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Review

The role of epinephrine in anaphylaxis at all stages of management in pediatric populations

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Abstract: Anaphylaxis is a severe and generalized form of hypersensitivity or allergic reaction. It can be life-threatening and requires rapid management. Cases of anaphylaxis are growing worldwide. The first line treatment in anaphylaxis is epinephrine. However, despite guidelines emphasizing the importance of this drug, studies show that use of epinephrine in anaphylaxis is suboptimal. In this article we describe the practical approach to recognizing and managing anaphylaxis in various settings.

Keywords: anaphylaxis; epinephrine; adrenaline; emergency treatment; emergencies; critical care; life support care

1. Anaphylaxis

Anaphylaxis is a severe and generalized form of hypersensitivity or allergic reaction, most commonly caused by an IgE-mediated hypersensitivity reaction after allergen exposure. In this mechanism the allergen-specific IgE/high-affinity receptor (FcεRI) on effector cells (mast and basophils) interacts with an allergen and leads to increased mediator synthesis, responsible for the symptoms [1,2]. Other mechanisms may also lead to anaphylactic reactions. These involve non-IgE-mediated pathways resulting in activation ofthe complement system (anaphylatoxins, C3a, and C5a), contact and coagulation system activation, or immunoglobulin G (IgG)-mediated anaphylaxis [2]. Rarely, a reaction may occur with no known triggers and those cases will be classified as idiopathic [2].

1.1. Clinical features of anaphylaxis

The definition of what constitutes anaphylaxis slightly varies amongst different sources. According to most recent guidelines, published in World Allergy Organizational Journal, the clinical diagnosis is highly likely when either of the following clinical criteria are met:

1. Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   With at least one of the following:
   a. Respiratory compromise (dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (hypotonia, syncope, incontinence)
   c. Severe gastrointestinal symptoms (severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens
2. Acute onset of hypotension or bronchospasm or laryngeal involvement after exposure to a known or highly probable allergen for that patient, even in the absence of typical skin involvement [1]

It is worth noting that disorders such as acute asthma, acute generalized urticaria, aspiration of a foreign body such as a peanut, vasovagal episode, and anxiety or panic attacks can present similar symptoms [1,2]. Furthermore, it has been noted that there are age-related differences in the clinical presentation of anaphylaxis [3].

There are many known causes of anaphylaxis. The most common triggers include food, drugs and insect venom [1,2]. In the pediatric population, food is the most frequent cause [4]. These act as allergens and exposure may result in pathways leading to the clinical features of anaphylaxis. Additionally, certain age- related co-factors and individual comorbidities may increase the severity of reaction [4,5].

Many studies have observed that cases of anaphylaxis have been increasing in the past years. Some studies also noted an increase in cases of anaphylaxis requiring hospitalization due to symptom severity [6,7]. Because of the unstable nature of this disease, all patients with anaphylaxis, or symptoms which are likely to progress to anaphylaxis, require immediate examination and treatment [1,2,8].

2. Epinephrine

The first line treatment in anaphylaxis is epinephrine [8]. This is a drug with vasoconstrictor effects, which help prevent upper airway mucosal edema, hypotension, and shock [9]. It also has important bronchodilator effects, cardiac inotropic and chronotropic effects [9]. By these actions it helps prevent progression of life-threatening anaphylaxis [2,9]. Studies show that early administration of epinephrine is associated with better outcomes: less intensive care unit and in-hospital admissions [10]. The method of choice is injection of intramuscular (IM) epinephrine into the antero-lateral thigh (vastus lateralis). There are no absolute contraindications preventing the use of this drug in the setting of anaphylaxis [1,2,8]. This method has a relatively safe profile in the pediatric population with low rates of serious adverse effects [11].

Some transient pharmacologic effects such as pallor, tremor, anxiety, palpitations, headache, and dizziness occur within minutes after epinephrine injection [9]. Rarely, serious adverse effects such as pulmonary edema or hypertension may occur, usually this is due to overdose [9,11].

The article will address the role of epinephrine at all stages of pediatric anaphylaxis management: pre-hospital, hospital, and post-hospital. We will mention a brief outline of gaps in the usage of the drug in clinical practice will be mentioned as well as suggestions on how to improve them.

3. Anaphylaxis—what to do?

3.1. Pre-hospital

Anaphylaxis most often occurs in non-healthcare settings, with bystanders frequently becoming the first responders. Epinephrine should be provided early on; delayed administration has been associated with an increased risk of hospitalization and severity of complications [1,12,13]. The initial treatment of anaphylaxis should consist of prompt injection of IM epinephrine in the mid-outer thigh (vastus lateralis muscle) in appropriately selected pre-set doses [1,2,8]. Commercially, epinephrine used in the pediatric population is often available in the form of prescription autoinjectors (EA) in the forms of 0.15 mg (recommended for those weighing 15–30 kg), 0.30 mg (for those weighing over 30 kg) or 0.5 mg (for adults and adolescents weighing over 60 kg) [1,2,14]. There may be some variation in the cut-off of these values in different areas, therefore it is worth consulting local guidelines. The 0.5 mg dose is available in Europe, although some devices recalled from the market, and since recently, Canada. Patients should be monitored, and doses should be repeated every 5–15 minutes if symptoms do not improve [1,2,8].

The pre-set dosages present with some of their own issues, as they are not appropriate for infants or children weighing between 7.5 kg to 15 kg. In the past, such cases were recommended to be treated with the smaller dosage of 0.15 mg [1,2,8]. Recently, in the United States, an EA with doses of 0.1 mg has been approved [15]. Thus, it is recommended to use it in appropriate cases when available. However, it is important to remember that in cases of anaphylaxis the use of epinephrine is always recommended regardless of age and weight as the life saving potential outweighs any side effects.

After an episode of anaphylaxis, the patient should receive a prescription for EA, when appropriate, along with instructions on how and when to use the medication [1,8]. Since many cases of anaphylaxis are subsequent events after trigger re-exposure, patients will often be carrying a prescribed epinephrine autoinjector already. In such cases, bystanders should inject the medication as soon as possible. A good practice is to carry an anaphylaxis action plan, with clear steps explaining how to proceed that can easily be understood by individuals who do not have much exposure with such situations [1,8].

However, in many cases, the emergency medical services will act as the first responders. In the pre-hospital setting, the first line management remains the same, as outlined above. This method of treatment is recommended for all ages. When presented in this form, it can be life saving and well tolerated.

3.2. Anaphylaxis in the Emergency Department

Anaphylaxis may also occur in the healthcare setting where the management slightly changes. According to guidelines, the first line treatment in the emergency department remains IM epinephrine [1,8]. However, the method of epinephrine dosing changes. If the patient is managed in this setting, the dosage of the drug should be calculated individually per weight. The dose recommended for use by healthcare professionals is 0.01 mg/kg of body weight, to a maximum total dose of 0.5 mg in children over 12 years old [1,8]. In children younger than that age, the dose should be calculated based on patient age, according to the following [1]:

1. In infants under 10 kg: 0.01 mg/kg
2. Children, 1–5 years: 0.15 mg
3. Children, 6–12 years: 0.3 mg

Dosing should be repeated every 5–15 minutes [1], if symptoms stay refractory to treatment. There is also an option of providing epinephrine by the intravenous route. However, this increases the risk of adverse effects such as fatal arrythmias [1,2]. If such treatment is required, it is to be provided only by experienced personnel with careful monitoring [8]. The indications for the IV route are anaphylaxis refractory to IM epinephrine, shock or respiratory failure [1]. The dose and rate of infusion should be adjusted for severity of symptoms.

3.3. Anaphylaxis in the hospital

Anaphylaxis may also occur in an in-hospital ward setting when a consultation from an experienced specialist may not be immediately available. Examples of these situations may occur in rural centers or small non-emergency facilities. Studies show that despite guidelines, epinephrine use remains suboptimal [1,16,17]. Our recommendation for wards that manage anaphylaxis cases often, is to dose epinephrine based on patient weight. The wards who do not have as much experience in these cases may choose to use the approximated doses of 0.15 mg, 0.3 mg or 0.5 mg as appropriate by weight and age. Both these methods are correct according to guidelines and may allow to lower rates of personnel apprehension and hesitancy regarding using epinephrine.

3.4. Post-hospital

Epinephrine also has roles in the out-patient management and follow-up of anaphylaxis. This includes patient education on how to minimize and manage further reactions; they must be educated on proper EA usage before leaving the hospital. Patients should receive training on trigger avoidance, specialist (allergist) referrals and EA prescriptions and training [1,8]. The provided prescription should include more than one EA, and patients should be recommended to have at least two EA's available [1,8]. This should be emphasized to all patients, as studies show that when responding to anaphylaxis, using a second dose of epinephrine will be required in 16–32% of cases [2]. Patient education is crucial, as many of these reactions will occur outside of the hospital. In the pediatrics population it is important to include guardians in the planning as they will be the ones responding frequently. Additionally, they should be advised to discuss the child's condition and its required management with teachers or any other adult who spends a substantial amount of time with them. All

healthcare professionals should familiarize themselves with guidelines, as they should also feel comfortable when explaining this topic and with using epinephrine when responding to anaphylaxis.

3.5. Data on epinephrine use in anaphylaxis

Epinephrine is underused when treating anaphylaxis [18,19]. In a North Carolina based study, Cristiano et al., observed that epinephrine is frequently underused by emergency medical services in the pre-hospital management of pediatric anaphylaxis. They observed that those under the age of ten are especially susceptible [20]. Carrillo et al., determined that epinephrine was provided by California based emergency medical services to only half of the anaphylaxis cases in which a clinical diagnosis of the disease was made [21]. Many also noted underusing of epinephrine in the hospital setting. Such were Dubus et al., who noted that physicians practicing in France decided to use the drug only in most severe pediatric anaphylaxis cases [22]. As mentioned, all patients who have presented an anaphylactic event should receive EA prescriptions, wherever these are available, or appropriate alternative adrenaline (prefilled syringe or vial plus intramuscular needle) if EA are not available [1,2]. However, there is a tendency for physicians to under-prescribe epinephrine to patients diagnosed with anaphylaxis in the ED [2]. Another issue is patients not carrying the proper number of EA as recommended. In a study examining the availability of a second dose of epinephrine (in anaphylaxis) if needed, Song et al., stated that half of the studied population required further emergency response due to inability to access a second dose of epinephrine [23].

As mentioned earlier, delayed administration of epinephrine is associated with increased hospital admissions and complications [1,14]. This emphasizes the gap that needs to be addressed to avoid missed opportunities when life-saving epinephrine should be administered at all levels. There is a need for prompt patient education on symptoms and usage of EA. They also need to be educated on the importance of proper management adherence. We also suggest that healthcare professionals working in environments which are likely to be required to manage anaphylaxis also receive clear training on epinephrine use and dosages to lessen the hesitancy when providing the treatment. Clear indications on which dosages to use in which wards may help with this.

4. Conclusions

Epinephrine plays a crucial role in the management of anaphylaxis at all stages of care. It is the first line treatment in both the non-healthcare and in-hospital treatment. Data on suboptimal use of the drug in emergency cases shows that steps should be taken to ensure that it is applied in all necessary situations. In this article, we outlined the most crucial, not to be omitted aspects of managing pediatric anaphylaxis using epinephrine.

Conflict of interest

The authors declare no conflict of interest.

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