survey found that 26 % of Canadian adults are obese, including 27.2% of men and 25.5% of women.²³ Accordingly, in an increasing proportion of the population, EAI needle lengths may need to compensate for the increased skin to muscle depth (STMD) due to increased subcutaneous tissue. Recent studies have investigated epinephrine injection by EAIs using ballistic gel models, computed tomography, pig subcutaneous tissue and ultrasonography in humans.^{13, 14, 24, 25} Findings from both CT and ultrasound studies found that 28% of women had STMD longer than the EAI needle length, factoring in eight pounds of compression.^{12, 26} In addition, a cross-sectional study of 60 men and 60 women presenting to an emergency department found that 28% of women had STMD longer than 15.9 mm (length of longest EAI needle at time of study).¹¹ Females therefore seem to be at an increased risk of subcutaneous injection from an EAI due to the increase in STMD.

Duvauchelle et al²⁷ compared EAI (Anapen®) and pre-filled syringes (PFS) in males with BMI of 18-26 kg/m² (defined as normal weight) and women with BMI of 26-34 kg/m² (defined as overweight). When using an EAI in overweight females, the epinephrine fluid depot was located subcutaneously in 10/12, intramuscularly in 1/12, and not located in 1/12 patients. Although the length of the depot traveled further than the length of the EAI needle, it was unable to reach IM in the vast majority. Epinephrine was injected in the inferior third anterolateral thigh in the overweight females and still not delivered to the muscle. Plasma adrenaline levels and systolic blood pressure were measured over time for each patient. Interestingly, the delivery of

epinephrine in the overweight women showed a nonsignificant delay in time to initial peak plasma level. Also of note, women in this group had delayed decline in plasma adrenaline level and prolonged heart rate increase, possibly suggesting higher bioavailability over the four hour period.

The Duvauchelle et al²⁷ study had limitations regarding possible gender related differences in epinephrine absorption, and mismatch of administration sites between men and women. However, the localization of the epinephrine by ultrasonography suggests that subcutaneous boluses of epinephrine remain in the subcutaneous compartment. This discrepancy has been brought to worldwide media attention after the tragic death of fifteen-year old Natasha Ednan-Laperouse, who had a severe allergic reaction to sesame while on a flight from London in 2016. During the inquest, the coroner's report concluded that the EpiPen® needle length was "inherently unsafe," leading to subcutaneously administered epinephrine.²⁸

Conversely, in children weighing <15 kg with confirmed food allergy, a significant proportion may be at risk of receiving the injection into the periosteum or bone, especially via the pediatric EAI needle length (12.7 mm). One study found that 29% of children had skin to bone depth (STBD) less than the pediatric needle length (Figure 1A).¹⁴ A more recent study found 43.1% of children between 7.5 kg and 15 kg at risk of intraosseous injection using a pediatric EAI.¹³ A new EAI with a needle length of 7.5 mm has been approved by the U.S. Food and Drug Administration as of November 2017 for children $\geq$ 7.5–15 kg. However, intraosseous injection has also been reported in a child of 25 kg.²⁹ Measurement of STBD (Figure 1A) in small children could have a role in determining the risk of injection into the intraosseous space.

The factors of compression and propulsion have been a topic of debate. Compression force required for EAI administration is estimated to be two to eight pounds. Dreborg et al²⁶ completed an ultrasound study of 401 patients at risk of anaphylaxis studying the risk of subcutaneous and intraosseous injection. It was found that the application of EAI with high pressure resulted primarily in muscle compression (>90%) affecting STBD rather than STMD. The subcutaneous space was compressed by only 11%. Song et al²⁴ reported that the injection bolus in pig subcutaneous tissue spread 94% beyond the needle tip through propulsion. However, Diacono et al²² reported that the fascia was an impermeable barrier to fluids injected by an EAI. In addition, proper intramuscular injection required the entire needle orifice to be in the muscle. Epinephrine spread within loose epimysium tissue when part of the needle orifice was within the epimysium.

There has been debate as to the clinical relevance of needle penetration through the deep fascia. Although epinephrine delivery has not been specifically studied, needle free auto-injectors have been shown to be capable of injecting through fascia into muscle. One study was able to complete successful IM saline delivery in 35 out of 37 patients validated by MRI imaging.³⁰ Although this has exciting implications as to future development of needle free EAI, the usage of this concept as validation of delivery by traditional EAI beyond needle length through fascia is limited. The mean maximum pressure delivered by the device to achieve this was 212 bars of pressure, with a mean initial pressure of 155 bars. This is significantly greater than the described spring force of the 0.3 mg Epipen® at 1.57 bar (1 bar equals 14.5 pound-force per square inch). Even taking into account the described eight pounds/inch of pressure required to activate the epinephrine injector, this difference is dramatic (Figure 1B).

While more evidence is needed to clarify the significance of optimal needle length in the setting of anaphylaxis, there is a potential role for epinephrine injectors of varying needle length. Imaging studies are warranted to reassess the clinical importance of intramuscular epinephrine and help characterize patients at risk of non-intramuscular injection. In an allergy clinic, ultrasonography can be a useful tool for both further research studies and patient education. Ideally, all patients prescribed EAI should have ultrasound measurement to assist in identifying patients at risk of subcutaneous or intraosseous injection. Findings by Johnston et al²⁵ suggest BMI > 30 and female gender as predictors for increased STMD and encourage ultrasound at point of prescription to aid needle length selection. For patients at risk of subcutaneous injections, an EAI with a longer needle could be prescribed to reduce the risk of subcutaneous epinephrine delivery. In addition, counseling regarding the importance of carrying a second prescribed EAI could be warranted to ensure that in the setting of anaphylaxis, patients can carry sufficient doses of epinephrine. Another possibility is modified administration of the EAI to the anterior thigh rather than the anterolateral thigh. Findings by Kim et al suggest weight <15 kg as a predictor for risk of intraosseous injection.¹⁴ For children at risk, an EAI with a shorter needle could be prescribed. Additionally, a modified administration of the EAI by pinching the thigh muscle to increase STBD could be used (Figure 2).

Ultrasonography as a clinical tool to enhance safety of subcutaneous immunotherapy

Introduced in 1911, allergen-specific subcutaneous immunotherapy (SCIT) is a longstanding, safe, and effective method to treat allergic rhinitis/conjunctivitis and allergic asthma.^{31, 32, 33, 34}

SCIT is indicated in patients with moderate to severe symptoms who do not respond adequately to allergen avoidance and medical pharmacotherapy.³⁵ Despite its clear benefits, SCIT is considered to be underutilized, possibly in part due to the lengthy treatment commitment and the potential for adverse systemic reactions.^{36, 37, 38} According to North American allergists surveyed by the American Academy of Allergy, Asthma, and Immunology (AAAAI) between 2008 and 2012, very severe systemic allergic reactions occurred once per 1 million injections, and overall systemic allergic reactions occurred at a rate of 0.1%.³⁹ Exact figures vary between studies due to differences in definitions, technique, and administration frequency, but it is estimated that the rates of severe systemic reactions are <1% and, in some cases, >30% in conventional immunotherapy and rush immunotherapy, respectively.⁴⁰

AAAAI guidelines recommend that SCIT be given using a syringe with a needle length of either 9.5 or 13 mm.³⁶ In Canada, the standard *BD Safety Glide*TM allergy syringe features a needle length of 13 mm.³⁵ In patients, these needles are injected into the subcutaneous space in the mid-posterolateral upper arm, where there is a greater amount of subcutaneous tissue than adjacent areas. Subcutaneous injections create a depot of allergen extracts that are slowly absorbed from the subcutaneous tissue. If the injection goes past the subcutaneous compartment, rapid absorption of the allergen may lead to a systemic reaction. As such, measuring a patient's skin-to-muscle depth (STMD), the distance from the outer skin to the inner aspect of the muscle

fascia, may characterize their risk of receiving injections intramuscularly and, potentially, anaphylaxis.

A recent observational study of 200 patients receiving SCIT between the ages 18 and 65 in Kitchener, Ontario, Canada found that 80% of patients had a STMD less than or equal to 13 mm (a standard needle length in the United States and Canada), and that 91% of patients had a STMD greater than 4 mm.³⁵ The latter implies that 9% of patients had an STMD less than or equal to 4 mm. Body mass index was the only significant predictor of STMD. While strategies exist to try to maximize the STMD and reduce the risk of intramuscular administration, by injecting the needle at a 45° angle to the skin and “pinching” the skin, the data suggest that the current needle length for SCIT may not be as suitable for many patients. This finding has parallels to observations in patients with diabetes. Disposable plastic insulin syringes (and, if necessary, raising of a skinfold) was assumed to consistently deposit insulin into subcutaneous tissue, with negligible risk of penetrating muscle. However, Smith et al⁴¹ demonstrated through measurements of STMD by ultrasonography that the majority of children with diabetes had insulin inadvertently injected into muscle. Vaag et al⁴² found intramuscular injections of insulin led to higher serum insulin levels when compared to subcutaneous injections, possibly impacting glycemic control and placing patients at risk for hypoglycemia. With the realization that patients with diabetes have differing STMD where insulin is injected, insulin needles of various lengths are now offered.³⁵

In light of the above, Kim et al³⁵ have proposed for all patients receiving SCIT to undergo an POC ultrasonography to confirm their STMD. Having this information would allow healthcare

workers administering SCIT to better appreciate the real depth to the intramuscular space, thereby reducing the risk of inadvertent intramuscular injections and, potentially, anaphylaxis. Although the routine use of ultrasonography would add to the associated costs, expertise, and time required to provide treatment, Kim et al believe that most allergists would find learning to read these relatively simple ultrasounds as straightforward. As well, recent cuts in costs have made ultrasonography equipment financially feasible for most clinics. These beliefs are supported by Bee and Thing⁴³, who write that even a one to two-day basic skills ultrasound course would be sufficient to train general practitioners to perform musculoskeletal ultrasound-guided joint and soft-tissue injections. They also speculate that declining costs of point-of-care ultrasound machines and the abundance of educational opportunities to train in MSK ultrasound will precipitate a new paradigm where such a scenario is commonplace. Programs that trained nurses to perform ultrasound-guided peripheral venous access have been found to be cost-effective and can even improve quality-of-care.⁴⁴ A study that looked at medical students found that 85% of students achieved adequacy in basic ultrasound skills after a 5-hour course.⁴⁵

With proper identification of a patient's STMD, healthcare workers can better gauge the depth required to inject needles of current standard needle lengths while remaining in subcutaneous tissue.³⁵ Alternatively, since 91% of patients have STMD greater than 4 mm, risk of intramuscular injections could be further decreased by reducing the standard needle length for syringes used for SCIT to 4 mm. This would have the additional benefit of simplifying administration in the majority of patients, as injection angles and pinching of skin would no longer be necessary for them. Proper administration of SCIT would likely reduce the risk of systemic reactions and may increase the use of SCIT generally.^{35, 38} As per current AAAAI and

220 CSACI recommendations, SCIT should only be performed in suitably staffed and equipped
221 clinics;^{36, 46} widespread prevalence of ultrasound machines in these clinics would enhance their
222 qualifications as the setting of choice for treatment administration.
223

How I use ultrasonography in the allergy clinic

In our pediatric and overweight patients with a history of anaphylaxis, who are at risk of intraosseous and subcutaneous epinephrine injections, respectively, we routinely perform ultrasonography to ensure adequate epinephrine delivery in case of a reaction. The EAI that are available in North America require high force to trigger the delivery of the epinephrine. In order to simulate the injection force of the EAI, we perform ultrasonography with firm force (estimated at 10 pounds of pressure) (Figure 1B). The ultrasound probe is held perpendicularly to the long axis of the femur. With an adequate transverse ultrasound image of the mid-thigh, we measure the STMD and STBD (Figure 1A). We document these distances in the patient record. We tell the patient if the prescribed EAI will deliver epinephrine intramuscularly as preferred. If there is a high risk of subcutaneous or intraosseous injection, we notify the patient and/or the caregivers about this risk. Because we do not have EAI with longer length needles (e.g., Emerade) in Canada, we instruct patients with a risk of subcutaneous injections to always carry two EAI, and to call emergency medical services as soon as possible to be taken to the ER for monitoring and further treatment. If the patient is at risk of intraosseous injections, we instruct the caregiver to squeeze the vastus lateralis muscle and carefully inject the EAI into the mid-thigh. With this technique, the soft tissues will not compress significantly so preventing deep injection into the bone.

As well, we determine skin to muscle distance in our patients undergoing subcutaneous allergen immunotherapy. Ultrasound of the mid posterior upper arm is performed to measure the STMD (Figure 1B). The image is captured applying minimal pressure because pressure is not applied for allergy injections. After an adequate ultrasound image is captured, the distance from the skin

247 to inner aspect of the fascia of the triceps muscle is measured. This distance is documented on
248 the health record and/or communicated to the physicians who will be giving the subcutaneous
249 immunotherapy. The nurses and/or physicians giving the injections are instructed not to inject
250 SCIT deeper than the measured skin to muscle distance, ensuring subcutaneous, but not
251 intramuscular, injections.

252

Future directions - emerging role of ultrasonography in Allergy and Immunology

Ultrasound guidance plays a key role in the provision of intralymphatic immunotherapy, a promising novel allergen immunotherapy approach.³³ In intralymphatic therapy, ultrasonography is used to guide delivery of low concentrations of allergenic antigens directly to a local lymph node (typically the inguinal nodes).^{15, 16} Compared to uptake of the antigen from a larger dose injected into subcutaneous tissue, direct lymph node delivery maximizes immunogenicity. As well, there is a lower risk for systemic adverse events and a significantly shorter course of therapy compared to SCIT (one to two months versus five years). Ultrasonography can also be helpful in reducing risk of intramuscular injection during the administration of omalizumab (which can enhance the tolerance of SCIT in patients with allergic asthma), and, potentially, in improving efficacy and safety of SCIT in patients of special considerations, including pregnant women, children, and the elderly.^{47, 48, 49} Similar to other areas of medicine, POC ultrasonography can thus be utilized in the Allergy and Immunology clinic as a rapid and cost-effective clinical tool that improves patient safety.

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Figure legends

Figure 1A. Schematic showing an epinephrine auto-injector (EAI) penetrating the skin, subcutaneous tissue, fascia lata, endomysium, and muscle.²⁶ STBD, skin to bone distance; STMD, skin to muscle distance.

Figure 1B. Ultrasound images in a patient with A. minimal pressure and B. maximal pressure.¹⁰

Figure 2. Modified technique for epinephrine administration in a pediatric patient. By pinching the thigh muscle, the skin to bone depth is increased, avoiding inadvertent intraosseous epinephrine delivery.

Table 1. Characteristics of epinephrine auto-injectors available in Europe and North America. Data obtained from respective companies or according to Reference 50.

Epinephrine autoinjector and dose	Needle length (mm)	Estimated Skin to Muscle Distance (mm)	Activation Force (N)		Maximum pressure applied (N)
			Range	Mean	
Epipen Jr® 0.15 mg	12.7	10.7	8.5-35	20-22 ^b	35
Epipen® 0.3 mg	15.2	13.2	8.5-35	20-21 ^b	35
Auvi-Q® 0.1 mg	7.5	5.5			
Auvi-Q®/Allerject® 0.15 mg	12.7	10.7			
Auvi-Q®/Allerject® 0.3 mg	15.2	13.2	8.5-53	27	53
Jext® 0.15/0.3 mg	15.7	13.7	21-43 ^a	28 ^a	43 ^a
Emerade® 0.15 mg	16	14	8-25	15-17 ^b	25
Emerade® 0.3/0.5 mg	23	21	8-25	15-17 ^b	25

Abbreviations: mm, millimeters; mg, milligrams; N, Newtons (1 N = 0.266 pound; 1 pound = 4.425 N).

^aEstimated from Figure 5, Reference 50.

^bVariation between batches.

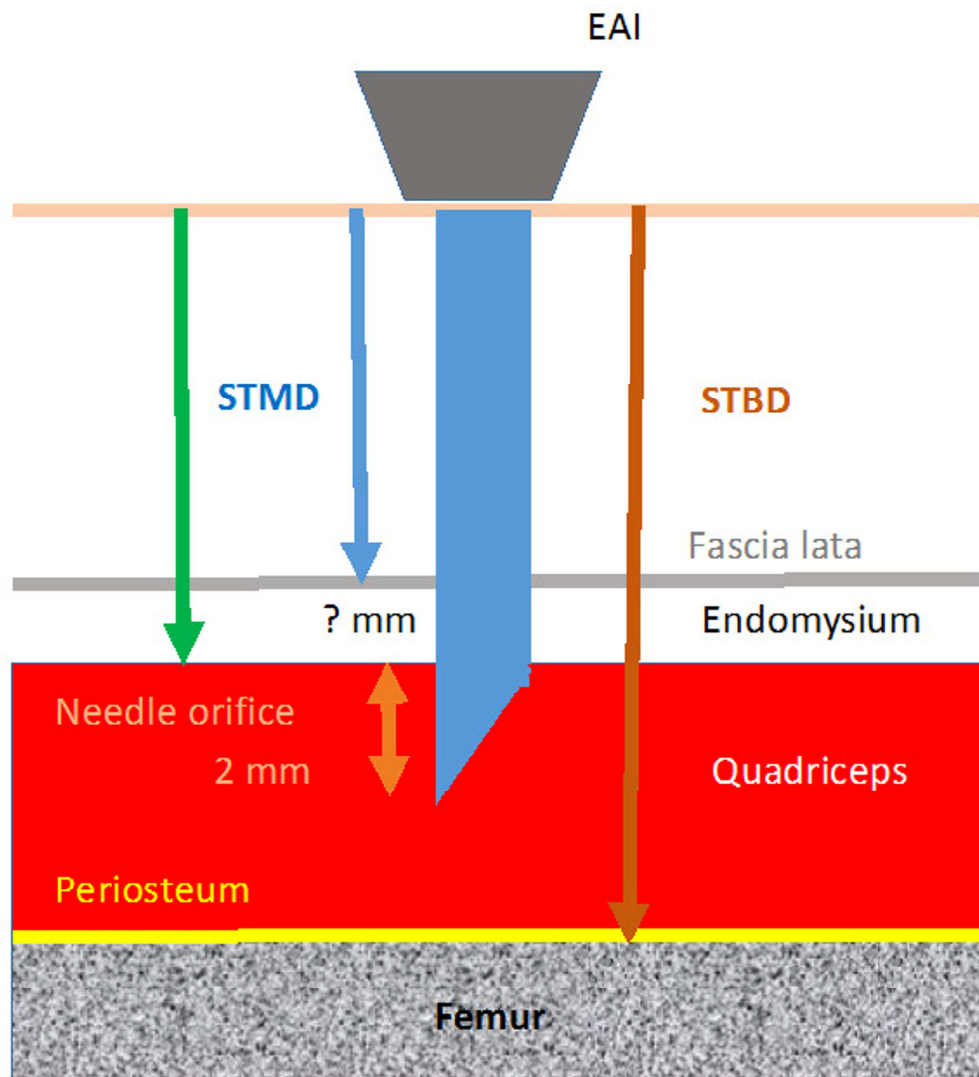


Figure 1A

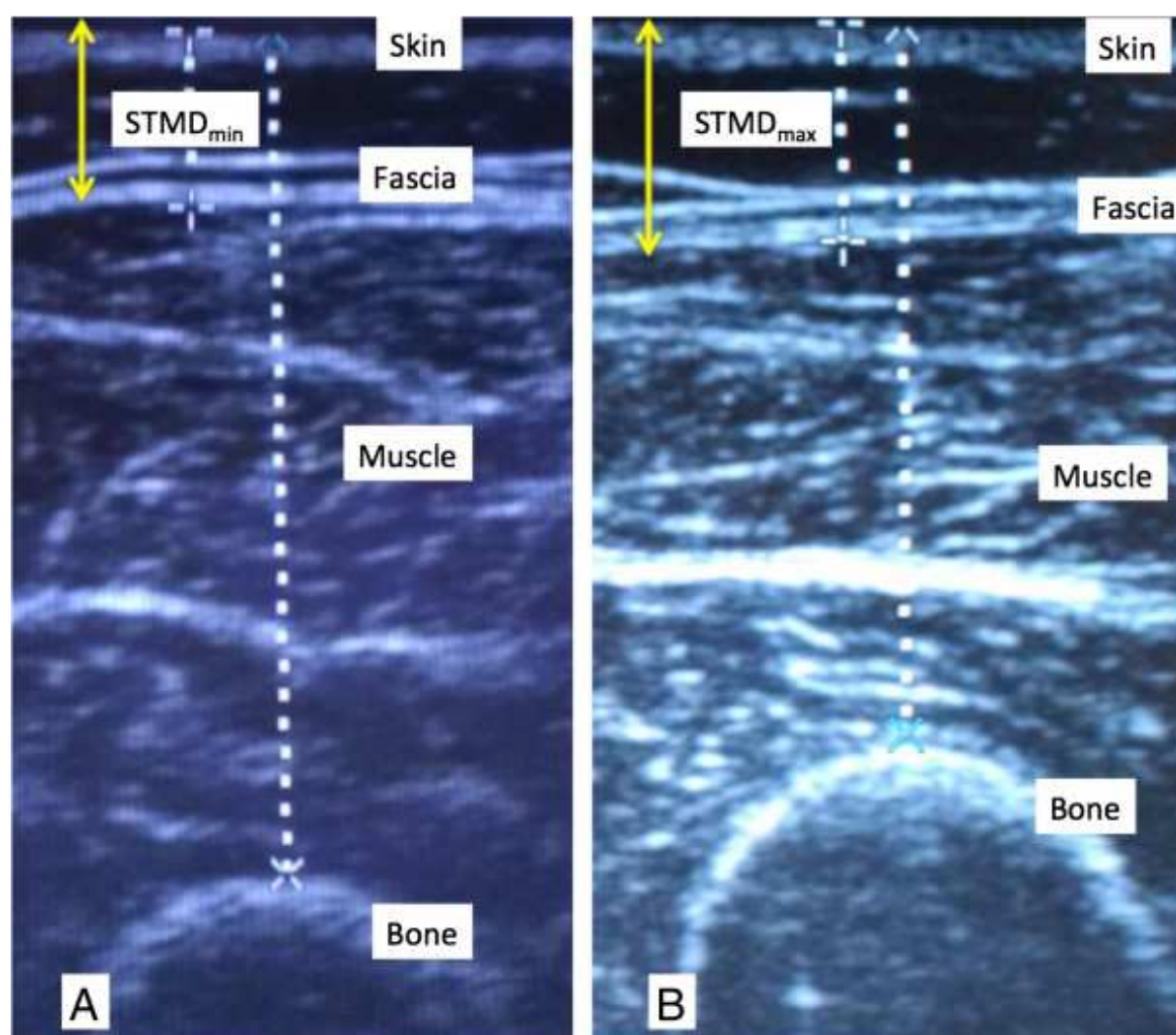


Figure 1B



Figure 2

Key Messages

1. Point of care (POC) clinical ultrasonography is used across multiple medical specialties to guide diagnosis and treatment, and to enhance the safety of invasive procedures.
2. In Allergy and Immunology, POC ultrasonography is underutilized.
3. The standard epinephrine autoinjector (EAI) needle length may be inadequate for intramuscular delivery of epinephrine, particularly for women, at risk of anaphylaxis.

Ultrasonography can identify the need for longer EAI needle lengths to compensate for increased skin to muscle depth (STMD) due to increased subcutaneous tissue in this patient population.
4. Conversely, for pediatric patients, commercially available EAI needle lengths may be too long, risking inadvertent intraosseous injection and resultant complications.

Ultrasonography can evaluate skin to bone depth (STBD) in these patients, which may require adjustment to epinephrine administration.
5. POC ultrasonography can also be used in needle guidance for subcutaneous allergen immunotherapy injections, to reduce the chance of inadvertent intramuscular injection and systemic side effects.