

Patient Communications

Why Is It Important to Quickly Use Epinephrine at the Onset of Symptoms and Signs of Anaphylaxis?



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KEYWORDS

- Anaphylaxis • Systemic allergic reaction • Epinephrine • Adrenaline
- Adverse effects

KEY POINTS

- Intramuscular epinephrine is extremely safe for management of anaphylaxis.
- Epinephrine should be administered at the first symptoms and signs of anaphylaxis, including any systemic allergic reaction (SAR).
- Affected individuals or caregivers should be educated on the safety profile of epinephrine and the importance of epinephrine use early in SAR and anaphylaxis.

INTRODUCTION

The authors define a systemic allergic reaction (SAR) and anaphylaxis as an acute, potentially fatal systemic allergic or nonallergic reaction expressed as a continuum encompassing grades 1 to 5 in the proposed modified World Allergy Organization (WAO) grading system.¹ Grades 4 and 5 meet the definition of anaphylaxis per the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network Expert Panel criteria.^{1,2} Although most cases of SAR and anaphylaxis resolve without treatment, it is impossible to accurately predict which subjects will develop SAR versus those who may progress to anaphylaxis and possibly death.³ The early administration of epinephrine in the potential course of SAR and anaphylaxis not only reduces mortality, but results in a reduction of its progression and can negate the onset of anaphylaxis.⁴

Although there is a trend toward an increasing lifetime prevalence of SAR and anaphylaxis, succumbing from this disease is rare with mortality rates between 0.63

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and 0.76 per million population in the United States.⁵ Mortality occurs from respiratory or cardiovascular compromise and often occurs in the absence of or delayed administration of epinephrine.^{2,6,7} The latter is also associated with increased biphasic reactions, that is, reactions that occur initially and reoccur 1 to 72 hours later, rarely longer, some of which are severe and even fatal.⁸

DISCUSSION

It is the responsibility of the affected subject, parent, or caregiver to recognize the symptoms and signs of SAR and anaphylaxis and to appropriately administer epinephrine intramuscularly into the anterolateral thigh.³ The symptoms and signs of SAR or anaphylaxis are illustrated in [Table 1](#), including reactions grades 1 to 5. Symptoms and signs generally appear in escalating order, but not necessarily. Some individuals can present with a feeling of impending doom, respiratory problems, or a drop in blood pressure, without any other symptoms or signs of SAR or anaphylaxis.³

Educating affected subjects or their parents and caregivers about SAR and anaphylaxis as a continuum, as illustrated in the cited modified WAO classification, allows physicians and other health care professionals to clearly indicate when to administer this drug. This is not only to stop the reaction, but to prevent its progression to potential death.⁴ Likewise, understanding the risk factors for SAR and anaphylaxis and death is necessary. Risk factors for severe or fatal anaphylaxis include asthma, cardiovascular disease, mast cell disorders, older age, route of administration of the allergen (parenteral greater than oral), dose of allergen administered, and time of onset.^{3,10} In addition, in 2020 Cardona and colleagues³ summarized possible cofactors that may contribute to “anaphylaxis” including exercise, medication use (β -blockers, angiotensin-converting enzyme inhibitors), active infection, sleep deprivation, alcohol use, and psychological factors. Risk factors for SAR or anaphylaxis following subcutaneous immunotherapy (SCIT) used to treat allergic rhinoconjunctivitis, atopic eczema, and allergic asthma include: prior anaphylactic reaction to SCIT, uncontrolled asthma, rush immunotherapy, high degree of sensitivity, and seasonal exacerbations.^{11,12} Intramuscular (IM) epinephrine, administered at the first symptom or sign of SAR associated with SCIT in a retrospective study of SARs following approximately 28,000 SCIT injections, resulted in the quick resolution of these reactions.¹³ With early IM epinephrine, none progressed beyond WAO grade 2 of 5 reactions. Timing of the onset of the reaction also is of utmost importance. Although SAR or anaphylaxis rarely can begin up to several hours, even longer, following allergen exposure, the earlier the onset of the reaction, the more potential for it to be serious.⁶ Major barriers to subjects appropriately using epinephrine include a lack of universal symptoms and signs as to when it should be administered, trypanophobia, administration via injection, and perceived or potential side effects.¹⁴

IM epinephrine is safe when administered in the appropriate dose, body site, and time interval. The recommended dose is 0.01 mg/kg with a maximum dose of 0.5 mg/kg body weight.^{2,3,10} The appropriate site is the anterolateral region of the middle third of the thigh.² The dose is repeated at increments of 5 to 15 minutes, as necessary, depending on the continuing or worsening symptoms and signs of SAR or anaphylaxis.^{2,3,10}

Approximately one in five individuals experience side effects from epinephrine.¹⁵ Side effects include transient tremors, restlessness, increased anxiety, headache, and palpitations.^{15,16} Other more uncommon adverse events (AEs) include needle lacerations; inappropriate injections sites; and, rarely, a secondary infection at the

Table 1
Proposed modification of the 2010 WAO grading system

Grading System for SAR				
Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anaphylaxis				
Administer epinephrine at the first symptom or sign of any of the following ^c				
Symptoms/signs from 1 organ system present	Symptoms/signs from ≥ 2 organ symptoms listed in grade 1	Lower airway Mild bronchospasm (eg, cough, wheezing, shortness of breath) that responds to treatment	Lower airway Severe bronchospasm (eg, not responding or worsening despite treatment)	Lower or upper airway Respiratory failure and/or Cardiovascular Collapse/hypotension ^b
Cutaneous Urticaria and/or erythema-warmth and/or pruritus, other than localized at the injection site		And/or Gastrointestinal Abdominal cramps ^a and/or vomiting/diarrhea	And/or Upper airway Laryngeal edema with stridor	And/or Loss of consciousness (vasovagal excluded)
And/or Tingling, or itching of the lips ^a or Angioedema (not laryngeal) ^a		Other Uterine cramps Any symptoms/signs from grade 1 would be included	Any symptoms/signs from grades 1 or 3 would be included	Any symptoms/signs from grades 1, 3, or 4 would be included
Or Upper respiratory Nasal symptoms (eg, sneezing, rhinorrhea, nasal pruritus, and/or nasal congestion)				
And/or Throat-clearing (itchy throat) ^a				
And/or Cough not related to bronchospasm				

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Table 1
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Grading System for SAR				
			Grade 4	Grade 5
Grade 1	Grade 2	Grade 3	Anaphylaxis	
Or				
Conjunctival				
Erythema, pruritus, or				
tearing				
Or				
Other				
Nausea				
Metallic taste				

The final grade of the reaction is not determined until the event is over, regardless of the medication administered to treat the reaction. The final report should include the first symptoms/signs and the time of onset after the causative agent exposure and a suffix reflecting if and when epinephrine was or was not administered: a, ≤ 5 minutes; b, >5 minutes to ≤ 10 minutes; c, >10 to ≤ 20 minutes; d, >20 minutes; z, epinephrine not administered.

Final report: grade 1 to 5; a-d, or z; first symptoms/signs; time of onset of first symptoms/signs.

Case example. Within 10 minutes of receiving an allergen-specific immunotherapy injection, a patient develops generalized urticaria followed by a tickling sensation in the posterior pharynx. Intramuscular epinephrine is administered within 5 minutes of symptoms/signs resulting in complete resolution of the reaction. The final report would be: grade 2; a; urticaria; 10 minutes.

A) Infants and children: low systolic blood pressure (age-specific) or $>30\%$ decrease in systolic blood pressure. Low systolic blood pressure for children is defined as follows.

- 1 month–1 year: <70 mm Hg
- 1–10 years: <70 mm Hg + $[2 \times \text{age}]$
- 11–17 years: <90 mm Hg

B) Adults: systolic blood pressure of <90 mm Hg or $>30\%$ decrease from that person's baseline.

^a Application-site reactions would be considered local reactions. Oral mucosa symptoms, such as pruritus, after sublingual immunotherapy (SLIT) administration, or warmth and/or pruritus at a subcutaneous immunotherapy injection site would be considered a local reaction. However, tingling or itching of the lips or mouth could be interpreted as SAR if the known allergen (eg, peanut) is inadvertently placed into the mouth or ingested in a subject with a history of a peanut-induced SAR. Gastrointestinal tract reactions after SLIT or oral immunotherapy would also be considered local reactions, unless they occur with other systemic manifestations. SLIT or oral immunotherapy reactions associated with gastrointestinal tract and other systemic manifestations would be classified as SARs. SLIT local reactions would be classified according to the WAO grading system for SLIT local reactions.⁹ A fatal reaction would not be classified in this grading system but rather reported as a serious adverse event.

^b Hypotension is defined per the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Expert Panel criteria²: reduced blood pressure after exposure to known allergen for that subject (minutes to several hours).

^c Recommendations as to when to use epinephrine were added by the authors and were not included in the original table cited.

From Cox LS, Sanchez-Borges M, Lockett RF. World Allergy Organization Systemic Allergic Reaction Grading System: Is a Modification Needed? *J Allergy Clin Immunol Pract*. 2017 Jan-Feb;5(1):58-62.e5.

injection site.^{17,18} These latter are not side effects from the epinephrine but sequelae from its parenteral administration. Severe AEs, usually associated with excessive intravenous administration, include arrhythmias; chest pain; QT prolongation; cardiac ischemia; and, rarely, death.^{15,16} Severe AEs occur more commonly in older subjects and subjects with cardiovascular disease.¹⁶ When given appropriately, the medical literature does not support the commonality of significant adverse effects. Therefore, there is no absolute contraindication to its use, even in subjects with older age or cardiovascular disease.

To reiterate, those at highest risk for epinephrine side effects are those subjects with cardiovascular disease.¹⁶ However, the drug of choice for an individual with cardiovascular disease who is having SAR or anaphylaxis is epinephrine. With that and possibly other rare exceptions, the dose of epinephrine administered is safe.¹⁶

Affected individuals who self-administer or parents or caregivers who administer epinephrine should be counseled on how and when to use it and on its safety profile. Receiving such counseling yearly or even more frequent may help negate the inappropriate fear of using it and may reassure the subject, parent, or caregiver of their ability to administer it. Where available, epinephrine autoinjectors (EAls) should be prescribed.³ These autoinjectors are designed to be easy to use and to ensure standardized dosing.¹⁶ They are available in 0.1-mg, 0.15-mg, and 0.3-mg doses in the United States and other parts of the world, whereas the 0.5-mg EAls are only available in limited countries. Even when appropriately used, underdosing of epinephrine remains of great concern.³ This is compounded by obesity. More than 70% of adults older than the age of 20 years in the United States meet the criteria for being overweight, and an estimated 42.5% meet criteria for obesity, defined as a body mass index of more than 30 kg/m², in a 2018 report.¹⁹ For subjects weighing greater than 36 kg, a 0.3-mg dose from an EAl is an inadequate dose of epinephrine, based on the expert consensus dose of 0.01 mg/kg up to a maximum of 0.5 mg.³

Although EAls are convenient and easy to use, they are not readily available throughout the world, particularly in developing countries.²⁰ Less than 35% of the worldwide population has access to EAls.²⁰ Even when they are available, cost is prohibitive. Cost-efficient alternatives include ampules of epinephrine with an empty syringe or an epinephrine prefilled syringe (EPS).²¹ The EPS is the preferred alternative because an affected individual or caregiver does not have to accurately draw up the epinephrine into a syringe.²¹ The shelf life of an EPS is approximately 3 months when stored at room temperature.²¹ However, EAls retain nearly 90% of their epinephrine potency 30 months past the labeled expiration date, a tremendous advantage over an EPS.²²

Alternative methods to administer epinephrine are under investigation, and two promising routes include intranasal and sublingual delivery. Early studies indicate that such administration results in plasma concentrations equivalent to IM epinephrine.²³ Five milligrams of intranasal epinephrine in healthy human subjects and 40 mg of sublingual in animals achieves comparable concentrations when compared with 0.3 mg of IM epinephrine.^{24,25} Further human studies are needed to ensure their clinical efficacy and respective safety profiles. In theory, these delivery systems may be more user friendly and safer than the current use of EAls, mainly through the avoidance of needles.

It is up to the affected individual, parent, or caregiver to know when and how to administer epinephrine because most SARs and anaphylaxis begin in the community from foods, medications, or insect stings to which an individual is allergic.³ However, affected individuals often have difficulty determining when to administer it.²⁶ In a survey of SAR and anaphylaxis survivors, 73% did not self-administer epinephrine, and of

those who did, almost a third questioned the appropriate time as to when it should be administered.²⁶

This problem is secondary to an unclear consensus among physicians and other health care professionals as to the time it should be used with the initial symptoms and signs of a SAR and anaphylaxis. Treatment of rare events may limit general applicability of the resulting rare observations. Proving that a given treatment or timing of treatment is essential is nearly impossible with anaphylaxis because of rapid onset, variability, and high rate of spontaneous resolution. IM epinephrine is safe, and use before development of definitive anaphylaxis is potentially life-saving.²⁷ However, recommendations to administer epinephrine before symptoms in a community setting is controversial. The art of anaphylaxis treatment requires risk assessment and individualization, and some physicians do not agree that IM epinephrine should be used for expected or anticipated symptoms in a community setting.

A discussion of risk should occur, incorporating such factors as route of allergen exposure (eg, insect sting or allergen immunotherapy injection vs food ingestion), comorbidities that increase risk (eg, asthma or underlying heart disease), anaphylaxis history including severity and pace of development, likelihood of allergen exposure (eg, known ingestion vs eating a food that “may contain” allergen), access to emergency health care, patient and family anxiety level, and baseline tryptase. The recommended timing of epinephrine administration varies based on these variables and not on a universal, one-size-fits-all approach. For example, most physicians would agree that a subject who receives an IM injection of penicillin and develops generalized urticaria and erythema within 5 minutes should receive epinephrine. Likewise, so too with peanut ingestion in an individual with peanut allergy. However, not everyone agrees when to give epinephrine to an individual with peanut allergy who presents with nausea and vomiting. Another example is a Boy Scout on the Appalachian Trail who receives an *Hymenoptera* insect sting and 1 hour later has the onset of generalized urticaria. A fourth example is an individual who has a past history of anaphylaxis secondary to peanut ingestion. He or she is at a summer camp and inadvertently ingests a cookie that contains peanuts. The prophylactic administration of epinephrine in this case in the authors’ opinion, is warranted. Each case is different, and this often leads to confusion as to whether epinephrine should or should not be given at the onset of the first symptoms and signs of SAR and anaphylaxis.

Therefore, the authors believe that epinephrine should be given at the first symptoms or signs of any SAR and anaphylaxis, in particular, those reactions that begin within an hour of an alleged administration of an allergen or suspected allergen. The quicker the onset of the reaction, the more potential it has to be serious.⁶ In such cases, it is absolutely necessary to administer epinephrine. The senior author tells his patients, when in doubt, administer epinephrine. He also informs them that epinephrine is safe and stops the reaction before it progresses beyond a WAO grade 1, 2, or 3 reaction, that is, anaphylaxis. He has each patient repeat three times, “Epinephrine is safe.” He also indicates that if the subject is not improving within several minutes, to administer the second dose of epinephrine.

The concept of when to administer epinephrine is further complicated by online resources from many different organizations with a wide variety of definitions of anaphylaxis and recommendations as to when to administer epinephrine. **Table 2** illustrates recommendations from 13 different organizations about the symptoms and signs of anaphylaxis and when to administer epinephrine. This information was derived from the patient-directed educational material on respective Web sites. Most of the organizations recommend epinephrine as soon as anaphylaxis is recognized, but the threshold and definition of anaphylaxis between them differ. For example, the Allergy

Table 2

Organization recommendations for the symptoms and signs of anaphylaxis and epinephrine administration

Organization	Symptoms and Signs of Anaphylaxis after an Exposure to an Allergen	When to Administer Epinephrine
Allergy & Asthma Network ²⁸	Symptoms typically involve more than 1 organ system of the body and can include: Skin: itching, redness, swelling, hives Mouth: itching, swelling of lips, tongue Stomach: vomiting, diarrhea, cramps Respiratory: shortness of breath, wheezing, coughing, chest pain, and/or tightness Heart: weak pulse, dizziness, faintness, cardiac arrest Headache, nasal congestion, watery eyes, sweating Confusion, feeling of impending doom Loss of consciousness	At the first symptom or sign of a reaction
Food Allergy Research & Education ²⁹	Severe symptoms: Lung: shortness of breath, wheezing, repetitive cough Heart: pale or bluish skin, faintness, weak pulse, dizziness Throat: tight or hoarse throat, trouble breathing or swallowing Mouth: significant swelling of the tongue or lips Skin: many hives over the body, widespread redness Gut: repetitive vomiting, severe diarrhea Other: feeling something bad is about to happen, anxiety, confusion Mild symptoms from more than 1 system area Nose: itchy or runny nose, sneezing Mouth: itchy mouth Skin: a few hives, mild itch Gut: mild nausea or discomfort	For any of the severe symptoms For mild symptoms from more than 1 system area

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Organization	Symptoms and Signs of Anaphylaxis after an Exposure to an Allergen	When to Administer Epinephrine
Allergy UK ³⁰	1 or more of the following: Airway: - Swollen tongue - Difficulty swallowing/ speaking - Throat tightness - Change in voice (hoarse or croaky sounds) Breathing: - Difficult or noisy breathing - Chest tightness - Persistent cough - Wheeze (whistling noise caused by a narrowed airway) Circulation: - Feeling dizzy or faint - Collapse - In babies and young children this may look like the sudden onset of paleness and floppiness - Loss of consciousness (unresponsive) May include symptoms of a mild to moderate allergic reaction including 1 or more of the following: - Rash/hives (red raised, itchy bumps) - Swelling of the lips, eyes, or face - Itchy or tingling mouth - Stomach pain, nausea, vomiting - In the case of sting or bites, localized swelling at sting site	Immediately when anaphylaxis is recognized; if in doubt, give it
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Organization	Symptoms and Signs of Anaphylaxis after an Exposure to an Allergen	When to Administer Epinephrine
European Academy of Allergy and Clinical Immunology – Patients ³¹	At least 2 body systems should simultaneously be involved: Skin: itching, urticaria, generalized redness or angioedema Respiratory system: acute rhinitis, asthma, or upper airway angioedema Digestive track: nausea, vomiting, stomach cramps, or diarrhea Cardiovascular system: palpitations, increased heart rate, or drop in blood pressure Other: dizziness, loss of consciousness, cardiac or respiratory arrest	If they have developed symptoms suggestive of anaphylaxis (always according to their personalized management action plan)
Asthma Allergy Foundation of America ³²	Symptoms usually involve more than 1 organ system (part of the body), such as the skin or mouth, the lungs, the heart, and the gut; some symptoms include: Skin rashes, itching, or hives Swelling of the lips, tongue, or throat Shortness of breath, trouble breathing, or wheezing (whistling sound during breathing) Dizziness and/or fainting Stomach pain, bloating, vomiting, or diarrhea Uterine cramps Feeling like something awful is about to happen	At the first sign of an anaphylactic reaction Otherwise it should be determined through discussions with a doctor for an allergy emergency care plan or anaphylaxis emergency action plan
The Mast Cell Disease Society ³³	Mouth: itching, swelling of lips and/or tongue Throat: itching, tightness, closure, hoarseness Skin: itching, hives, redness, swelling, flushing Gut: nausea, vomiting, diarrhea, cramps Lung: shortness of breath, cough, wheeze Heart: weak pulse, dizziness, passing out	Determined through an emergency plan with the primary mast cell physician

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Table 2 (continued)		
Organization	Symptoms and Signs of Anaphylaxis after an Exposure to an Allergen	When to Administer Epinephrine
Australian Society of Clinical Immunology and Allergy ³⁴	Abdominal pain, vomiting (these are signs of anaphylaxis for insect allergy) Difficult/noisy breathing Swelling of tongue Swelling/tightness in throat Wheeze or persistent cough Difficulty talking and/or hoarse voice Persistent dizziness or collapse Pale and floppy (young children)	For any of the symptoms listed or if someone with known asthma and allergy to food, insects, or medication has sudden breathing difficulty (including wheeze, persistent cough, or hoarse voice)
Food Allergy Canada ^{35,36}	Generally includes 2 or more of the following body systems: Skin: hives, swelling (face, lips, tongue), itching, warmth, redness Respiratory (breathing): coughing, wheezing, shortness of breath, chest pain/tightness, throat tightness, hoarse voice, nasal congestion or hay fever-like symptoms (runny itchy nose and watery eyes, sneezing), trouble swallowing Gastrointestinal (stomach): nausea, pain/cramps, vomiting, diarrhea Cardiovascular (heart): paler than normal skin color/blue color, weak pulse, passing out, dizziness or lightheadedness, shock Other: anxiety, sense of doom (the feeling that something bad is about to happen), headache, uterine cramps, metallic taste However, a drop in blood pressure without other symptoms may also indicate anaphylaxis	At the first sign of a known or suspected anaphylactic reaction

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Organization	Symptoms and Signs of Anaphylaxis after an Exposure to an Allergen	When to Administer Epinephrine
Global Allergy & Airways Patient Platform ³⁷	Skin reactions, including hives along with itching Flushed or pale skin A feeling of warmth The sensation of a lump in your throat Wheezing, shortness of breath, throat tightness, cough, hoarse voice, chest pain/tightness, trouble swallowing, itchy mouth/throat, nasal stuffiness/congestion A weak and rapid pulse Nausea, vomiting or diarrhea Dizziness Headache Anxiety Low blood pressure Loss of consciousness	During an anaphylactic attack
Anaphylaxis Campaign ³⁸	Any 1 or more of the following ABC symptoms: Airway: - Persistent cough - Vocal changes (hoarse voice) - Difficulty in swallowing - Swollen tongue Breathing: - Difficult or noisy breathing - Wheezing (like an asthma attack) Circulation/consciousness: - Feeling lightheaded or faint - Clammy skin - Confusion - Unresponsive/unconscious (caused by a drop in blood pressure) In addition to the ABC symptoms listed above, the following, less severe symptoms may occur: - Widespread flushing of the skin	The injection should be given as soon as any ABC symptoms of anaphylaxis are present; if in doubt, give it

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Table 2 (continued)		
Organization	Symptoms and Signs of Anaphylaxis after an Exposure to an Allergen	When to Administer Epinephrine
	Nettle rash (otherwise known as hives or urticaria) Swelling of the skin (known as angioedema) anywhere on the body (eg, lips, face) Abdominal pain, nausea, and vomiting	
Allergy Foundation of South Africa ³⁹	Can range from mild skin changes and swelling of the face to life-threatening lung and heart involvement Skin signs: flushing, redness, itching, hives, and local swelling especially of the face Abdominal symptoms: cramps, nausea, vomiting, and diarrhea Respiratory involvement: can cause swelling of the upper airways, such as the tongue, the back of the throat and the area of the voice box or larynx. This may start with a hoarse voice and a persistent dry cough and then progress to throat tightness causing difficulty breathing. The airways of the lung may be involved causing chest tightness and a wheezing noise. Heart and circulation: a sudden drop in blood pressure, irregular heartbeat, and general collapse	As soon as anaphylaxis occurs
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Organization	Symptoms and Signs of Anaphylaxis after an Exposure to an Allergen	When to Administer Epinephrine
Allergy and Immunology Awareness Program-Qatar ^{40,41}	Includes 2 or more of the following body systems: skin, respiratory, gastrointestinal and/or cardiovascular; however, low blood pressure alone (ie, cardiovascular system), in the absence of other symptoms, can also represent anaphylaxis Skin: hives, swelling (face, lips, tongue), itching, warmth, redness Respiratory (breathing): coughing, wheezing, shortness of breath, chest pain or tightness, throat tightness, hoarse voice, nasal congestion or hay fever-like symptoms (runny, itchy nose and watery eyes, sneezing), trouble swallowing Gastrointestinal (stomach): nausea, pain or cramps, vomiting, diarrhea Cardiovascular (heart): paler than normal skin color/blue color, weak pulse, passing out, dizziness or lightheadedness, shock Other: anxiety, sense of doom (the feeling that something bad is about to happen), headache, uterine cramps, metallic taste	It is recommended that epinephrine be given at the start of a known or suspected anaphylactic reaction

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Table 2 (continued)		
Organization	Symptoms and Signs of Anaphylaxis after an Exposure to an Allergen	When to Administer Epinephrine
American Academy of Pediatrics ⁴²	Shortness of breath, wheezing, or coughing Skin color is pale or has a bluish color Weak pulse Fainting or dizziness Tight or hoarse throat Trouble breathing or swallowing Swelling of lips or tongue that bother breathing Vomiting or diarrhea (if severe or combined with other symptoms) Many hives or redness over body Feeling of “doom,” confusion, altered consciousness, or agitation	After any of these severe symptoms Action plan after discussion with physician may include epinephrine being given for MILD symptoms after a sting or eating these foods if child has a history of a severe reaction

Derived and adapted from each respective organization’s public Web site, most of which are directed toward patients, as individually cited.

& Asthma Network recommends using epinephrine at the first symptoms and signs of SAR and anaphylaxis.²⁸ However, the Food Allergy Research & Education recommends administering it for severe symptoms or mild symptoms from more than one organ system.²⁹ Allergy UK recommends it as soon as anaphylaxis is recognized, but describes anaphylaxis as severe symptoms involving airway, breathing, and circulation.³⁰ A fourth example is the European Academy of Allergy and Clinical Immunology–Patient site, which recommends administering it at symptoms suggestive of anaphylaxis, but further goes to clarify that it should always be according to their personalized management action plan.³¹ The recommendations of the other organizations fall within a spectrum of these four examples.

In summary, using the modified WAO definition of SAR and anaphylaxis, the authors recommend that verbal and written instructions be given to the affected subject, parent, or caregiver and that they administer IM epinephrine at the appropriate doses at the first symptoms and signs of SAR and anaphylaxis as illustrated in [Table 1](#).

SUMMARY

IM epinephrine is the treatment of choice for SAR and anaphylaxis.^{2,3,16} It is safe when given in the appropriate doses and route.¹⁶ Severe adverse reactions are extremely unusual and occur most commonly with inappropriate intravenous administration.¹⁶ Its early administration can prevent progression of SAR to anaphylaxis and thereby avoid the serious problems of hypotension, respiratory difficulties, and ultimately a fatal reaction.⁴ Despite its safety and efficacy, its underuse continues to be a major problem among affected subjects, parents, and caregivers and physicians and other health care professionals.^{3,14} The modified WAO definition of SAR and anaphylaxis is an excellent way to guide its early and appropriate administration. The

recommendation of the authors is to instruct subjects to administer IM epinephrine at the first symptoms and signs of any grades 1 to 5 SAR and anaphylaxis. It is also appropriate to educate the affected individual or parent or caregiver on its use and instructions as to when and how it should be administered at least on a yearly basis.

CLINICS CARE POINTS

- IM epinephrine is extremely safe at the recommended doses.
- Early administration of IM epinephrine in the treatment of any symptoms and signs of SAR or anaphylaxis is critical to prevent progression to a more serious reaction and death.
- Subjects, parents, and caregivers should be provided with clear verbal and written instructions as to how and when to administer IM epinephrine at the first symptoms and signs of SAR and anaphylaxis.
- Subjects, parents, and caregivers should have the educational process of when and how to administer epinephrine repeated at least yearly.

DISCLOSURE

Dr J.C. Collie has nothing to disclose. Dr R.F. Lockey is a consultant for ARS Pharmaceuticals, Inc.

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