Diagnosis and management of anaphylaxis

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Abstract

Anaphylaxis is a severe systemic allergic reaction that is potentially fatal. It requires prompt recognition and immediate management. Anaphylaxis has a rapid onset with multiple organ–system involvement and is mostly caused by specific antigens in sensitized individuals. Reactions typically follow a uniphasic course, however, 20% will be biphasic in nature. The second phase usually occurs after an asymptomatic period of 1–8 hours, but there may be a 24-hour delay. Protracted anaphylaxis may persist beyond 24 hours. Concurrent β-blocker therapy may adversely affect the response to management. Epinephrine is the treatment of choice and should be administered immediately. Secondary measures include circulatory support, H1 and H2 antagonists, corticosteroids and, occasionally, bronchodilators. Post-treatment observation of these patients is necessary, and they should remain within ready access of emergency care for the following 48 hours.

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Diagnosis

Anaphylaxis represents a severe systemic allergic reaction. No universally accepted definition exists because anaphylaxis comprises a constellation of features. A good working definition, however, is that used by the Canadian Pediatric Surveillance Program,4 which defines anaphylaxis as “a severe allergic reaction to any stimulus, having sudden onset and.......

Box 1: Features of anaphylaxis

Neurologic
Dizziness, weakness, syncope, seizures

Ocular
Pruritus, conjunctival injection, lacrimation

Upper airway
Nasal congestion, sneezing, hoarseness, stridor, oropharyngeal or laryngeal edema, cough, obstruction

Lower airway
Dyspnea, bronchospasm, tachypnea, accessory muscle use, cyanosis, respiratory arrest

Cardiovascular
Tachycardia, hypotension, arrhythmias, myocardial ischemia/infarction, cardiac arrest

Skin
Flushing, erythema, pruritus, urticaria, angioedema, maculopapular rash

Gastrointestinal
Nausea, vomiting, abdominal pain, diarrhea

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generally lasting less than 24 hours, involving one or more body systems and producing one or more symptoms such as hives, flushing, itching, angioedema, stridor, wheezing, shortness of breath, vomiting, diarrhea, or shock."

**Clinical features**

Because anaphylaxis is a generalized reaction, a wide variety of clinical signs and symptoms may be observed (Box 1). Often, patients will describe an impending sense of death (*angor animi*). Infrequently, seizures have been reported during anaphylaxis. Death due to anaphylaxis usually occurs as a result of respiratory obstruction or cardiovascular collapse, or both. It is thought that there is a direct correlation between the immediacy of onset of symptoms after exposure to the triggering agent and the severity of the episode, with the more rapid the onset, the more severe the event. Any delay before the administration of epinephrine and a history of asthma are also significant risk factors for anaphylactic death.

Symptoms of anaphylaxis generally have their onset within minutes, but occasionally occur as late as 1 hour after exposure to the offending antigen. The signs and symptoms may follow a uniphasic course, with resolution of symptoms within hours of treatment, but about 20% of anaphylactic reactions will follow a biphasic course. Because the initial report by Stark and Sullivan described asymptomatic periods of 1–8 hours, this is the time frame often quoted in the medical literature, although some authors report a smaller window of 1–3 hours based on another case series. Recently, the mean time to onset of second-phase reactivity has been documented to be 10 hours. A number of cases have been documented of biphasic reactivity occurring as late as 24–38 hours after the initial manifestation of the anaphylactic reaction (Fig. 1). We have found that about one-third of the second-phase reactions were more severe than the initial reaction, one-third were similar and one-third were milder. Mortality from biphasic reactions is possible but is not adequately documented in the literature.

Currently, many authors recommend the administration of corticosteroids to prevent or minimize the second phase, as this has been demonstrated to be beneficial. However, there have also been several documented cases of patients who received corticosteroid therapy and yet went on to experience severe biphasic or protracted reactions. Thus, physicians must anticipate the occurrence of severe second-phase reactions, even when corticosteroids have been administered. Protracted anaphylaxis, which is frequently associated with profound hypotension and sometimes lasts longer than 24 hours, is minimally responsive to aggressive therapy, and has a poor prognosis.

**Differential diagnosis**

In practical terms, it is not necessary to differentiate between anaphylactic and anaphylactoid reactions at the time of patient presentation, as both respond to the same treatment, however, anaphylactic shock must be differentiated from other causes of circulatory collapse. The most common conditions that mimic anaphylaxis are vasovagal reactions, which are characterized by hypotension, pallor, bradycardia, weakness, nausea, vomiting and diaphoresis. Urticaria, pruritus, angioedema, tachyycardia and bronchospasm are not vasovagal responses.

Acute respiratory decompensation from severe asthma attacks, foreign body aspiration and pulmonary embolism can feature respiratory symptoms suggestive of anaphylaxis, but other characteristics (e.g., pruritis, urticaria, angioedema) are lacking. Hereditary angioedema, precipitated by nonspecific environmental, physiological and emotional stressors, usually presents with swelling of the lips, tongue, upper airway and other mucosal surfaces, as well as gastrointestinal symptoms such as cramping and diarrhea, but does not involve pruritis and urticaria. As this is an autosomal dominant condition, a family history of hereditary angioedema is usually present. Other conditions such as seizure disorders, myocardial infarction and/or arrhythmias may infrequently present initially with similarities to anaphylaxis, but are readily distinguished clinically. A full differential diagnosis is presented in Box 2.

**Management**

Anaphylaxis is a medical emergency that requires immediate treatment. The management of acute anaphylaxis
is summarized in Table 1. Parenteral epinephrine is the cornerstone of management. The dosage for adults is 0.3–0.5 mL of a 1:1000 dilution, and recent research has established the intramuscular route to be superior to the subcutaneous route. The dosage for children is 0.01 mL/kg, up to a maximum 0.3 mL of a 1:1000 dilution. Epinephrine can be re-injected every 5–15 minutes until there is resolution of the anaphylaxis or signs of hyperadrenalinism (including palpitations, tremor, uncomfortable apprehension and anxiety) occur. Intravenous epinephrine (1:10 000 dilution) should be administered only in severe hypotensive shock because of its potential for tachyarrhythmias. An adequate airway must be established and maintained, and supplemental oxygen given to all patients with anaphylactic reactions.

Other supplementary therapy for anaphylaxis includes the use of H1 and H2 antihistamines, for example, diphenhydramine, 25–50 mg intravenously, and ranitidine, 50 mg intravenously or 150 mg orally. Current recommendations are to administer these agents in combination, because H1 and H2 blockade is more effective than H1 blockade alone in preventing symptomatology of anaphylaxis in experimental models. Inhaled β2-agonists (e.g., salbutamol) are useful when bronchospasm is present. Corticosteroids (e.g., methylprednisolone, 125 mg intravenously, or prednisone, 50 mg orally; the intravenous route of administration is often used for more severe reactions) may help prevent or minimize second-phase reactions, but biphasic reactions are well documented in patients who received corticosteroids as part of their initial management. Hypotensive patients should receive intravenous fluid support with crystalloid or colloid, and severe cases may require vasopressor agents such as dopamine or high-dilution epinephrine (1:10 000). Individuals who use β-blockers (and possibly angiotensin-converting-enzyme inhibitors, although the evidence is incomplete) may not respond completely to epinephrine, in which case glucagon should be administered at a dose of 5–15 µg/min intravenously. Glucagon has inotropic, chronotropic and vasoactive effects that are independent of β-receptors, and it also causes endogenous catecholamine release. Considering the reported incomplete prophylactic coverage of corticosteroids and the acknowledged benefit of histamine blockade to prevent anaphylactoid reactions (i.e., to radiocontrast media), it is the standard practice in our unit to provide 4 days of regularly dosed prednisone and diphenhydramine upon discharge post anaphylaxis.

Finally, post-treatment observation of these patients is required, owing to the potential for a second phase of reactivity. Although most of these reactions will occur within 1–8 hours, prolonged asymptomatic windows of up to 25 and 38 hours have been reported. Observation in a monitored setting for 24 hours post anaphylaxis would be ideal, but is often not practical. We recommend that patients be discharged from the emergency department only with adequate supervision, and to environments with easy access to the emergency medical response system should symptoms recur. Following successful treatment of anaphylaxis, the patient should stay where he or she can call 911 with timely delivery to hospital for the next 48 hours.

### Table 1: Initial pharmacologic management of acute anaphylaxis

<table>
<thead>
<tr>
<th>Drug and route of administration</th>
<th>Frequency of administration</th>
<th>Dose (adult)</th>
<th>Dose (child)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine 1:1000, IM</td>
<td>Immediately, then every 5–15 min as needed*</td>
<td>0.3–0.5 mL</td>
<td>0.01 mL/kg (up to 0.3 mL)</td>
</tr>
<tr>
<td>Diphenhydramine, IV, IM or PO</td>
<td>Once patient’s condition is stabilized with epinephrine and fluids, then every 4–6 h as needed</td>
<td>25–50 mg</td>
<td>1.25 mg/kg</td>
</tr>
<tr>
<td>Ranitidine, IV or PO</td>
<td>Once patient’s condition is stabilized with epinephrine and fluids, then every 8 h as needed</td>
<td>50 mg IV or 150 mg PO</td>
<td>1.25 mg/kg IV or 2 mg/kg PO</td>
</tr>
<tr>
<td>Steroids: methylprednisolone, IV, or prednisone, PO</td>
<td>Once patient’s condition is stabilized with epinephrine and fluids, then every 6 h as needed</td>
<td>125 mg IV or 50 mg PO</td>
<td>1 mg/kg IV or 1 mg/kg PO</td>
</tr>
</tbody>
</table>

Note: IM = intramuscularly, IV = intravenously, PO = by mouth.

*Until resolution or signs of palpitation, tremor, uncomfortable apprehension and anxiety occur.
Prevention

The first essential step in the prevention of anaphylaxis is identification of the causative agent, if possible. Confirmation of the cause requires referral to an allergist for a skin prick test and, when deemed necessary, in-vitro assessment for the presence of specific IgE antibodies. Referral for skin prick testing is particularly important when no causative agent can be clearly identified by history or for bee or wasp stings, because confirmation of IgE-mediated reactivity is necessary to offer potentially curative immunotherapy (see Table 2).20-24 Specific management and preventive strategies by allergen are discussed in Table 2. In the case of drug or food allergy, not only must the offending substance be avoided, but the potential for cross-reactivity (e.g., cephalosporins in the case of penicillin allergy) must also be recognized.

Patients should be prescribed, and be instructed in the use of, self-injectable epinephrine (e.g., EpiPen). They should also obtain a MedicAlert bracelet or necklace. Subsequent reactions typically escalate in severity, but they may remain the same or even be diminished. If sufficient time elapses without contact with the triggering agent, a decrease in or loss of sensitivity occurs in a significant number of patients.6

Case revisited

The family doctor immediately assessed the patient’s condition, recognized anaphylactic reactivity and administered an adult self-injectable epinephrine device and an intramuscular injection of diphenhydramine, 50 mg. The patient began to feel better within 5–10 minutes of the epinephrine injection, and at 30 minutes claimed to feel “completely fine.” At her physician’s insistence, however, she was transported to the local hospital’s emergency department for further monitoring, where about 3 hours after initial resolution of symptoms, she noted whole-body urticaria and shortness of breath and had swelling of her lips and hands. She was given an additional injection of epinephrine at 1:1000 dilution, 0.3 mL intramuscularly, followed by ranitidine, 50 mg intravenously, and methylprednisolone, 125 mg intravenously. Her symptoms abated over the ensuing 30 minutes, and she was monitored for an additional 5 hours in the emergency department without further incident. She was discharged home with her mother with a prescription for self-injectable epinephrine and a referral back to her allergist for reassessment of her immunotherapy schedule, and was advised to remain in an area with ready access to the emergency response system for the next 48 hours.

Conclusion

Many cases of anaphylaxis, and especially the potential for second-phase reaction, are underrecognized and undertreated, with potentially life-threatening consequences. Immediate administration of epinephrine intramuscularly is often life saving, but repeated doses may be necessary in combination with other medications. Once recovered, patients must be monitored in some capacity for up to 48 hours.

This article has been peer reviewed.

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Contributors: Dr. Ellis was responsible for the literature search, review and appraisal. Dr. Day was responsible for critically revising the article for important intellectual content. Both authors were responsible for conceiving the article and gave final approval of the version to be published.

Table 2: Strategies to prevent or manage exposure to known allergens

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hymenoptera</td>
<td>Be alert when eating outdoors (wasps are attracted to food)</td>
</tr>
<tr>
<td></td>
<td>Wear shoes and long pants when in fields</td>
</tr>
<tr>
<td></td>
<td>Have nests or hives near to homes removed</td>
</tr>
<tr>
<td></td>
<td>Proven venom-sensitive patients should be offered specific immunotherapy</td>
</tr>
<tr>
<td>Latex</td>
<td>Avoid contact with all latex products</td>
</tr>
<tr>
<td></td>
<td>Surgical or dental procedures should be performed in latex-free areas</td>
</tr>
<tr>
<td></td>
<td>Foods with known crossreactivity to latex, such as kiwi, must be avoided</td>
</tr>
<tr>
<td>Penicillin</td>
<td>Desensitization protocols are available for penicillin-allergic patients</td>
</tr>
<tr>
<td></td>
<td>who have serious infections requiring penicillin or a derivative</td>
</tr>
<tr>
<td></td>
<td>Avoid use of cephalosporins, due to cross-reactivity</td>
</tr>
</tbody>
</table>

References


Supplementary reading

Related Web sites
- Anaphylaxis Canada: www.anaphylaxis.org
- Food Allergy & Anaphylaxis Network: www.foodallergy.org/anaphylaxis.html
- Canadian Society of Allergy and Clinical Immunology: http://csaci.medical.org

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A patient information sheet appears on page 312

Chers lecteurs et lectrices,
pourriez-vous nous accorder un moment?
Le sondage annuel auprès des lecteurs du JAMC débute le 22 septembre. En nous parlant un peu de vous et de ce que vous pensez du JAMC, vous nous aiderez à améliorer encore le journal. Pendant deux semaines, lorsque vous rendez visite au journal électronique, nous vous demanderons de passer une fois par la page du sondage. Nous espérons que vous accepterez de faire ce détour qui contribuera à nous garder sur la bonne voie.
Appendix

Questions and answers about anaphylaxis

An information sheet for patients

What is anaphylaxis?

Anaphylaxis is a severe allergic reaction that may affect your whole body, resulting in a profound sense of discomfort, and may involve an extensive rash, swelling and shortness of breath. It occurs soon after exposure to a specific allergen (the substance you are allergic to). Anaphylaxis is potentially fatal and thus requires immediate attention and treatment. It may subside quickly with treatment, or it may last 2–3 hours. It may also recur after you feel better, occasionally up to 24 hours later.

Who is most at risk?

People with previous anaphylactic reactions are most at risk of future reactivity. People with multiple allergies and/or a family history of food allergies and other allergies are at a slightly increased risk. Some people who develop anaphylaxis are allergic to just one substance, whereas others may react to a number of substances, especially within the same group (e.g., walnuts and pine nuts). People with asthma who develop anaphylaxis are at risk of having a more severe reaction.

What causes anaphylaxis?

Any substance has the potential to cause anaphylaxis, but the most common causes are insect stings (particularly wasps), foods (especially peanuts, tree nuts, shellfish and fish, milk and eggs), medications (particularly penicillin and other antibiotics) and latex. Exercise can produce anaphylaxis, and sometimes no obvious cause can be determined; this is referred to as “idiopathic anaphylaxis.”

How do I recognize if I’m having an anaphylactic reaction?

Symptoms may occur suddenly or come on gradually. Typically, one or more of the listed symptoms may occur and usually follow the same pattern each time, although the degree of severity may change:

- Itching/hives
- Shortness of breath
- Wheezing
- Flushing
- Swelling of your lips, tongue, face or throat
- Abdominal pain and vomiting
- Palpitations (the sensation of your heart beating fast)
- Dizziness/light-headedness
- Any feelings/symptoms that you experienced with your last reaction

Any one of these symptoms in isolation may not indicate anaphylaxis, but if multiple symptoms occur at the same time immediate treatment is required. Sometimes the cause of anaphylaxis is not clear, or you may be inadvertently exposed to the agent you react to. In these circumstances, early recognition of the signs and symptoms of anaphylaxis is essential.

How is anaphylaxis treated?

The best treatment for anaphylaxis is prevention. Avoidance of triggers is vital. Your doctor can give you specific advice about how to avoid the cause of your particular reaction. When anaphylaxis does occur, the most important medication is epinephrine, which is adrenaline. This can be given by paramedics or emergency department doctors, or administered by the patient or a family member using a self-injectable device, such as an EpiPen.

What is an EpiPen and how do I use it?

An EpiPen is a device that automatically administers the usual dose of epinephrine. The proper use of an EpiPen is shown below:

In addition, your physician or pharmacist can provide you with a demonstration and more information.

Do I need to watch for anything after I’ve been treated?

Even if you respond to the EpiPen, you should seek medical attention immediately, because you may need further treatment and monitoring. Sometimes the epinephrine may make you feel anxious or as if your heart is racing — this is a normal side effect of the medication. After you feel better, there is a possibility of a recurrence of some or all of your anaphylactic symptoms. This will usually happen in the first 10 hours after you get better, but it may sometimes occur as long as 24 hours after the first reaction. Thus, it is essential that you remain within close access of a hospital or the emergency response system (i.e., 911). MedicAlert bracelets or wallet cards are also often recommended to help communicate information about your serious allergies to caregivers and medical personnel (see www.medicalert.ca).