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Updates in Epinephrine Guidelines

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Introduction

Epinephrine is the first line treatment for anaphylaxis, which is a serious allergic reaction that can rapidly progress and may cause death.[1] As a nonselective adrenergic agonist, epinephrine rapidly works to increase vasoconstriction and peripheral vascular resistance, increase cardiac output, reverse bronchoconstriction and mucosal edema, and inhibit the release of mediators of inflammation from mast cells and basophils.[2] The anaphylaxis guidelines developed by the Joint Task Force on Practice Parameters (JTFPP) in 2020,[2] the World Allergy Organization (WAO) in 2020,[3] and the European Academy of Allergy and Clinical Immunology (EAACI) in 2021[4] advise clinicians to prescribe self-injectable epinephrine to individuals at risk of anaphylaxis and educate them on when and how to administer it. In 2023, the JTFPP updated its anaphylaxis practice parameter to address seven key topic areas, including multiple questions and recommendations related to epinephrine prescription and use.[5] The practice parameter authors graded each recommendation as conditional or strong, based in part on the certainty of the supporting evidence. We provide an overview of key recommendations and discuss their applications in the Canadian context.

It is important to note that in Canada, EpiPen® autoinjectors are currently the sole epinephrine delivery devices available with premeasured doses of epinephrine for the emergency treatment of allergic reactions. These autoinjectors should be administered intramuscularly into the anterolateral thigh. Additional epinephrine devices may become available in the future, including the first epinephrine nasal spray (neffy®).[6] There is a wider variety of epinephrine devices available in the United States, including multiple brands of epinephrine autoinjectors (Adrenaclick®, Auvi-Q®, EpiPen®/EpiPen® Jr., and generic versions). Additionally, there is one brand of epinephrine prefilled syringe (Symjepi™) and one brand of nasal spray (neffy®). Although the anaphylaxis practice parameter update was published before the U.S. Food and Drug Administration had approved neffy®, we believe its recommendations for epinephrine prescription and use may be appropriately extended to include epinephrine nasal spray where it is available.

When Should Clinicians Prescribe Epinephrine?

The anaphylaxis practice parameter update recommends that clinicians routinely prescribe epinephrine to patients who are at higher risk of anaphylaxis.[5] When deciding whether to prescribe epinephrine to patients at lower risk, the guideline suggests that clinicians should engage patients in shared decision making (SDM), taking into consideration their individual risk factors, values, and preferences. This recommendation is graded as conditional, based on evidence with very low certainty. Researchers have not yet validated any risk-stratification algorithms to guide epinephrine prescription. The practice parameter authors advise clinicians to consider the patient's specific diagnosis, history of allergic reactions, likelihood of allergen exposure, and potential comorbidities and cofactors that might affect the severity of an allergic reaction when assessing the patient's risk level. They also advise clinicians to discuss not only the potential benefits but also the potential financial and psychosocial burdens of epinephrine prescription. **Table 1** provides a non-exhaustive list of factors that may either reduce or increase a patient's likelihood of requiring treatment with epinephrine, which may help guide SDM on whether to prescribe it.

How Many Doses of Epinephrine Should Clinicians Prescribe?

The practice parameter update suggests that clinicians should consider a patient's risk factors for severe anaphylaxis, their values and preferences, and context-specific considerations when deciding whether to prescribe a single dose of epinephrine versus multiple doses.[5] It advises routinely prescribing more than one dose of

Allergic Condition	Lower Likelihood	Higher Likelihood
IgE-mediated Food allergy		• History of prior systemic allergic reaction after exposure
Pollen food Allergy syndrome	• No history of anaphylaxis to causative food	• History of anaphylaxis to causative food
Venom or insect bite/sting allergy	• History of only large local or cutaneous systemic reaction(s) • History of anaphylaxis, but on maintenance VIT or discontinued VIT after more than 5 years of treatment with no high-risk factors	• History of anaphylaxis, not treated with a complete course of VIT • Current VIT, with history of prior systemic reaction(s) to VIT • Honeybee allergy • Elevated basal tryptase level • Frequent exposure
Latex allergy	• Low likelihood of exposure	• Occupational exposure
Drug allergy	• Low likelihood of exposure	• Occupational exposure (e.g., compounding, mixing, or preparation of medications)
Exercise-induced anaphylaxis		• All cases
Physical urticarias		• Cold induced
Aeroallergen immunotherapy	• No history of prior systemic reaction(s) to AIT and no relevant comorbidities (e.g., asthma)	• History of prior systemic reaction(s) to AIT and/or relevant comorbidities (e.g., asthma)

Table 1. Likelihood of Requiring Treatment With Prescribed Epinephrine; *reprinted from Golden DBK, Wang J, Waserman S, Akin C, Campbell RL, Ellis AK, et al. Ann Allergy Asthma Immunol. 2024 Feb;132(2):124-176, with permission from Elsevier.*

Abbreviations: AIT: aeroallergen immunotherapy, **EAI:** epinephrine autoinjector; **VIT:** venom immunotherapy

epinephrine to patients who have a history of prior biphasic reactions or who have previously required multiple doses of epinephrine to treat an episode of anaphylaxis. For patients without such history, the burdens of prescribing multiple doses may in some cases outweigh the anticipated benefits. This recommendation is graded as conditional, based on evidence with very low certainty. A 2021 systematic review and meta-analysis found that fewer than 10% of reported cases of anaphylaxis were treated with multiple doses of epinephrine.[7] Most cases of anaphylaxis resolve with a single dose. However, it is impossible to predict with certainty whether a patient will require multiple doses to treat anaphylaxis. The practice parameter authors identified multiple risk factors and cofactors for severe and fatal anaphylaxis that may help guide SDM (**Table 2**). They note that the presence of one or more risk factors does not necessarily indicate an absolute need for multiple doses of epinephrine, nor does the absence of any risk factor preclude the possibility that a patient will experience anaphylaxis requiring multiple doses to treat. Additionally, context-specific considerations, such as the proximity of local emergency services, are also important to discuss while engaging in SDM.

Drug-induced Anaphylaxis	Food-induced Anaphylaxis	Venom Bite- or Sting-induced Anaphylaxis	Non-trigger–related Cofactors/Risk Factors
• Age >60 years • Cardiovascular diseases • Respiratory diseases • Antihypertensive drugs	• Adolescence • Uncontrolled asthma • Alcohol consumption • Peanut- or tree nut-induced reaction • Exercise	• Older age • Male sex • Hereditary α-tryptasemia • Mast cell disorders • Cardiovascular diseases • NSAIDs • Antihypertensive drugs	• Mast cell disorders • Infections • Perimenstrual period • NSAIDs • Alcohol consumption • Psychological burden • Exercise • Unknown cause

Table 2. Risk Factors and Cofactors Potentially Associated With Severe or Fatal Anaphylaxis; *reprinted from Golden DBK, Wang J, Waserman S, Akin C, Campbell RL, Ellis AK, et al. Ann Allergy Asthma Immunol. 2024 Feb;132(2):124-176, with permission from Elsevier.*

Abbreviation: NSAIDs: nonsteroidal anti-inflammatory drugs

Which Epinephrine Device Should Clinicians Prescribe?

The practice parameter update advises clinicians to consider dosage, needle length, affordability, access, and patient treatment preferences when deciding which epinephrine device to prescribe.[5] This recommendation is graded as conditional, based on evidence with very low certainty. Most of the listed considerations are more relevant in the United States, where multiple devices are available. In Canada, the primary consideration is dosage. The standard dosing of intramuscular epinephrine in healthcare settings is 0.01 mg/kg of bodyweight, up to a maximum dose of 0.5 mg per administration; however, epinephrine autoinjectors for emergency treatment of allergic reactions in the community are only available with certain premeasured doses.[8] EpiPen® autoinjectors are currently available in 0.15 mg and 0.3 mg doses. According to the manufacturer, the 0.15 mg dose is appropriate for children weighing 15–30 kg, and the 0.3 mg dose is appropriate for children and adults weighing ≥30 kg. However, the practice parameter supports switching to the 0.3 mg dose at 25 kg to limit underdosing. It also advises clinicians that the 0.15 mg dose is appropriate to prescribe to infants and toddlers weighing <15 kg. These recommendations are consistent with previous position statements issued by the Canadian Society of Allergy and Clinical Immunology (CSACI).[9,10]

The introduction of neffy® or other epinephrine devices to the Canadian market would expand treatment options. We expect that neffy® would provide an appealing option for many patients. A recent survey of physicians revealed that 86% agreed that patients would prefer needle-free epinephrine administration.[11] According to the manufacturer, neffy® can be thawed after accidental freezing without impacting product quality,[12] and a recent analysis found it to be more shelf-stable at high temperatures (40–50°C), compared with EpiPen®.[13]

When Should Patients Administer Epinephrine?

The practice parameter update suggests that clinicians should counsel patients to promptly administer epinephrine at the first sign of suspected anaphylaxis,[5] which is consistent with previously published guidelines.[2-4] Definitions and clinical criteria for anaphylaxis have been published by multiple organizations, including the National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis Network (FAAN)[14] and WAO.[3] The Global Allergy and Asthma Excellence Network (GA²LEN) recently issued a consensus report aimed at resolving the differences between the NIAID/FAAN and WAO criteria.[1] According to this report: "[Anaphylaxis] may involve the skin/mucosa (e.g., urticaria, flushing, angioedema), respiratory system (e.g., upper airway obstruction, bronchospasm, cough), cardiovascular system (e.g., syncope, hypotension, shock), and/or gastrointestinal system (e.g., severe abdominal pain, repetitive vomiting, diarrhea). Life-threatening anaphylaxis is characterized by airway, breathing, and/or

cardiovascular compromise and may occur without skin/mucosa involvement".[1]

The practice parameter update generally recommends against pre-emptive epinephrine use when no signs or symptoms of an allergic reaction have yet developed after a suspected or known exposure to a causative allergen.[5] This recommendation is graded as conditional, based on evidence with very low certainty. The authors found no evidence that pre-emptive epinephrine use prevents anaphylaxis in asymptomatic patients. However, there are scenarios in which administering epinephrine may be warranted before a reaction meets the clinical criteria for anaphylaxis. For example, a more proactive approach to epinephrine administration may be appropriate for patients with underling mastocytosis or a history of rapidly progressive near-fatal anaphylaxis.

When Should Clinicians Counsel Patients to Activate Emergency Medical Services?

The practice parameter update suggests that immediate activation of emergency medical services (EMS) may not be necessary if a patient experiences a prompt, complete or near complete, and durable response to treatment with epinephrine.[5] It may be appropriate for patients and caregivers to consider managing anaphylaxis at home in such cases. Clinicians should counsel patients and caregivers to always activate EMS if the anaphylaxis is severe, if it does not promptly and completely or nearly completely resolve, or if it returns or worsens after the first dose of epinephrine. This recommendation is graded as conditional, based on evidence with very low certainty. CSACI issued similar guidance in 2023,[15] advising that home management of anaphylaxis after epinephrine use may be appropriate in certain circumstances. Both the practice parameter and the CSACI statement emphasize the importance of SDM to determine whether home management is suitable to consider. **Table 3** presents several considerations for and against home management, which the practice parameter authors have adapted from Casale et al. 2022.[16]

What Other Counselling Should Clinicians Provide Regarding Epinephrine?

Clinicians should educate and counsel patients and caregivers on:

- The essentials of epinephrine carriage, storage, and use
- How to properly administer their epinephrine device
- The most common adverse effects of epinephrine
- How to manage rare serious adverse events
- Strategies to overcome barriers to adherence

These recommendations are consistent with current standard practice and are worth reiterating, given the gaps that researchers have identified in patients' epinephrine-related education, knowledge, skills, carriage, and use.[17,18] There are no absolute contraindications to administering epinephrine for anaphylaxis. The adverse effects are typically mild and transient, with tremors, palpitations, and anxiety being most commonly reported.[19] Cardiac adverse events, such as arrhythmias or myocardial infarction, may occur in rare cases but are primarily associated with intravenous administration of epinephrine in hospital settings.[20]

What About Stock Epinephrine?

Prescription and self-carriage of epinephrine help to ensure that treatment is available for patients at risk of anaphylaxis. However, epinephrine carriage rates remain suboptimal, and anaphylaxis can sometimes occur in individuals with no prior history of allergic reaction. To improve treatment access, the practice parameter update suggests that childcare centres and schools should stock undesignated epinephrine.[5] It also encourages other community venues to stock undesignated epinephrine, if feasible. For example, such venues may include theme parks, sports arenas, restaurants, or other settings. These recommendations are graded as conditional, based on evidence with very low certainty. Identified barriers to stocking and administering undesignated epinephrine include the cost of epinephrine devices, gaps in administrative support, training requirements, and concerns about legal liability.[21,22] Collaboration among stakeholders is necessary to address feasibility concerns and strengthen institutional capacity for stock epinephrine programs.

Considerations for Home Management	Considerations Against Home Management
• Patients/caregivers engaged in the shared decision-making process	• Patients/caregivers not comfortable with managing anaphylaxis without activating EMS/ED
• Immediate access to at least two EAIs	• No availability of EAIs or only one EAI
• Immediate access to person(s) who can provide help if needed	• Being alone, without immediate access to person(s) who can provide help if needed
• Clear understanding of the symptoms warranting the immediate use of EAI, availability of the anaphylaxis treatment plan	• Being unaware of the allergic symptoms that warrant the use of an EAI
• Familiarity with the EAI device administration technique	• Lack of technical proficiency with administration of an EAI • Hesitance about intramuscular injection (needle phobia)
• Clear understanding of the benefits of early epinephrine treatment in anaphylaxis	• Concerns about the potential epinephrine adverse effects
• Good adherence to previous treatment recommendations, for example, using an EAI for anaphylaxis in the past or using controller medications for chronic conditions	• Poor adherence to previous treatment recommendations, for example, not administering EAI for anaphylaxis in the past or not using controller medications for chronic conditions
	• History of severe/near-fatal anaphylaxis treated with more than two doses of epinephrine, hospitalization, intubation

Table 3. Considerations for and Against Home Management of Anaphylaxis; *reprinted from Golden DBK, Wang J, Waserman S, Akin C, Campbell RL, Ellis AK, et al. Ann Allergy Asthma Immunol. 2024 Feb;132(2):124-176, with permission from Elsevier.*

Abbreviations: EAI: epinephrine autoinjector, **ED:** emergency department, **EMS:** emergency medical services

Conclusions

The JTFPP's 2023 anaphylaxis practice parameter update affirms the benefits of prescribing epinephrine devices with premeasured doses of epinephrine to patients at higher risk of anaphylaxis. While patients at lower risk may also benefit from epinephrine prescription, the financial or psychosocial burdens might outweigh the anticipated benefits in some cases. The practice parameter update emphasizes the importance of engaging patients in SDM and considering their individual risk factors, values, preferences, and context-specific considerations when deciding whether to prescribe epinephrine, how many doses to prescribe, and how to counsel them on managing anaphylaxis after epinephrine is administered.

Clinicians should counsel patients to immediately activate EMS after administering epinephrine if anaphylaxis is severe, if it does not promptly and completely or nearly completely resolve, or if symptoms return or worsen after the first dose. Home management of anaphylaxis without EMS activation may be appropriate if the patient experiences a prompt, complete or nearly complete, and durable response to treatment with the first dose of epinephrine, has additional epinephrine available, and determines with their clinician that it is a suitable option for them. The certainty of the evidence underlying the practice parameter recommendations is generally very low, indicating that more research is needed to confirm the best strategies for epinephrine prescription and use.

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