Anaphylaxis: Diagnosis and Management in the Rural Emergency Department

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Abstract

It is not uncommon for patients to present to a rural emergency department with one of the syndromes of anaphylaxis: urticaria, angioedema, and severe anaphylaxis. Therefore, it is important for the rural health care provider to be able to recognize these anaphylaxis syndromes and manage them appropriately. Urticaria and/or angioedema may present as isolated entities or may be combined with asthma and/or hypotension to produce severe anaphylaxis. The mainstays of treatment of urticaria are the H1 and H2 receptor anatagonists, most effective when given in combination intravenously. Acute angioedema may occur with or without urticaria and is treated with epinephrine. In severe anaphylaxis, urticaria and/or angioedema are accompanied by acute bronchospasm and or hypotension. Immediate therapy with parenteral epinephrine as well as rapid fluid resuscitation is critical for its successful management. Patients with angioedema or severe anaphylaxis should be given epinephrine auto-injectors prior to discharge. Follow-up with an allergist is recommended for most patients with anaphylaxis.

Introduction

A 16-year-old female was diagnosed as having acute cystitis. She was given sulfamethoxazole trimethaphan double strength one b.i.d. for three days. On the second day of therapy she presented to the emergency department with a generalized patchy erythematous, raised rash involving her neck, chest, back, abdomen, and all extremities. The rash was very pruritic.

A 35-year-old male had a history of lip and tongue swelling when eating peanuts. He was offered a cookie by his aunt who assured him that she had used no peanuts in its preparation. Within five minutes he developed swelling of his face, lips, and tongue. His aunt rushed him to the emergency department. Upon arrival in the emergency department his voice was very hoarse and he was beginning to develop inspiratory stridor.

A 23-year-old male IV drug abuser presented to the emergency department with an abscess on his left arm with surrounding cellulitis. He had a history of developing "hives" to some antibiotic, but he did not remember the name of the antibiotic. The abscess was incised and drained, and the patient given cefazolin 1 g IV and Bactrim DS 2 tablets orally. Ten minutes later he complained of diffuse itching, and his skin became very erythematous. The patient was wheezing, his blood pressure decreased from 130/82 to 70/30, and his pulse increased from 70 to 140 beats per minute.

These patients may all present to a rural emergency department, and all represent varying degrees of anaphylaxis: urticaria, angioedema, and severe anaphylaxis (with asthma and/or anaphylactic shock). Therefore, it is important that the rural health care provider understand their pathophysiology, clinical presentation, differential diagnosis, and management.

According to a multidisciplinary panel of experts who met in 2006, anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death. This same group published new diagnostic criteria for anaphylaxis.[1] This group established three criteria, each reflecting a different clinical presentation of anaphylaxis. They stated that anaphylaxis is very likely when any **one** of the following criteria is met:

Criterion 1 – Acute onset of an illness (over minutes to several hours) involving the skin, mucous membranes, or both (e.g., generalized urticaria, pruritis or flushing with swelling of the lips, tongue, or uvula) and at least one of the following:

a. Respiratory compromise (e.g., wheezing/bronchospasm, stridor, dyspnea, hypoxemia, and decreased peak expiratory flow)
b. Decreased blood pressure or associated symptoms of end-organ dysfunction (e.g., syncope, hypotonic collapse, incontinence)

Criterion 2 – **Two or more** of the following that occur rapidly after exposure to an allergen that is likely for that patient (may occur minutes to hours after allergen exposure):

a. Involvement of the skin and/or mucous membranes (e.g., generalized urticaria, flushing with pruritis, and swollen lips, tongue, uvula)
b. Respiratory compromise (e.g., wheezing/bronchospasm, stridor, dyspnea, hypoxemia, and decreased peak expiratory flow)
c. Decreased blood pressure or associated symptoms (syncope, hypotonia, collapse, incontinence)
d. Persistent gastrointestinal symptoms (e.g., vomiting, cramping, abdominal pain)

Criterion 3 – Decreased blood pressure after exposure of a known allergen for that patient (minutes to hours). Decreased blood pressure is defined in adults as a systolic BP of less than 90 mmHg or >30% decrease from that patient's baseline. In infants and children, decreased BP is defined as low systolic BP of less than 70 mmHg from one month up to one year; less than (70mmHg + [2 x age]} from one to ten years; less than 80 mmHg from 11 to 17 years.

The author disagrees with this definition of anaphylaxis for the following reasons: 1) This definition is much too restrictive. Some patients may present with generalized urticaria and go on to develop angioedema and/or severe anaphylaxis over minutes to hours. Other patients may present with generalized urticaria and never go on to develop the more serious syndromes that meet the expert panel's criteria for the diagnosis of "anaphylaxis." 2) It is more reasonable to consider all of the IgE-mediated syndromes (urticaria, angioedema, and severe anaphylaxis) as "anaphylaxis," even though some patients with urticaria and angioedema may not fulfill all the criteria for "anaphylaxis" recommended by the expert panel.

Therefore, this article will discuss the pathophysiology, clinical presentations, differential diagnosis, and management of all three syndromes of anaphylaxis: acute urticaria, acute angioedema, and severe anaphylaxis (asthma and/or hypotension [anaphylactic shock]). Emphasis will be on clinical presentations, differential diagnosis, and management, since these are the most important for the physician practicing in a rural environment.

ACUTE URTICARIA

Pathophysiology

Acute urticaria results from the release of histamine, bradykinin, leukotriene C4, and other vasoactive substances from mast cells and basophils in the dermis. These substances cause extravasation of fluid into the dermis that lead to the formation of the urticarial "wheal." The intense pruritis is caused by the histamine released into the dermis. Histamine is the ligand for two membrane-bound receptors, the H1 and H2 receptors. The activation of the H1 receptors on endothelial cells in the capillaries leads to increased capillary permeability and results in plasma leaking from the capillaries, resulting in the urticarial wheal. The activation of the H2 histamine receptors in the arterioles and venules leads to arteriolar and venule dilation, adding to the capillary leak and increasing the size of the urticarial wheal.[2]

There are several mechanisms causing this process. The so-called "Type 1" response is initiated by antigen-mediated IgE immune complexes that bind and cross-link Fc receptors on the surface of mast cells and basophils, thus causing degranulation and histamine release. This type of urticaria is the most common and may be caused by infections, insect stings, foods (particularly shellfish, eggs, nuts, berries, chocolate, cheeses, and tomatoes), drugs (NSAIDs, penicillins, sulfonamides, codeine, etc.), latex exposure, emotional stress, exercise, and pregnancy (e.g., pruritic urticarial papules and plaques of pregnancy [PUPPP]). The so-called "Type 2" response is mediated by cytotoxic T cells that cause deposits of immunoglobulins, fibrin, and complement around arterioles leading to urticarial vasculitis. The so-called "Type 3" response is caused by immune complexes than cause the urticaria and is seen in patients with systemic lupus erythematosis and other autoimmune diseases. The type 3 response is often chronic and recurrent. To date, no reliable tests exist to identify if these chronic urticarias are autoimmune or non-autoimmune in a specific patient.[3]

Complement-mediated urticarias include viral and bacterial infections, serum sickness, transfusion reactions, certain drug-mediated reactions (opioids, succinylcholine, vancomycin, and other drugs) as well as radiocontrast agents.

In the physical urticarias, some physical stimulus causes urticaria. These stimuli include immediate pressure urticaria, delayed pressure urticaria, cold urticarial, and cholinergic urticarial.[8] The remainder of this discussion will be limited to IgE-mediated acute urticaria, the least life-threatening of the anaphylaxis syndromes.

Clinical Presentation

Patients with urticaria (or "hives," the lay term for urticaria) have varying clinical presentations. Patients receiving opioids intravenously may have an urticarial eruption in the distribution of the vein proximal to the injection site. Patients with known allergens, who are exposed to these allergens, may pres-

ent with a diffuse urticarial rash covering almost their entire body associated with wheezing and tightness in the throat. The urticarial lesions are usually raised and intensely pruritic. They may present as multiple isolated lesions, or the lesions may become confluent, producing a very large "wheal." The lesions are usually intensely pruritic. Urticarial lesions that are painful are suggestive of urticarial vasculitis. Urticaria is diagnosed clinically, based on a detailed history and finding the classical urticarial wheals on physical examination.[4]

An attempt should be made to elicit signs and symptoms of a generalized allergic reaction. A history of a hoarse voice or throat tightness, nausea, vomiting, or crampy abdominal pain may suggest angioedema in addition to the urticarial.[5] Symptoms such as chest tightness, wheezing or difficulty breathing may suggest a more severe, generalized anaphylactic reaction. Symptoms such as lightheadedness with hypotension would also suggest a more severe anaphylactic reaction such as anaphylactic shock.[6]

Patients should be queried regarding a previous history of urticaria in the past as well as a history of systemic diseases, such as lupus erythematosus, that may be associated with urticaria. Also, a history of unusual food intake as well as recent drug exposure, use of new hair dyes, or insect stings should be sought out.

Physical examination should include looking for swelling of the lips, tongue, or uvula as well as careful auscultation of the lungs for wheezing. Also, the patient's vital signs should be taken immediately and, if the patient is hypotensive, large bore IVs as well as systemic epinephrine should be considered.[7]

Differential Diagnosis

There are several conditions that may mimic various features of urticaria. The presence or absence of pruritus may be used to narrow the differential diagnosis. Nonpruritic conditions that may mimic urticaria are viral exanthems, such as erythema infectiosum (fifth disease), measles, and the rash associated with Epstein-Barr viral infection. Also, Sweets syndrome is associated with a nonpruritic rash similar to urticaria.[8]

Pruritic conditions that may be confused with urticaria include contact dermatitis, atopic dermatitis, insect bites, erythema multiforme, toxic drug eruptions, and cutaneous small vessel vasculitis.[8,9]

Management

Urticaria Without Symptoms or Signs of Angioedema or Anaphylactic Shock

1. **H1 and H2 antihistamines**. If the urticaria is mild, oral therapy with the first generation (sedating) H1 antihistamines, such as diphenhydramine (Benadryl, etc.), chlorpheniramine (Chlor-Trimeton, etc.), and hydroxyzine (Vistaril, Atarax, etc.), or second generation ("non-sedating") H1 antihistamines, such as cetirizine (Zyrtec), levocetirizine (Xyzal), loratadine (Claritin, Tavist, etc.), and fexofenadine (Allegra), may resolve the urticarial.[10] However, if these oral drugs do not resolve the urticaria, giving diphenhydramine intravenously (12.5-25mg in adults) combined with an H2 antihistamine IV (ranitidine [Zantac] 50mg or famotidine [Pepcid] 20mg) has been demonstrated to be more effective in treating acute urticaria than the H1 antihistamines given IV alone.[11,12]
2. **Glucocorticoids**. Although probably not necessary in many cases of acute, non-vasculytic urticaria, these drugs have been shown to decrease itching and lead to a more rapid resolution of the urticaria than placebo, when used in combination with hydroxyzine.[13]
3. **Epinephrine**. There are no studies that show a benefit of epinephrine in acute urticaria that is not associated with angioedema or severe anaphylaxis with asthma and/or anaphylactic shock.

Urticaria With Symptoms of Angioedema and/or Asthma and/or Anaphylactic Shock

1. **With angioedema.** These patients should be treated with the combination of H1 and H2 antihistamines IV in addition to intramuscular epinephrine (0.3-0.5mg). The antihistamines alone are not effective in treating angioedema.[14]
2. **With asthma.** These patients probably have systemic anaphylaxis and should be given epinephrine 3-0.5 mg IM as well as albuterol nebulization in addition to the H1 and H2 antihistamines.
3. **With hypotension (anaphylactic shock).** These patients should be treated with very large volumes of crystalloid (NS) as well as an infusion of epinephrine IV (see severe anaphylaxis management below). If the urticaria does not respond to the epinephrine, intravenous H1 and H2 blockers may be employed (see management of severe anaphylaxis management below).

Disposition and Follow-up

1. If the patient has only acute urticaria and responds to therapy with H1 and H2 blockers (cessation of itching and the urticarial wheals should have become less intensely erythematous, but may still be present), they should be observed for 30-60 minutes. If they remain pruritis free and the wheals have not reappeared or become more erythematous, they may be discharged on a regimen of H1 and H2 blockers orally (hydroxizine 50 mg q 6 hours for 24 hours and then q 6 hours prn itching with ranitidine 150 mg bid for 24 hours prn itching. Although recommended by some authors, the H2 blockers have not been demonstrated to add to the effect of the H1 blockers when given orally, although

randomized controlled trials have not been published. Also, because of the results of a single trial, many "experts" recommend giving prednisone orally in a tapering daily dose of 40-40-20-20-10-10mg and off.[13]

2. If the patient has angioedema in addition to the urticaria, particularly if it involves the larynx, the patient should be observed for two to four hours to be certain that the angioedema does not recur and, if discharged, treated as above for urticaria plus the patient should be given two epinephrine auto-injectors or their equivalent to take home with them and told to use them should they become hoarse. Another option would be to admit the patient to the hospital under observation status, although this is not necessary if the patient has isolated urticaria/angioedema that has completely resolved with antihistamine and epinephrine therapy.[14]
3. If the patient has urticaria plus severe anaphylaxis (asthma, hypotension, etc.), the patient should be admitted to a monitored unit (an ICU, if available) because of the possibility of biphasic anaphylaxis (see below).
4. If discharged, the patient should follow up with their primary care provider within one week. The primary care provider may elect to refer the patient to an allergist for further work-up to determine if the patient has allergens that could have precipitated the urticaria.

Angioedema

Pathophysiology

Angioedema is a localized subcutaneous or submucosal swelling resulting from extavasation of fluids into interstitial tissues. Angioedema, like urticaria, may occur in isolation or may be accompanied by urticaria, asthma, or anaphylactic shock. Angioedema may be thought of as urticaria of deeper tissues, rather than involving the dermis and epidermis. Much of the pathophysiology of urticaria also applies to angioedema. Exposure of the vasculature to inflammatory mediators causes venule dilation and increased permeability of capillaries. Angioedema results from loss of vascular integrity allowing intravascular fluids to extravasate locally into the skin and subcutaneous tissues, especially the mucous membranes.

The known causes of angioedema can be divided into three groups, depending upon the underlying mechanism:

1. Mast cell-mediated etiologies in which angioedema results from release of mast cell mediators that increase vascular permeability. Mast cell-mediated angioedema is associated with urticaria and or pruritus in most cases.[15]
2. Bradykinin-mediated etiologies in which angioedema results from the generation of bradykinin and complement-arrived mediators that increase vascular permeability. This form of angioedema may be caused by ACE-inhibitors and is not associated with urticaria and or pruritus and is treated differently than the IgE-mediated angioedema.[16]
3. Etiologies of unknown mechanism.

Mast cell-mediated etiologies are similar to those of urticaria. Activated mast cells release inflammatory mediators, including histamine, heparin, leukotriene C4, and prostaglandin D2, which causes dilation of the venules in the dermis and enhance capillary permeability, with resultant tissue edema. One of the mast cell-mediated etiologies is allergic reactions. Acute angioedema, with or without other symptoms of allergic reactions may be triggered by drugs, latex, foods, exercise, insect stings, etc. Angioedema resulting from allergic reaction is usually accompanied by other signs and symptoms, including urticaria, pruritus, flushing, throat tightness, bronchospasm, and hypotension. However, allergic angioedema may occur in isolation, although this is uncommon.[15] Angioedema may also be due to direct release by mast cells of inflammatory mediators by certain medications such as opioids and radiocontrast media. This type of angioedema is accompanied by urticaria in most cases. IgE is not involved, and skin testing or in vitro testing is not helpful in identifying a cause. Nonsteroidal anti-inflammatory drugs, such as aspirin and ibuprofen, may cause acute urticaria/angioedema. This adverse effect of NSAIDs is believed to be due to the pharmacologic properties of the medications on mast cells. NSAID administration results in increased formation of inflammatory mediators, leading to angioedema in some individuals. Patients who have developed acute angioedema to COX 1 and COX 2 inhibitors (ibuprofen, naproxen, aspirin, etc.) usually can be given a COX 2 inhibitor (celecoxib, etc.) without the patient developing angioedema.[17]

Other non-allergic causes of angioedema include angiotensin II receptor blockers that may cause angioedema by a non-bradykinin mechanism.[18] Other drugs have been demonstrated to cause angioedema by a non-IgE mediated mechanism. Finally, there is hereditary and acquired angioedema, neither of which is IgE mediated. These non-allergic angioedemas are beyond the scope of this discussion and can be read about elsewhere.[19, 20]

Clinical Presentation

Mast cell-mediated angioedema usually begins with ten minutes of exposure to the allergen and builds over a few hours, then resolves in 24-48 hours. The most commonly affected areas are the mucous membranes with swelling of the lips, tongue, and uvula. Angioedema of the larynx may develop rapidly (over minutes) or more slowly over several hours. The first symptom that patients experience is usually hoarseness followed by throat tightness and difficulty swallowing. The patient may present with severe stridor, which indicates marked swelling of the laryngeal tissues and warrants immediate therapy (see below). Angioedema may affect the wall of the GI tract and often presents as colicky abdominal pain, sometimes accompanied by nausea, vomiting, and/or diarrhea. Angioedema is usually a benign condition but may be life-threatening if it

involves the larynx or other upper airway structures in which the patient presents with symptoms of upper airway obstruction or if it is associated with severe anaphylaxis (e.g., asthma and/or hypotension).

Differential Diagnosis

Cutaneous or mucosal swelling that can mimic angioedema may result from contact dermatitis, cellulitis, autoimmune disease, superior vena cava syndrome, blepharochalasis (causing eyelid edema), some parasitic infections, hypothyroidism, idiopathic edema, and some rare disorders. Laryngeal edema may be mimicked by infectious laryngitis (usually viral), parapharyngeal abscess or neoplasm, severe tonsillitis, peritonsillar cellulitis or abscess, and pharyngeal/laryngeal foreign bodies. Angioedema of the gut may be mimicked by inflammatory bowel disease (especially Chrohn's ileitis or colitis), acute bacterial ileitis (Campylobacter, Yersinia infections), mesenteric ischia or infarction, intramural hemorrhage, vasculitis inflammatory disorders near the bowel wall, and many others.[21]

Management

Management of isolated, "benign" allergic angioedema affecting only the skin, lips, or minimal swelling of the tongue with or without acute urticaria is the same as management of acute urticaria, e.g., H1 and H2 antihistamines given orally or IV and glucocorticoids (see management of acute allergic urticaria above).

Management of laryngeal edema or severe angioedema of the tongue, uvula, or soft palate requires immediate assessment for signs of airway obstruction. If the patient is only hoarse and there is only minimal swelling of the other upper airway structures, the patient should be placed in a critical care room with emergency airway management equipment immediately available. An IV should be started and the patient placed on high flow oxygen. As soon as possible, the patient should be given 0.3-0.5 mg of epinephrine intramuscularly (in children 0.01 mg/kg to a maximum of 0.5 mg). The patient should also be given diphenhydramine 25 mg IV, ranitidine 50mg IV, as well as intravenous corticosteroids, such as 125 mg of methylprednisolone (Solumedrol). However, none of these agents has been shown to reverse allergic angioedema-induced airway obstruction without the concomitant use of epinephrine.[7] Usually the epinephrine will start working within 10-15 minutes, and the patient's symptoms will improve. However, if there has been no improvement within 15 minutes, and the patient's airway status has not deteriorated, another dose of 0.3-0.5 mg IM should be administered. This therapy is indicated even if the patient has a history of coronary artery disease. Most patients will respond to this therapy. Should the patient's airway status deteriorate after epinephrine administration, particularly if the patient becomes stridorous, immediate rapid sequence orotracheal intubation (RSI) should be accomplished. **The orotracheal intubation should be attempted by the most experienced operator available.** In the rural setting, this may be the nurse anesthetist or anesthesiologist, if available.[6,7]

If the tongue and posterior pharynx or the laryngeal structures themselves are markedly swollen, orotracheal intubation may be very difficult, and, if unsuccessful, a surgical airway (emergency cricothyroidotomy) should be attempted. An otolaryngologist or experienced general surgeon should be standing by (if available) to assist with the cricothyroidotomy or, if this is not successful in obtaining an airway, perform a tracheostomy. **The surgical airway should be attempted by the most experienced operator available.**[6,7]

If the patient is stridorous on presentation, the epinephrine and, time permitting, the other drugs noted above should be administered, but, unless there is immediate (less than 10-15 minutes) dramatic improvement in the stridor, emergent RSI should be performed with setup for an emergent surgical airway if needed.

Disposition and Follow-up

The disposition and follow-up depends upon the severity and location of the angioedema and the response to therapy to epinephrine and antihistamines. If the angioedema does not involve the tongue, uvula, soft palate, larynx, or GI tract, the patient should be observed for a period of one to two hours after resolution of the angioedema. If the angioedema involves the above structures, and the edema has resolved with therapy, the patient should be watched for at least four hours, either in the ED, an observation unit, or in the hospital, admitted under "observational status." It is unusual for the angioedema to recur following complete resolution of symptoms and signs, but it is possible – similar to patients with biphasic anaphylaxis (see below). If the angioedema involves these structures and has not resolved, it is probably advisable to admit the patient either as an inpatient or under observational status. When the patient is discharged, they should be given two epinephrine auto-injectors and given instructions on their use should the angioedema recur, as well as printed materials regarding angioedema and its treatment. They should have follow-up arranged with their primary care physician or an allergist.[22]

SEVERE ANAPHYLAXIS (Urticaria and/or Angioedema with Bronchospasm and/or Hypotension)

Pathophysiology

Severe anaphylaxis may be immunologic, e.g., IgE-mediated reactions or immune complex/ complement-mediated anaphylaxis, versus nonimmunologic anaphylaxis, e.g., caused by agents that cause sudden mast cell or basophil degranulation in the absence of immunoglobins. Mast cells and basophils release mediators such as histamine that act on the H1 and H2 receptors to cause a generalized capillary leak of plasma into the interstitial tissues as well as a reduction in venous tone, leading to hypovolemic shock. Stimulation of these receptors by

histamine may also lead to depressed myocardial function and bronchospasm, contributing to the shock and resulting in respiratory failure.[23] These more severe effects may be combined with urticaria and/or angioedema. Autopsy findings in fatal anaphylaxis may not reveal any specific pathology, since many of these patients die very rapidly (within one hour in 39 of 56 cases of fatal anaphylaxis in one study). Findings at autopsy include mucous plugging and hyperinflation of the lungs, laryngeal and/or pharyngeal edema, petechial hemorrhages in the bronchi and cerebral edema. The "empty ventricle syndrome" resulting from inadequate right ventricular filling may occur in patients who have significant hypotension and may lead to pulseless electrical activity (PEA). Therefore, the patient with severe anaphylaxis should always be placed in the supine position as soon as possible.[24]

Clinical Presentation

Severe anaphylaxis has many clinical presentations, varying from mild-to-moderate asthma to rapid development of profound shock in less than 15 minutes after exposure to the allergen. The patient may exhibit urticaria and/or angioedema, although most cases of fatal anaphylaxis do not have these findings at autopsy. They often appear flushed, with generalized erythema. The patient usually presents with a combination of bronchospasm and hypotension, although they may have only one or the other. Patients with fatal anaphylaxis usually present with profound anaphylactic shock, with either PEA or occasionally bradycardia and/or very severe bronchospasm. Occasionally, the patient may initially have either urticaria or angioedema for one to three hours and then rapidly progress to severe asthma and/or severe hypotension. The most common causes of death are cardiovascular collapse or asphyxia. Ten to twenty percent of patients with severe anaphylaxis may develop biphasic anaphylaxis, a recurrence of symptoms following an asymptomatic period lasting from one to thirty hours. Although the recurrent episode is usually less severe than the initial, the second phase may be even more severe.[16]

Differential Diagnosis

Conditions that may mimic severe anaphylaxis include acute asthma exacerbation, other causes of respiratory distress (choking from foreign body aspiration), vasodepressor (vasovagal) syncope, anxiety disorder, acute isolated severe urticaria, acute isolated angioedema, vocal cord dysfunction, administration of medication causing flushing (e.g., niacin, levodopa, vancomycin, etc.), other causes of shock (myocardial infarction with cardiogenic shock, septic shock, etc.), CVAs, carcinoid tumors, mastocytosis, capillary leak syndrome, scombroid poisoning, and others.[26]

Unfortunately, severe anaphylaxis does not always present with the classic findings of a combination of flushing or urticaria/angioedema associated with bronchospasm and hypotension. Thus, treatment may be delayed in some patients, with occasionally fatal consequences.

Management

Initial Assessment and Management

As with any patient with a potentially fatal disease, patients with suspected severe anaphylaxis should immediately have an assessment of their airway, breathing, and circulation. Occasionally, patients may present with generalized erythema with no pulse and with apnea. These patients should be immediately orotracheally intubated and ventilated and have an ECG monitor and two large bore (16 gauge or larger) IVs started (if not already intubated and resuscitation begun by prehospital personnel). They should have initial CPR, and the ACLS protocols should be followed, depending upon their cardiac rhythm. These patients should all be given epinephrine 1 mg V.

However, most patients with severe anaphylaxis are not in such extremis. They usually present with urticaria and/or angioedema with asthma and/or hypotension. These patients also require evaluation of their ABCs as well as an evaluation of their skin and mucous membranes, and a blood pressure should be obtained immediately. The patient should be placed in the supine position, given supplemental oxygen (6-8 liters via face mask) and two large bore IVs started (usually antecubital). The cardiac rhythm and pulse oximetery should be continuously monitored and their BP and respiratory rate monitored at least every five minutes. If these patients have severe asthma but have systolic blood pressures above 90 mmHg, they should be given 0.5 mg of 1:1,000 epinephrine IM into the mid-anterolateral thigh (adults) or .01 mg/kg IM to a maximum of 0.5 mg in infants and children.[28] Epinephrine should always be given IM rather than subcutaneously because its absorption is more rapid and predictable.[29] These patients should have NS running at 200-300 cc/hr, unless they have a history of congestive heart failure and/or renal failure, in which case the NS infusion rate should be no more than 150cc/hr.

If the patient is hypotensive (<90 mmHg in adults), they should be given the NS wide open in both large bore IVs and, if their systolic BP is <70 mm/Hg, blood pressure cuffs should be placed around the NS bags and inflated to >250 mmHg to infuse the NS as rapidly as possible. These patients should receive the epinephrine IV rather than IM. Most authorities recommend giving the epinephrine by intravenous infusion.[28] In adults, begin the IV infusion at 2 mcg/min, with titration upward if the patient continues to be hypotensive despite massive infusion of NS after 10-15 minutes. Children should receive 0.2 mcg/kg/min with titration upward if there is no response in blood pressure after 10-15 minutes. Adults should receive 1-2 liters of NS in the first 10-15 minutes, with continued high volume infusion if the blood pressure does not increase above 90 mmHg after the first two liters and continuation of the epinephrine infusion. Although the epinephrine may be given by IV boluses of 0.1 mg, errors in dosing (the patient receiving 1 mg, rather than 0.1 mg IV) have resulted in death. If given in IV boluses, epinephrine should always be given utilizing the 10 cc 1:10,000 syringes, giving no more than 1cc boluses.[30]

Some patients may require up to 10 liters of NS on the first one to three hours because of the massive fluid shifts from the intravascular to the extravascular spaces in severe anaphylactic shock. Children should be given NS boluses of 20 cc/kg until they are no longer hypotensive.

Again, patients with CHF and/or renal failure should be closely monitored for fluid overload. Although there may be a reluctance to use epinephrine in patients with known CAD, those receiving monoamine oxidase inhibitors, those receiving stimulant medications (cocaine, methamphetamines, etc.), and those with known aortic aneurysms or recent intracranial surgery, the benefits of epinephrine outweigh the risks in severe anaphylaxis, even in these high risk patients.[28] If the patient is on beta blocker medications, they may be refractory to epinephrine in severe anaphylaxis. If so, glucagon should be administered in doses of 2-4 mg IV in adults and 20-30 mcg/kg to a maximum of 1 mg in children. The drug should be given by slow IV infusion (over five minutes) because rapid infusion may cause vomiting.[31] If the patient is refractory to intravenous epinephrine, vasopressin (100 units in 500 cc D5W, with a dose of 0.04 units per minute or administration of a slow bolus of two units over five minutes, titrating upward to eight units) has been shown to benefit some patients with severe anaphylaxis that is refractory to epinephrine.[32]

Adjunctive therapy in severe anaphylaxis includes H1 antihistamines, H2 antihistamines, inhaled beta2 agonist bronchodilators, such as albuterol (if the bronchospasm is not relieved with epinephrine), and glucocorticoids. However, there is no good evidence that these adjunctive medications provide any additional benefit to the use of epinephrine in patients with severe anaphylaxis.[33, 34, 35]

Most patients with severe anaphylaxis will respond relatively quickly (within 15-30 minutes) to aggressive therapy with IM epinephrine in those without hypotension and to IV epinephrine and large quantities of IV NS in those with even severe hypotension.[64] However, if the patient persists with hypotension and/or severe bronchospasm, they should be admitted to an ICU, either at the treating hospital or transferred to an ICU at the closest facility via paramedic and/or nurse transport, in order to provide airway support and if continued IV epinephrine is required. Often, they will require aeromedical transport if the treating hospital is in a rural area with few resources. Some authorities recommend transferring the patient from a small hospital with few resources to either an ICU or monitored bed at a major hospital, even if the patient is normotensive and has little bronchospasm because of the concern of the patient developing biphasic anaphylaxis (see below).

Disposition and Follow-up

Currently, there is no consensus regarding the optimum observation period following successful treatment for severe anaphylaxis. Because of the possibility of biphasic anaphylaxis, it is probably prudent to admit the patient to the hospital with close monitoring for at least 24 hours. However, the optimal observation time is unclear. If the patient's symptoms have resolved promptly and completely, some guidelines recommend observing the patient for at least six hours. At the time of discharge, the patient should receive two epinephrine auto-injectors and be instructed in their use. Early epinephrine use is associated with improved outcomes in severe anaphylaxis.[28] Patients should be given information regarding severe anaphylaxis. In addition, they should be told to return immediately if symptoms recur. They should follow up with their primary care physician or an allergist within a few days. The mnemonic "SAFE" has been developed by the American College of Emergency Physicians and the American College of Allergy, Asthma, and Immunology to guide physicians in instructing patients with severe anaphylaxis prior to discharge from the ED or hospital.[36] The S.A.F.E. instructions can be incorporated into the patient discharge instructions for severe angioedema and/or anaphylaxis.

S – Seek support – the patient should be advised that:

1 - They have experienced a very severe allergic reaction.

2 - Symptoms similar to the acute episode may recur up to 72 hours (biphasic anaphylaxis).

3 - If such symptoms recur, they should immediately self-inject epinephrine with the auto-injector and call 911 to transport them to the nearest ED.

4 - They are at higher risk for repeat episodes of severe anaphylaxis in the future.

5 - They should read about anaphylaxis (give the patient resources on anaphylaxis, especially the recognition of its symptoms by the patient).

A – Allergen identification and avoidance – the physician should:

1 - Attempt to identify the patient's anaphylaxis trigger via a thorough history and in vitro testing (measure specific IgE to the allergen in the serum) prior to discharge.

2 - Recommend allergy testing by an allergist to confirm the trigger, so that the patient can avoid it in the future.

F – Follow up with an allergist or a physician well versed in the diagnosis and management of severe anaphylaxis.

E – Epinephrine (self-injected) to be used at the first sign of allergic symptoms:

1 - Instruct the patient to carry the epinephrine auto-injector with them at all times

2 - Instruct them on how to use the auto-injector as well as encourage them to instruct their family and close friends on its use (in case the patient is unable to give the injection).

Summary

The physician or mid-level practitioner in a rural emergency department should be able to recognize and manage patients with anaphylaxis, whether it is isolated acute urticaria and/or angioedema or severe anaphylaxis with associated bronchospasm and/or hypotension. In the case of severe angioedema or anaphylaxis, epinephrine should be administered as soon as possible. If the patient does not respond to therapy relatively rapidly, they should consider transfer to a facility that has the resources to deliver a higher level of care, especially if the patient has severe anaphylaxis. Patients with angioedema or severe anaphylaxis should always be discharged with two epinephrine auto-injectors and be instructed in their use. They should be told to return if their symptoms recur and to follow up with a medical provider who specializes in the diagnosis and management of anaphylaxis.

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