INTRODUCTION — Angioedema is self-limited, localized subcutaneous (or submucosal) swelling, which results from extravasation of fluid into interstitial tissues. Angioedema may occur in isolation, accompanied by urticaria, or as a component of anaphylaxis.

The clinical features, diagnosis, differential diagnosis, and management of angioedema will be reviewed here. The pathogenesis and causes of angioedema are discussed separately. (See "An overview of angioedema: Pathogenesis and causes".)

CLINICAL FEATURES — Angioedema typically affects areas with loose connective tissue, such as the face, lips, mouth, and throat, larynx, uvula, extremities, and genitalia. Bowel wall angioedema presents as colicky abdominal pain.

Angioedema can be distinguished clinically from other forms of edema by the following characteristics:

- Onset in minutes to hours
- Asymmetric distribution
- Tendency not to involve gravitationally dependent areas
- Involvement of face, lips, larynx, and bowels
- Association of some forms of angioedema with other signs and symptoms of allergic reactions or anaphylaxis

Types of angioedema — Two types of angioedema can be distinguished: mast cell-mediated angioedema and bradykinin-mediated angioedema. However, for many of the known triggers of angioedema, the mechanism is unclear. (See "An overview of angioedema: Pathogenesis and causes".)

- In mast cell-mediated angioedema, such as allergic reactions to foods or insect stings, there are often (not always) other signs and symptoms of mast cell mediator release. These signs and symptoms include urticaria, flushing, generalized pruritus, bronchospasm, throat tightness, and/or hypotension. Mast cell-mediated angioedema usually begins within minutes of exposure to the allergen, builds over a few hours, and resolves in 24 to 48 hours. (See "An overview of angioedema: Pathogenesis and causes", section on 'Mast cell-mediated etiologies'.)

- Bradykinin-induced angioedema is not associated with urticaria, bronchospasm, or other symptoms of allergic reactions. It has a somewhat more prolonged time course, usually developing over 24 to 36 hours and resolving within two to four days [1]. In this type of angioedema, the relationship between
the trigger and the onset of symptoms is often not apparent. As an example, in ACE inhibitor-induced angioedema, swelling may appear within a week of starting or increasing the medications, or after years of use. (See "An overview of angioedema: Pathogenesis and causes", section on 'Bradykinin-mediated etiologies'.)

Anatomic sites

**Larynx** — Laryngeal edema can develop rapidly (over minutes) or more slowly over several hours. Early symptoms include hoarse voice, throat tightness, and difficulty swallowing. Assessment and treatment are discussed below (see 'Angioedema in or near the airway' below).

**Skin and mucous membranes** — Angioedema affects the subcutaneous and submucosal tissues (picture 1 and picture 2 and picture 3). Pruritus is absent, unless the angioedema is associated with urticarial lesions, which are intensely pruritic (picture 4). The skin is either normal in color or mildly erythematous. Mild pain and warmth may be present, but are much less prominent than the pain and warmth of cellulitis. Some patients describe the discomfort of angioedema as burning in nature. Angioedema resolves without leaving residual markings on the skin, unless there has been trauma induced by rubbing or scratching.

**Bowel wall** — Angioedema affecting the bowel wall presents as colicky abdominal pain, sometimes accompanied by nausea, vomiting and/or diarrhea. Bowel wall edema can often be visualized by abdominal CT or ultrasound. Bowel wall angioedema is seen in patients on ACE inhibitors and in those with hereditary or acquired C1 inhibitor deficiency:

- ACE inhibitors should be suspected in an older adult (particularly women) taking these medications, in whom the problem is newly-developed [2-6]. (See 'Imaging for suspected bowel wall edema' below.)
- Acquired C1 inhibitor deficiency also typically presents in older patients. (See "Acquired C1 inhibitor deficiency: Clinical manifestations, epidemiology, pathogenesis, and diagnosis".)
- Hereditary angioedema should be considered in an adolescent or adult, particularly if there is a family history of recurrent, episodic swelling. A more detailed discussion of the evaluation of abdominal pain in patients with hereditary angioedema is found separately. (See "Clinical manifestations and pathogenesis of hereditary angioedema", section on 'Gastrointestinal attacks'.)

**Life-threatening situations** — Angioedema is usually a benign condition, although it can be life-threatening in the following situations:

- Angioedema of the larynx, upper airway, or tongue (of any mechanism) can progress to airway obstruction and asphyxiation.
- Angioedema may be a presenting symptom of anaphylaxis (a serious allergic reaction that is rapid in onset and may cause death). The diagnosis and treatment of anaphylaxis are presented separately. (See "Anaphylaxis: Rapid recognition and treatment".)

**DIAGNOSTIC EVALUATION** — In patients presenting with angioedema affecting the airway, airway protection must be given priority over a comprehensive diagnostic evaluation. (See 'Angioedema in or near the airway' below.)

**Clinical history** — The history should be directed at identifying possible causes, as well as determining if
the patient has had previous episodes of angioedema. Causes are reviewed elsewhere. (See "An overview of angioedema: Pathogenesis and causes").

- The patient should be questioned about any unusual exposures (eg, insect stings), activities (eg, exercise), foods or other ingestions in the 24 hours before the onset of symptoms.

- A review of the patient's medications is important, with particular attention to the following:

  Nonsteroidal antiinflammatory drugs (NSAIDs)
  ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)
  Calcium channel blockers
  Estrogens
  Fibrinolytic agents

Any new medications or significant increases in doses of medications

Patients with previous episodes of angioedema (cutaneous swelling or abdominal pain) should be asked about activities and exposures surrounding those episodes, to see if any pattern is apparent. Individuals with ACEI-induced angioedema may have several episodes of swelling before the drug is recognized as the culprit and discontinued [7]. Patients with recurrent orofacial angioedema after dental work or episodes of unexplained abdominal pain may have hereditary or acquired C1 inhibitor deficiency.

Patients should be asked about family members with similar episodes of cutaneous or laryngeal angioedema or with recurrent abdominal pain, to identify families with hereditary angioedema (HAE). However, about 25 percent of patients with HAE have a new mutation and so do not have a positive family history. (See "Clinical manifestations and pathogenesis of hereditary angioedema").

**Physical examination** — The presence of other signs and symptoms of an allergic reaction (or more precisely, of mast cell activation) is helpful in narrowing the list of possible causes, as mentioned previously. These signs and symptoms include urticaria, flushing, generalized pruritus, bronchospasm, throat tightness, and/or hypotension. If one or more of these other signs or symptoms is present, the history should be directed toward mast cell-mediated etiologies, such as allergic reactions to foods, drugs, and stinging insects (table 1) [8]. (See "An overview of angioedema: Pathogenesis and causes", section on 'Mast cell-mediated etiologies'.)

If signs and symptoms of mast cell activation are absent, then bradykinin-mediated angioedema, such as that caused by ACE inhibitors and the rare disorders hereditary or acquired C1 inhibitor deficiency, should be considered. (See "An overview of angioedema: Pathogenesis and causes", section on 'Bradykinin-mediated etiologies'.)

**Laboratory tests** — The laboratory tests that are indicated in a patient presenting with angioedema are influenced by the presence of other signs and symptoms and by the suspected cause, as described below. However, we suggest that the following laboratories be considered in all patients with new onset angioedema: complete blood count with differential, basic chemistry panel with liver function tests, CRP, ESR, and C4 and C3 levels.

Depressed C4 levels should prompt further evaluation for complement mediated angioedema, and low levels C3 and C4 levels suggest an immune complex mediated process, such as systemic lupus erythematosus.
Angioedema with prominent urticaria — Guidelines for the evaluation of urticaria (with or without angioedema) suggest that the following tests be obtained: a complete blood count with differential, urinalysis, erythrocyte sedimentation rate, and liver function tests [9]. This evaluation is reviewed separately. A specific cause can sometimes be identified in patients with new onset urticaria/angioedema. (See "New onset urticaria: Diagnosis and treatment" and "New onset urticaria: Epidemiology, clinical manifestations, and etiologies").

Urticaria/angioedema is considered chronic when it has been present on most days of the week for a period of six weeks or more. The evaluation of chronic urticaria/angioedema differs from that of new onset symptoms, since a specific external trigger or allergy is not found in most patients and laboratory studies are most often normal. (See "Chronic urticaria: Clinical manifestations, diagnosis, pathogenesis, and natural history").

Angioedema with anaphylaxis — A serum total tryptase level drawn shortly after the onset of anaphylaxis may be useful in confirming that the episode was a mast cell-mediated event. Serum tryptase is a mast cell-specific protease that is released upon mast cell activation. Any elevation in serum tryptase suggests an anaphylactic event. However, a normal level does not exclude anaphylaxis because tryptase elevations are variable and transient. Tryptase elevations are most consistently found in patients with hypotension during anaphylaxis. Instructions for proper sample collection are provided in the table (table 2). (See "Laboratory tests to support the clinical diagnosis of anaphylaxis").

Angioedema due to a suspect allergen — In cases in which an allergic reaction to an identifiable substance is suspected, there may be commercially-available tests for IgE antibodies to the substance in question. Allergen-specific IgE immunoassays are available for a variety of foods, insect venoms, inhaled allergens, and latex. These tests vary in sensitivity and specificity, but a positive result can be helpful. IgE immunoassays are not altered by recent allergic reactions, so they can be obtained at any time. Allergy skin testing provides similar information and is more sensitive in many cases, but it requires referral to an allergy specialist and should be deferred until the patient has fully recovered. (See "Overview of in vitro allergy tests", section on 'Immunoassays' and "Overview of skin testing for allergic disease").

Patients taking an ACE inhibitor — Some authors have advised screening for underlying defects in C1 inhibitor with a serum C4 level [10], although the likelihood of finding such a disorder in a patient with no other suggestive history is probably low.

Isolated angioedema — Screening tests for C1 inhibitor deficiency should be obtained in patients with isolated mucosal or cutaneous angioedema (ie, without urticaria or other evidence of mast cell involvement) or bowel wall angioedema on imaging of the abdomen [11]. The recommended tests are:

- C4 level
- C1 inhibitor (antigenic level)

The evaluation and diagnosis of C1 inhibitor deficiency are reviewed in more detail separately. (See "Diagnosis of hereditary angioedema" and "Acquired C1 inhibitor deficiency: Management and prognosis").

Imaging for suspected bowel wall edema — Bowel wall edema may be imaged by ultrasound or abdominal CT. Multidetector CT (MDCT) has been suggested as particularly helpful for diagnosis of ACE inhibitor-induced angioedema. Most reported cases of ACE inhibitor-induced intestinal angioedema involved the small bowel, with abdominal CT demonstrating circumferential thickening of the small bowel wall with ascites or subobstruction [3,5,12]. The thickened area of bowel wall may have a stratified appearance, and
mesenteric lymphadenopathy has not been reported [12]. Recognition of this complication of ACE inhibitor therapy can spare the patient unnecessary surgical intervention.

**Diagnosis** — The diagnosis of angioedema is made clinically, based on a suggestive history and physical findings. Laboratories may be helpful in confirming an underlying allergy or a complement disorder. However, laboratories are normal in many cases of angioedema.

**The utility of extensive empiric testing** — Extensive testing beyond the laboratory tests already mentioned is of relatively low yield. (See ‘Laboratory tests’ above.)

The utility of extensive testing was evaluated in a large series of 776 patients with recurrent angioedema, without major urticaria, who presented to a referral center over a 10 year period [13]. In the majority of these patients, neither the patient nor the referring clinician could detect an association between the episodes of angioedema and an obvious trigger. All patients underwent a careful history and physical examination, sinus and dental radiographs, complete blood count, serum protein electrophoresis, complement studies, erythrocyte sedimentation rate, C-reactive protein, hepatic enzymes, renal function, thyroid function and anti-tissue antibodies, stool examination for ova and parasites, urinalysis, pharyngeal cultures, and urine cultures. Further studies, including allergy testing or medication withdrawal and challenge, were performed only if allergy was suggested by the clinical history. A condition or trigger was considered causative only if the angioedema improved after treatment/discontinuation.

The following potentially causative conditions were identified (figure 1):

- Hereditary or acquired angioedema due to C1 inhibitor deficiency was identified in 23 and 2 percent, respectively.

- ACE inhibitors were implicated in 11 percent, with a median duration of treatment of one year before symptoms began.

- A specific causative factor (a food, drug, insect bite, environmental allergen, or physical stimulus) was identified in 16 percent.

- Other disorders, most commonly chronic infection or autoimmune disease, were identified in 7 percent. Within this group, chronic infections were identified in 27 patients, 19 of whom had resolution of the angioedema following treatment of the infection.

- Three percent did not have angioedema, but rather other types of peripheral or generalized edema. (See ‘Differential diagnosis’ below.)

No trigger could be identified in 38 percent, and these patients were deemed to have idiopathic angioedema. Thus, if the initial approach suggested above, (ie, obtaining complete blood count with differential, basic chemistry panel with liver function tests, CRP, ESR, and C4 and C3 levels and stopping any ACE inhibitors) were applied to this referral group, patients with hereditary or acquired angioedema and those with ACE inhibitor-related angioedema would have been reliably detected. A detailed clinical history and review of systems would likely have identified many of the remaining patients (those with a specific causative factor or an underlying infection or autoimmune disease) as requiring further evaluation.

**Idiopathic angioedema** — Idiopathic angioedema is the term applied to recurrent episodes of angioedema without urticaria, for which no explanation can be found after a thorough evaluation (as previously described) to exclude allergic disorders, drug reactions, and defects in complement pathways [13].
DIFFERENTIAL DIAGNOSIS — There are several conditions that may be mistaken for angioedema [10,14].

Disorders resembling cutaneous edema — Cutaneous edema mimicking angioedema can result from contact dermatitis, cellulitis, autoimmune diseases, superior vena cava syndrome, and other disorders.

- **Contact dermatitis** — Contact dermatitis is a common mimic of facial angioedema and can cause dramatic swelling of the facial and periorbital skin when it develops in response to cosmetics or topical pharmaceuticals (picture 5 and picture 6). Microvesiculation and/or deep erythema of the skin can help distinguish contact dermatitis from complement-mediated angioedema. Poison ivy can cause severe facial swelling, although linear patterns of vesiculations are often present.

  Patients with contact dermatitis often report prominent pain, pruritus, and burning of the skin. Resolution of contact dermatitis may be followed by peeling, which does not occur in angioedema. (See "Overview of dermatitis" and "Contact dermatitis in children".)

- **Cellulitis and erysipelas** — Cellulitis and erysipelas are infections of various layers of the dermis, which present as areas of skin erythema, edema and warmth in the absence of an underlying suppurative focus. Cellulitis involves the deeper dermis and subcutaneous fat and has relatively smooth, flat borders. In contrast, erysipelas involves the upper dermis and superficial lymphatics and is characteristically raised above the level of surrounding skin, with a clear line of demarcation between involved and uninvolved tissue (picture 7 and picture 8).

  Compared with angioedema, cellulitis and erysipelas are deeply erythematous, painful, and may be accompanied by fever. The involved areas of skin are more clearly demarcated than angioedematous skin. Resolution may be followed by peeling, whereas angioedema resolves without peeling.

- **Facial lymphedema** — Facial lymphedema can be associated with rosacea, although there are other characteristic skin changes in rosacea. Patients may also experience prominent flushing and warmth of the face, and the combination of flushing, heat, and swelling is interpreted by some patients as a possible allergic reaction. However, lymphedema does not develop or resolve rapidly, in contrast to angioedema. (See "Rosacea: Pathogenesis, clinical features, and diagnosis".)

- **Autoimmune conditions** — Edema of the face, periorbital areas, and sometimes the hands can be seen in systemic lupus, polymyositis, dermatomyositis, and Sjögren's syndrome. Early stages of both sclerodema and systemic sclerosis can present as swelling. Sclerodema often involves the posterior neck, and systemic sclerosis often affects the hands and is accompanied by Raynaud's phenomenon [15]. These disorders can be distinguished from angioedema by their persistence, and by the presence of associated systemic rheumatologic findings. (See "Diagnosis and differential diagnosis of systemic sclerosis (scleroderma) in adults".)

- **Eyelid edema** — Blepharochalasis is an uncommon disorder in which recurrent and episodic eyelid edema leads to atrophic eyelid skin with fine wrinkling and bronze discoloration (picture 9) [9,16,17]. This is seen predominantly in children and young adults. The etiology is unknown, although IgA deposits have been described in the periorbital tissues, suggesting an immunological pathogenesis [18].

- **Parasitic infections** — In areas of the world where parasitic infections are prevalent, certain infections can cause periorbital edema that is persistent rather than episodic. Specific infections that can present with this finding include trichinosis and American trypanosomiasis (ie, Romana's sign)
Hypothyroidism — Severe hypothyroidism can cause a puffiness of the face and lips that can be mistaken for angioedema, but is not transient. Nonpitting edema (myxedema) may be generalized. Myxedema results from infiltration of the skin by glycosaminoglycans with associated water retention. (See "Clinical manifestations of hypothyroidism".)

Superior vena cava syndrome and tumors — Occasionally, edema of the face, neck, or upper extremities, accompanied by venous engorgement, is observed with superior vena cava syndrome [19]. (See "Malignancy-related superior vena cava syndrome".) Tumors of the head and neck, lymphoma, and superior (pulmonary) sulcus (Pancoast) tumors can also cause localized edema. With these entities, protracted or progressive swelling would be expected, in contrast to the transient swelling of angioedema.

Cheilitis granulomatosa (Miescher's cheilitis) and Melkersson-Rosenthal syndrome — These are rare disorders of recurrent angioedema involving the lips and face that lead to eventual permanent enlargement of the affected areas (picture 10 and picture 11) [20,21].

Idiopathic edema — Idiopathic edema (as opposed to idiopathic angioedema) is a syndrome of persistent and recurrent fluid retention, typically occurring in young, menstruating women in the absence of cardiac, hepatic, or renal disease. (See "Idiopathic edema".)

Disorders resembling laryngeal edema — The differential diagnosis of laryngeal edema includes tonsillitis, peritonsillar abscess, and pharyngeal foreign body [10]. Historical information should differentiate these entities from angioedema, as infectious causes should have accompanying fever and other signs of illness. The diagnosis of a pharyngeal foreign body can be difficult, however, particularly in the preverbal infant. (See "Emergent evaluation of acute upper airway obstruction in children".)

Other causes of bowel wall edema — Thickening of the wall of the small bowel can be seen in multiple disorders, including mesenteric infarction, vasculitis, intramural hemorrhage, inflammatory bowel disease, acute ileitis (Yersinia, Campylobacter infections), peritoneal carcinomatosis, inflammatory conditions adjacent to the bowel wall, and other disorders [12,22-24].

TREATMENT — The treatment of angioedema depends upon the acuity, severity, and proposed mechanism.

Angioedema in or near the airway — The patient with angioedema near or involving the tongue, uvula, soft palate, or larynx must be immediately assessed for signs of airway compromise. The airway should be managed by the most experienced person available, as intubation in the presence of laryngeal angioedema can be difficult due to distortion of the normal anatomy. Angioedema sometimes spreads to adjacent areas, and frequent monitoring of airway patency is critical throughout treatment. (See "The difficult airway in adults" and "The difficult pediatric airway".)

Angioedema in anaphylaxis — Anaphylaxis should be treated with intramuscular epinephrine, intravenous fluids, and oxygen. Rapid overview tables are provided for treatment of anaphylaxis in adults (table 3) and children (table 4). The treatment of anaphylaxis is reviewed in greater detail elsewhere. (See "Anaphylaxis: Rapid recognition and treatment".)

All patients who have experienced anaphylaxis should be equipped with an anaphylaxis emergency action...
plan, one or more epinephrine autoinjectors, a plan for arranging further evaluation, and printed information about anaphylaxis and its treatment. These materials can be found separately. (See "Anaphylaxis: Rapid recognition and treatment", section on 'Discharge care'.)

**Acute allergic angioedema (less severe than anaphylaxis)** — Antihistamines and glucocorticoids are the main therapies for isolated angioedema that appears to be allergic (ie, mast-cell mediated) but is NOT part of a larger anaphylactic reaction. In contrast, anaphylaxis should be treated with intramuscular epinephrine because antihistamines are not sufficient. Angioedema that is accelerating and could affect the airway would also be appropriately treated with intramuscular epinephrine, although this is unlikely to help if the angioedema is bradykinin-mediated (as in hereditary angioedema).

Suggested treatment includes the following:

- H1 and H2 antihistamines at standard doses
- Glucocorticoids (the dosing in acute angioedema has not been specifically studied):
  - **Methylprednisolone**, 60 to 80 mg initially, replaced with oral preparations and tapered over five to seven days, in adults requiring hospitalization for severe angioedema
  - **Prednisone** (20 to 40 mg daily) in adults or **prednisolone** (0.5 to 1 mg/kg/day) in children, tapered over five to seven days in patients discharged to home

The use of antihistamines for angioedema is extrapolated from the treatment of acute urticaria/angioedema, as the data on isolated allergic angioedema are scant [10]. (See "New onset urticaria: Diagnosis and treatment", section on 'Treatment'.)

**C1-inhibitor deficiency (hereditary angioedema)** — The treatment of acute attacks of hereditary and acquired C1 inhibitor disorders is outlined here and discussed in detail separately.

The treatment of laryngeal attacks, which are the leading cause of mortality in patients with hereditary angioedema, must always begin with immediate and meticulous attention to airway patency, regardless of the therapies available. (See ‘Angioedema in or near the airway’ above.) Those with respiratory distress or stridor may require intubation, because even the first line therapies take approximately 30 minutes or more to begin working.

Briefly, treatment options include:

- Purified C1 inhibitor concentrate (Cinryze®, Berinert®)
- **Ecallantide** (Kalbitor®) (a kallikrein inhibitor available in the United States)
- Fresh frozen plasma (used in the US) or solvent-detergent treated plasma (used in the European Union [EU])

Another option is **icatibant** (Firazyr®), a bradykinin B2 receptor antagonist.

The dosing and administration of each of these therapies is reviewed separately. (See “Treatment of acute attacks in hereditary angioedema”, section on 'Medication options' and "Acquired C1 inhibitor deficiency: Management and prognosis".)

**ACE inhibitor-induced angioedema** — Treatment of ACEI-induced angioedema primarily involves discontinuation of the drug. Discontinuation of ACE inhibitors usually results in resolution of edema within 24 to 48 hours [25]. The airway must be protected if swelling involves the mouth or throat, as several deaths
have been attributed to asphyxiation from massive tongue swelling [26].

The utility of other medications (including antihistamines, glucocorticoids, and epinephrine) in the treatment of ACEI-induced angioedema has not been reported.

**Treatment of severe or persistent symptoms** — Case reports describe successful treatment of life-threatening ACE inhibitor-induced angioedema with several of the agents used in hereditary angioedema:

- C1-inhibitor concentrate [27,28]
- Fresh frozen plasma [25,29]
- Icatibant [30]

Ecallantide (available in the US but not elsewhere) is another agent of interest. Its use to treat ACE inhibitor-induced angioedema has not been described, although the drug blocks bradykinin production by inhibiting plasma kallikrein and would be theoretically helpful.

The dosing and administration of each of these therapies is reviewed separately. (See "Treatment of acute attacks in hereditary angioedema", section on 'Medication options'.)

Once the ACE inhibitor has been discontinued, some patients have no further episodes of angioedema, although others continue to have attacks, particularly in the first few months after stopping the drug, suggesting either that the biochemical changes take time to normalize after the drug is discontinued, or that the patient has an underlying predisposition to develop angioedema that was exacerbated by the ACE inhibitor, or possibly both [31-34]. In one series of 111 Caucasian patients, 46 percent continued to have episodes of angioedema after stopping the ACE inhibitor, and of these, the frequency was unchanged in 16 percent [34].

Regardless of the patient’s subsequent course, any patient who developed angioedema while on an ACE inhibitor should not receive these drugs in the future because there is a significant risk of recurrent angioedema if ACE inhibitors are continued, as shown in a report of 82 patients who had a first episode of angioedema while on an ACE inhibitor [35]. The risk of recurrence was much higher in those with continued exposure to ACE inhibitors compared to those who were switched to other agents (19 versus 2 per 100 patient years). Review of the medical records of those who were continued on ACE inhibitors revealed that clinicians often attributed the angioedema to other causes, even after multiple recurrences.

**Use of alternative medications** — Patients who developed angioedema while taking one ACE inhibitor should avoid all ACE inhibitors in the future and consider obtaining a medical identification bracelet or tag listing their sensitivity to these medications. They should also be counseled that additional episodes of angioedema may occur even after the drug is stopped and should be given clear instructions on how to proceed if it develops.

Patients can be switched to any number of other antihypertensives, as there is no compelling evidence that the risk of recurrent angioedema differs among the commonly-used alternatives:

- In the series of 111 patients mentioned previously, there were no differences in the rates of relapse among patients switched to angiotensin receptor blockers (ARBs), calcium channel blockers, beta blockers, or other drugs [34]. The majority of patients with ACE inhibitor-associated angioedema who are subsequently switched to an ARB do not have recurrent episodes of angioedema [36,37]. This was demonstrated in a trial of 5926 patients who were intolerant to ACE inhibitors for various
reasons, including 75 patients with angioedema or anaphylaxis \[37\]. All patients were randomly assigned to receive either an ARB (telmisartan) or placebo. After a median follow-up period of 54 months, none of the patients receiving telmisartan developed angioedema. Despite these observations, some patients who have had angioedema associated with ACE inhibitors do develop recurrent angioedema while being treated with an ARB \[32,36,38,39\].

**Recurrent, idiopathic angioedema** — A trial of nonsedating antihistamines, administered twice daily, is suggested as an initial intervention to prevent recurrence in patients with idiopathic recurrent angioedema without urticaria.

In the largest series available, 294 patients with idiopathic recurrent angioedema without urticaria were treated with nonsedating antihistamines initially (ie, either cetirizine 10 mg twice daily or desloratadine 5 mg twice daily) for at least one month \[13\]. With this intervention, 86 percent experienced significant improvement or resolution of the angioedema. In those that did not improve significantly (40 patients), the addition of hydroxyzine (25 mg three times daily) did not result in additional symptom control. Responsiveness to antihistamines suggests that mast-cell or basophil-mediated processes were underlying the symptoms of these patients, despite the lack of identifiable triggers.

Other experts describe less success in preventing recurrence with antihistamines, even with high doses (ie, up to 200 mg of hydroxyzine or diphenhydramine) and no response in up to 30 percent of patients \[10,40\].

For adult patients with idiopathic angioedema who have infrequent attacks (ie, a few attacks per year) and do not wish to take regular medications for prevention, we (the authors and editors of UpToDate) have found the following to be helpful. We instruct patients to take 40 mg of prednisone and 25 to 50 mg of diphenhydramine, all at once, at the first sign of swelling, with no further doses. Some patients have identifiable sensations in the skin just before the onset of angioedema, and the medications should be taken when these sensations appear. This approach has not been formally studied.

**REFERRAL** — Patients with severe or recurrent angioedema or angioedema/urticaria, for which no cause is readily apparent, should be referred to a specialist for further evaluation. An allergy specialist is most appropriate if an allergic cause or C1 inhibitor deficiency is suspected. Dermatology specialists also manage mast cell-mediated urticaria/angioedema.

**INFORMATION FOR PATIENTS** — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topic (see “Patient information: Angioedema (The Basics)”)

**SUMMARY AND RECOMMENDATIONS**
• Angioedema typically affects the skin and mucosal tissues of the face, lips, mouth, and throat, larynx, extremities, and genitalia, often in an asymmetric pattern (picture 1). Angioedema can also affect the bowel wall and present as colicky abdominal pain. (See 'Clinical features' above.)

• Two types of angioedema can be distinguished: mast cell-mediated angioedema (e.g., allergic reactions) and bradykinin-mediated angioedema (e.g., ACE inhibitor induced angioedema, hereditary angioedema). However, there are other causes of angioedema for which the mechanism unknown. (See "An overview of angioedema: Pathogenesis and causes".)

• Angioedema may be life-threatening if it causes airway obstruction or when it represents a component of anaphylaxis. (See 'Life-threatening situations' above.)

• If the clinical history or physical exam reveals a possible external cause or concomitant condition, then these findings should guide further testing. If there is no information to suggest an external cause and the patient has isolated angioedema (without pruritus or urticaria), then a C4 and a C1 inhibitor antigenic level should be obtained. (See 'Diagnostic evaluation' above.)

• Immediate assessment and ongoing protection of the airway is critical in any patient with angioedema near or affecting the larynx, mouth, soft palate, or tongue. (See 'Angioedema in or near the airway' above.)

• The treatment of angioedema depends upon the acuity, severity, and the mechanism believed responsible (mast cell or bradykinin-mediated). Mast cell-mediated angioedema responds to epinephrine (if severe), glucocorticoids, and antihistamines. In contrast, bradykinin-mediated angioedema responds to C1-inhibitor concentrate, fresh frozen plasma, and other agents that interfere with the production or action of bradykinin. (See 'Treatment' above.)

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REFERENCES


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Angioedema is a diffuse, nonpitting, tense swelling of the dermis and subcutaneous tissue. It develops over minutes to hours, and resolves over subsequent hours or days. Angioedema typically does not itch, unless it is associated with urticaria.

Angioedema of the lips

Unilateral angioedema of the tongue

Angioedema and hives face

**Major causes of mast cell-mediated angioedema**

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<th>IgE-dependent allergic reactions</th>
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<tr>
<td>Foods</td>
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<td>Drugs (antibiotics, local anesthetics, hormones)</td>
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<td>Stinging insects</td>
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<td>Latex</td>
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<td>Contact (fresh fruits and vegetables, animal saliva)</td>
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<th>Direct mast cell mediator release</th>
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<td>Opiates</td>
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<td>Muscle relaxants (succinylcholine, curare)</td>
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<td>Radiocontrast agents</td>
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<thead>
<tr>
<th>Perturbations in arachidonic acid metabolism within mast cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs)</td>
</tr>
</tbody>
</table>
Instructions for optimal collection and handling of blood samples for measurement of tryptase and histamine following suspected anaphylaxis

<table>
<thead>
<tr>
<th>Tryptase* (serum or plasma)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When to collect the sample:</strong></td>
</tr>
<tr>
<td>Blood should be collected between 15 minutes and 3 hours after symptom onset whenever possible; samples collected &lt;15 min or &gt;3 h after symptom onset are less likely to be informative.</td>
</tr>
<tr>
<td><strong>How to collect the sample:</strong></td>
</tr>
<tr>
<td>Blood can be drawn using usual technique. Collect blood for serum (red top tube) or plasma (tube with heparin, citrate or EDTA). A minimum of 1 mL is required.</td>
</tr>
<tr>
<td>For postmortem samples, collect blood from the femoral artery or vein, not the heart.</td>
</tr>
<tr>
<td><strong>How to process the sample:</strong></td>
</tr>
<tr>
<td>Serum or plasma should be placed on ice and frozen as soon as possible. Samples should be shipped frozen by overnight courier if the assay cannot be performed on site.</td>
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<tr>
<th>Histamine (plasma)*</th>
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<tr>
<td><strong>When to collect the sample:</strong></td>
</tr>
<tr>
<td>Plasma for histamine levels should be collected between 15 and 60 minutes after symptom onset; samples collected &lt;15 min or &gt;60 min after symptom onset are less likely to be informative.</td>
</tr>
<tr>
<td><strong>How to collect the sample:</strong></td>
</tr>
<tr>
<td>Pull blood manually (DO NOT use vacuum tubes) under gentle pressure through a 20 gauge or larger needle into a syringe containing either citrate or EDTA.</td>
</tr>
<tr>
<td><strong>How to process the sample:</strong></td>
</tr>
<tr>
<td>Anticoagulated blood should be placed on ice and centrifuged to separate plasma from cells as soon as possible, and then frozen until ready to be analyzed.</td>
</tr>
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</table>


- Plasma is used to avoid the artifactual release of histamine from basophils that can occur during blood clotting.
Etiologies of angioedema in referral populations

- Autoimmune disease, chronic infection, or other underlying disorder: 30 percent
- Related to a specific factor (food, drug, insect bite, environmental allergen, or physical stimulus): 16 percent
- Peripheral or generalized edema: 7 percent
- Unknown etiology: 3 percent
- ACE inhibitor: 11 percent
- CI inhibitor deficiency (hereditary + acquired): 25 percent

Contact dermatitis of the periorbital skin

Contact dermatitis involving the facial and periorbital skin

Erysipelas involving the groin and thigh

Erysipelas involving the buttock

Granulomatous cheilitis

Granulomatous cheilitis is a rare disorder in which recurrent swelling of the lips leads to permanent areas of enlargement. 

Granulomatous cheilitis is a rare disorder in which recurrent swelling of the lips leads to permanent areas of enlargement.

**Rapid overview: Emergent management of anaphylaxis in adults**

### DIAGNOSIS IS MADE CLINICALLY:

The most common signs and symptoms are cutaneous (eg, sudden onset of generalized urticaria, angioedema, flushing, pruritus). However, 10 to 20 percent of patients have no skin findings.

**Danger signs:** Rapid progression of symptoms, respiratory distress (eg, stridor, wheezing, dyspnea, increased work of breathing, persistent cough, cyanosis), hypotension, dysrhythmia, chest pain, collapse

### ACUTE MANAGEMENT:

The first and most important therapy in anaphylaxis is epinephrine. There are **NO absolute contraindications** to epinephrine in the setting of anaphylaxis.

**Airway:** Immediate intubation if evidence of impending airway obstruction from angioedema; delay may lead to complete obstruction; intubation can be difficult and should be performed by the most experienced clinician available; cricothyrotomy may be necessary

**Promptly and simultaneously, give:**

**IM Epinephrine (1 mg/mL preparation):** Give epinephrine 0.3 to 0.5 mg intramuscularly, preferably in the mid-anterolateral thigh; can repeat every 5 to 15 minutes as needed. If symptoms are not responding to epinephrine injections, prepare IV epinephrine for infusion (see below).

**Place patient in recumbent position, if tolerated, and elevate lower extremities**

**Oxygen:** Give 6 to 8 liters per minute via face mask, or up to 100 percent oxygen as needed

**Normal saline rapid bolus:** Treat hypotension with rapid infusion of 1 to 2 liters IV; repeat as needed; massive fluid shifts with severe loss of intravascular volume can occur

**Also consider administration of:**

**Albuterol:** For bronchospasm resistant to IM epinephrine, give 2.5 to 5 mg in 3 mL saline via nebulizer; repeat as needed

**H1 antihistamine:** Consider giving diphenhydramine 25 to 50 mg IV (for relief of urticaria and itching only)

**H2 antihistamine:** Consider giving ranitidine 50 mg IV

**Glucocorticoid:** Consider giving methylprednisolone 125 mg IV

**Monitoring:** Continuous non-invasive hemodynamic monitoring and pulse oximetry monitoring should be performed; urine output should be monitored in patients receiving IV fluid resuscitation for severe hypotension or shock

### TREATMENT OF REFRACTORY SYMPTOMS:

**Epinephrine infusion**: For patients with inadequate response to IM epinephrine and IV saline, give epinephrine continuous infusion, 2 to 10 micrograms per minute by infusion pump. Titrate the dose continuously according to blood pressure, cardiac rate and function,
and oxygenation.

| **Vasopressors**: Some patients may require a second vasopressor (in addition to epinephrine). All vasopressors should be given by infusion pump, with the doses titrated continuously according to blood pressure, cardiac rate and function, and oxygenation. |
| **Glucagon**: Patients on beta-blockers may not respond to epinephrine and can be given glucagon 1 to 5 mg IV over 5 minutes, followed by infusion of 5 to 15 micrograms per minute |

* All patients receiving an infusion of epinephrine and/or another vasopressor require continuous non-invasive monitoring of blood pressure, heart rate and function, and oxygen saturation.
Rapid overview: Emergent management of anaphylaxis in infants and children

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<th>DIAGNOSIS IS MADE CLINICALLY:</th>
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<td>The most common signs and symptoms are cutaneous (eg, sudden onset of generalized urticaria, angioedema, flushing, pruritus). However, 10 to 20 percent of patients have no skin findings.</td>
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| Danger signs: Rapid progression of symptoms, evidence of respiratory distress (eg, stridor, wheezing, dyspnea, increased work of breathing, retractions, persistent cough, cyanosis), signs of poor perfusion*, dysrhythmia, hypotension, collapse |

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<th>ACUTE MANAGEMENT:</th>
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<tr>
<td>The first and most important therapy in anaphylaxis is epinephrine. There are <strong>NO absolute contraindications</strong> to epinephrine in the setting of anaphylaxis.</td>
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| Airway: Immediate intubation if evidence of impending airway obstruction from angioedema; delay may lead to complete obstruction; intubation can be difficult and should be performed by the most experienced clinician available; cricothyrotomy may be necessary |

| IM Epinephrine (1 mg/mL preparation): Give epinephrine 0.01 mg per kilogram intramuscularly (maximum per dose: 0.5 mg), preferably in the mid-anterolateral thigh, can repeat every 5 to 15 minutes as needed. If signs of poor perfusion* are present or symptoms are not responding to epinephrine injections, prepare IV epinephrine for infusion (see below). |

| Place patient in recumbent position, if tolerated, and elevate lower extremities |

| Oxygen: Give 6 to 8 liters per minute via face mask, or up to 100 percent oxygen as needed |

| Normal saline rapid bolus: Treat poor perfusion* with rapid infusion of 20 mL per kilogram; re-evaluate and repeat fluid boluses (20 mL per kilogram) as needed; massive fluid shifts with severe loss of intravascular volume can occur; monitor urine output |

| Albuterol: For bronchospasm resistant to IM epinephrine, give albuterol 0.15 mg per kilogram (minimum dose: 2.5 mg) in 3 mL saline inhaled via nebulizer; repeat as needed |

| H1 antihistamine: Consider giving diphenhydramine 1 mg per kilogram (max 40 mg) IV |

| H2 antihistamine: Consider giving ranitidine 1 mg per kilogram (max 50 mg) IV |

| Glucocorticoid: Consider giving methylprednisolone 1 mg per kilogram (max 125 mg) IV |

| Monitoring: Continuous non-invasive hemodynamic monitoring and pulse oximetry monitoring should be performed; urine output should be monitored in patients receiving IV fluid resuscitation for severe hypotension or shock |

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<th>TREATMENT OF REFRACTORY SYMPTOMS:</th>
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<tr>
<td>Epinephrine infusion*: Patients with inadequate response to IM epinephrine and IV saline, give epinephrine continuous infusion at 0.1 to 1 microgram per kilogram per minute, titrated to effect</td>
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**Vasopressors**: Patients may require large amounts of IV crystalloid to maintain blood pressure; if response to epinephrine and saline is inadequate, dopamine (5 to 20 micrograms per kilogram per minute) can be given as continuous infusion, titrated to effect.

* A child is defined as a prepubertal patient weighing less than 40 kg.
* See the topic "Assessment of perfusion in pediatric resuscitation".

Δ All patients receiving an infusion of epinephrine and/or another vasopressor require continuous non-invasive monitoring of blood pressure, heart rate and function, and oxygen saturation. We suggest that pediatric centers provide instructions for preparation of standard concentrations and also provide charts for established infusion rate for epinephrine and other vasopressors in infants and children.