An overview of angioedema: Pathogenesis and causes

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INTRODUCTION

Angioedema is self-limited, localized swelling of the skin or mucosal tissues, which results from extravasation of fluid into the interstitium due to a loss of vascular integrity. Angioedema may occur in isolation, accompanied by urticaria, or as a component of anaphylaxis.

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

EPIDEMIOLOGY

Data regarding the epidemiology of angioedema are limited, although it affects both adults and children and is not a rare disorder. In a retrospective review of all hospital admissions in New York State over 13 years, angioedema was the second most common "allergic" disease to necessitate hospitalization, exceeded only by asthma [1]. In this study, the number of angioedema hospitalizations per year more than doubled during the study period, suggesting that the prevalence may be increasing.

African Americans were disproportionately affected as they accounted for 42 percent of the admissions for angioedema but only 16 percent of the state's population.

The epidemiology of specific forms of angioedema, such as hereditary angioedema (HAE) due to C1 inhibitor (C1INH) deficiency, is discussed separately. (See "Hereditary angioedema: Epidemiology, clinical manifestations, exacerbating factors, and prognosis".)

PATHOGENESIS

Angioedema results from a loss of vascular integrity that allows fluid to move into tissues. Exposure of the vasculature to inflammatory mediators causes dilation and increased permeability of capillaries and venules. Fluid collects asymmetrically in the areas in which the vasculature has been altered, and these areas (eg, face, larynx, bowel wall) are **not** typically gravitationally dependent. Angioedema differs from the edema associated with cardiovascular, kidney, and liver disease (eg, heart failure, kidney failure, venous obstruction). Edema is usually due to an alteration in Starling's forces, such as an increase in intracapillary pressure or a reduction in the plasma oncotic pressure (ie, any cause of severe hypoalbuminemia) in the presence of normal vasculature. Edema affects gravitationally dependent parts of the body, and fluid collects symmetrically in those areas. (See "Pathophysiology and etiology of edema in adults".)

CAUSES

The known causes of angioedema can be subdivided into three groups, depending on the underlying mechanism (table 1):

- Mast cell-mediated etiologies, in which angioedema results from release of mast cell-derived mediators that increase vascular permeability. Mast cell-mediated angioedema is associated with urticaria and/or pruritus in most cases.
- Bradykinin-mediated etiologies, in which angioedema results from the generation of bradykinin, leads to increased vascular permeability. These forms of angioedema are **not** associated with urticaria and/or pruritus and are diagnosed and treated differently from other types of angioedema. (See "An overview of angioedema: Clinical features, diagnosis, and management".)
- Etiologies of unknown mechanism.

Mast cell-mediated etiologies — Mast cell-mediated angioedema is associated with urticaria and/or pruritus in many instances. This form of angioedema is pathologically similar to urticaria, although it takes place in the deeper levels of the dermis and subcutaneous tissues,

most often involving the face or mouth. Mast cells can be activated via several mechanisms (table 2). Activated mast cells release inflammatory mediators, including histamine, heparin, leukotriene C_4, and prostaglandin D_2, which cause dilation of venules in the dermis and enhance venule permeability with resultant tissue edema. (See "Mast cells: Development, identification, and physiologic roles" and "Mast cells: Surface receptors and signal transduction" and "Mast cell-derived mediators".)

Acute mast cell-mediated angioedema is treated with antihistamines and with epinephrine, if severe and accompanied by symptoms in other organ systems beyond the skin. The treatment of mast cell-mediated angioedema is discussed in detail separately. (See "An overview of angioedema: Clinical features, diagnosis, and management".)

Allergic reactions — Acute angioedema, with or without other symptoms of allergic reactions, may be triggered by foods, drugs, latex, exercise, the stings of various insects, and a growing list of other uncommon allergens (table 3). Angioedema is a common component of anaphylaxis, and, since anaphylaxis is treated differently from isolated angioedema (ie, with epinephrine), the clinician must be vigilant for other signs and symptoms of anaphylaxis (such as urticaria, pruritus, flushing, throat tightness, bronchospasm, and hypotension) in patients presenting with angioedema.

The classic type of allergic reaction results from immunoglobulin E (IgE) mediated, Gell and Coombs type I hypersensitivity (table 4). The reaction typically occurs within minutes to two hours following exposure to the trigger. However, some IgE-mediated allergic reactions are delayed in onset, such as allergic reactions to certain meats (lamb, beef, and/or pork) that can lead to reactions with prominent angioedema beginning two to six hours after ingestion [2]. (See "Anaphylaxis: Acute diagnosis" and "Food-induced anaphylaxis" and "Allergy to meats".)

Isolated angioedema is a relatively uncommon presentation of an allergic reaction. In a series of 112 patients with penicillin allergy confirmed by skin testing, only 1 patient had experienced isolated angioedema without urticaria during the presenting allergic reaction [3]. However, it can occur. Examples include reactions to nonsteroidal antiinflammatory drugs (NSAIDs). (See 'Aspirin and NSAIDs' below.)

Direct mast cell release — Mast cells can be nonspecifically stimulated to release their proinflammatory mediators by certain medications and pharmaceuticals, such as opiates 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 rarely helpful. (See "Diagnosis and treatment of an acute reaction to a radiologic contrast agent".)

Aspirin and NSAIDs — Nonsteroidal antiinflammatory drugs (NSAIDs), such as aspirin and ibuprofen, can cause acute urticaria/angioedema and can exacerbate chronic urticaria/angioedema. There are six known types of hypersensitivity reactions to NSAIDs, which are often difficult to distinguish from one another based on clinical history alone (table 5). (See 'Chronic urticaria with or without angioedema' below and "NSAIDs (including aspirin): Allergic and pseudoallergic reactions".)

The more common type of NSAID reaction is believed to be due to the pharmacologic properties of the medications on mast cells. NSAIDs inhibit the enzyme cyclooxygenase 1 (COX-1), which mediates the generation of prostaglandins from arachidonic acid within mast cells and other leukocytes. NSAID administration results in increased formation of proinflammatory mediators, leading to angioedema in susceptible individuals. NSAIDs that nonselectively inhibit both COX-1 and COX-2 enzymes (aspirin, ibuprofen, and most others) can potentially induce this effect, and patients often react to multiple agents. Selective COX-2 inhibitors, such as celecoxib, are tolerated by most patients who have reacted to nonselective NSAIDs [4], although rare exceptions are reported [5]. Management of patients with these reactions is reviewed separately. (See "NSAIDs (including aspirin): Allergic and pseudoallergic reactions", section on 'Types 1 to 4: Treatment options'.)

NSAIDs can also cause rare IgE-mediated allergic reactions, which are typically triggered by a single agent. The diagnostic approach to NSAID reactions is reviewed separately. (See "NSAIDs (including aspirin): Allergic and pseudoallergic reactions".)

Chronic urticaria with or without angioedema — Chronic urticaria refers to urticaria that continues to recur for a period of six weeks or longer [6]. Angioedema is present in at least one-half of patients with chronic urticaria [7].

Chronic urticaria may persist over months to years and is more common in females, particularly between the ages of 40 and 50 years. In most cases of chronic urticaria/angioedema, a specific cause cannot be identified. This disorder is reviewed in more detail separately. (See "Chronic spontaneous urticaria: Clinical manifestations, diagnosis, pathogenesis, and natural history" and "Chronic spontaneous urticaria: Standard management and patient education".)

Bradykinin-mediated etiologies — Angioedema can occur due to vasodilation and increased vascular permeability resulting from other inflammatory mediators, especially bradykinin. Angioedema can result from either overproduction of bradykinin or inhibition of bradykinin degradation. Mast cells are not believed to be involved in this form of angioedema, and **pruritus and urticaria are absent**. Bradykinin-mediated angioedema, unlike histamine-

mediated angioedema, frequently affects the gastrointestinal mucosa, leading to bowel wall edema and presenting with episodes of abdominal pain, nausea, vomiting, and/or diarrhea.

Perturbations in kinin pathways resulting directly from the actions of medications (eg, angiotensin-converting enzyme [ACE] inhibitors) or from deficiencies of C1 inhibitor (C1INH) are the main recognized causes of bradykinin-mediated angioedema. The treatment of bradykinin-induced angioedema is discussed separately. (See "An overview of angioedema: Clinical features, diagnosis, and management".)

Bradykinin-mediated angioedema does not respond to epinephrine, antihistamines, or glucocorticoids. Instead, this type of angioedema is treated with drugs that act on the bradykinin pathway (eg, icatibant, ecallantide, lanadelumab), preparations of C1INH concentrate (human), or plasma replacement (depending on the cause).

ACE inhibitors — Angiotensin-converting enzyme (ACE) inhibitors account for approximately 30 percent of all angioedema cases presenting to emergency departments in both community and tertiary care settings [8,9]. ACE inhibitors impair degradation of multiple peptides, including bradykinin and substance P (figure 1). Angioedema related to ACE inhibitors most often affects the lips, tongue, mouth, larynx, pharynx, and subglottic tissues. Urticaria and itching are absent. ACE inhibitors can also cause intestinal edema, and the sudden onset of abdominal pain, nausea, and sometimes vomiting in an older adult should prompt inquiries about the use of ACE inhibitors. The epidemiology, pathophysiology, diagnosis, and management of patients with ACE inhibitor-induced angioedema is discussed separately. (See "ACE inhibitor-induced angioedema".)

The risk of angioedema with the use of angiotensin II receptor blockers (ARBs), such as losartan, valsartan, and telmisartan, appears to be considerably lower than with ACE inhibitors [10-12]. The development of angioedema following therapy with ARBs is surprising since these drugs are not thought to affect kinin metabolism directly (figure 1). The administration of ARBs to a patient with past ACE inhibitor-induced angioedema is discussed separately. (See "ACE inhibitor-induced angioedema".)

ACE inhibitors and ARBs may also unmask deficiencies of C1INH [13-16].

DPP-4 inhibitors — Dipeptidyl peptidase 4 (DPP-4) inhibitors (ie, gliptins) can also inhibit degradation of bradykinin and substance P and have been associated with an increased risk of angioedema, especially when used together with immunosuppressive drugs or ACE inhibitors [17]. (See "ACE inhibitor-induced angioedema", section on 'Dipeptidyl peptidase-4 inhibitors'.)

Hereditary and acquired angioedema due to C1 inhibitor deficiency — Angioedema can occur in patients with abnormalities in the level or function of the regulatory serpin C1INH (previously referred to as C1 esterase inhibitor), leading to increased generation of bradykinin due to contact system (also known as plasma kallikrein-kinin system) activation. Angioedema in these disorders typically asymmetrically affects the face, lips, tongue, throat, ears, hands and feet, bowel wall, and genitalia and does not characteristically occur in dependent parts of the body. Clinical manifestations and diagnosis are reviewed in detail separately. (See "Hereditary angioedema: Epidemiology, clinical manifestations, exacerbating factors, and prognosis" and "Acquired C1 inhibitor deficiency: Clinical manifestations, epidemiology, pathogenesis, and diagnosis".)

Summarized briefly, both hereditary and acquired forms of C1INH deficiency exist, with similar clinical manifestations. The main differences between the two conditions are the age of presentation and the underlying health of the patient:

- Patients with hereditary angioedema (HAE) typically present in childhood or early adolescence with angioedema, including recurrent abdominal attacks. Angioedema may follow trauma, infection, dental procedures, or emotional stress. There is typically an increasing frequency and severity of episodes with the onset of puberty. Exposure to estrogens, either through contraception, hormone replacement therapy, or pregnancy, may trigger attacks. These patients are otherwise healthy.

- In contrast, the acquired form typically occurs at an older age, and most patients have an associated lymphoproliferative disorder or autoimmune diathesis. (See "Acquired C1 inhibitor deficiency: Clinical manifestations, epidemiology, pathogenesis, and diagnosis", section on 'Associated disorders'.)

The swelling with both forms of C1INH deficiency can range in severity during a given episode from a minor inconvenience to life-threatening laryngeal edema. Overall, there is a significant risk of morbidity and mortality from angioedema attacks.

Hereditary angioedema with normal C1 inhibitor — Familial angioedema with an autosomal dominant inheritance pattern but normal C1INH levels has been identified [18]. The clinical presentation of angioedema in these patients resembles but is subtlety different than HAE due to C1INH deficiency. (See "Hereditary angioedema with normal C1 inhibitor".)

Specifically, these patients tend to be somewhat older at onset of swelling and have a greater ratio of orofacial swelling to abdominal swelling than HAE due to C1INH deficiency. Several subtypes of HAE with normal C1INH have been identified:

- HAE-FXII, defined by mutations involving coagulation factor XII
- HAE-Plasminogen, defined by a mutation in the plasminogen gene
- HAE-Angiopoietin-1, defined by a mutation in the angiopoietin-1 gene
- HAE-Kininogen, defined by a mutation in the kininogen gene
- HAE-Myoferlin, defined by a mutation in the myoferlin gene
- HAE-HS3ST6, defined by a mutation in the heparan sulfate-glucosamine 3-O-sulfotransferase 6 gene
- HAE-Unknown, which is the terminology used when patients meet the HAE with normal C1 inhibitor diagnostic criteria but have no recognized mutation

Fibrinolytic agents — Angioedema without urticaria has been reported following fibrinolysis with streptokinase and alteplase in patients treated acutely for stroke and thrombosis [19,20]. The swelling associated with fibrinolytic agents is likely bradykinin mediated as plasmin has been reported to activate coagulation factor XII of the contact system [21]. This complication is discussed separately. (See "Intravenous thrombolytic therapy for acute ischemic stroke: Therapeutic use", section on 'Angioedema'.)

Etiologies of unknown mechanism — There are several recognized causes of angioedema for which mechanisms are not defined (table 1). The treatment of these disorders is reviewed separately. (See "An overview of angioedema: Clinical features, diagnosis, and management".)

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 to exclude allergic disorders, drug reactions, and defects in complement pathways. Idiopathic angioedema may be divided into idiopathic histaminergic angioedema and idiopathic nonhistaminergic angioedema. The diagnosis and management of idiopathic angioedema are presented separately. The former is often associated with chronic spontaneous urticaria or inducible forms of urticaria (ie, physical urticaria). Idiopathic histaminergic angioedema without hives may have distinct pathophysiology compared with chronic spontaneous urticaria with or without angioedema [22]. Idiopathic nonhistaminergic angioedema may represent new probands with HAE-Unknown because the penetrance of HAE with normal C1INH can be relatively low. (See "An overview of angioedema: Clinical features, diagnosis, and management", section on 'Recurrent, idiopathic angioedema'.)

Infections — Infections have been associated with angioedema in children [23]. In a prospective study of 95 consecutive children with isolated angioedema (without urticaria or anaphylaxis) referred to an allergy clinic, angioedema was associated with infection in 19 (21 percent) [24]. Identified infections included the common cold (17 patients), streptococcal pharyngitis, and urinary tract infection. Infection was the most commonly associated disorder, followed by allergic etiologies. The association between angioedema and infections is not reported as regularly in adults. (See 'Children' below.)

Calcium channel blockers — Both dihydropyridines (eg, amlodipine, nifedipine) and nondihydropyridines (eg, diltiazem and verapamil) have been associated with angioedema, either of the skin or small bowel [25-29]. However, no mechanism has been proposed.

Other drugs — Other drugs that have been reported to cause angioedema without urticaria include sirolimus, everolimus, amiodarone, metoprolol, risperidone, paroxetine, and etanercept and other biologic agents [30-38]. Inhaled cocaine has been implicated in uvular angioedema [39-42].

Herbal medicines — Several herbal medicines have been associated with angioedema, including garlic, sanyak, and *Ecballium elaterium* [43-45].

Other rare causes — Other rare causes of angioedema include selected disorders with eosinophilia and urticarial vasculitis.

- **Disorders with eosinophilia** – Angioedema is associated with a peripheral eosinophilia in two disorders, the hypereosinophilic syndromes (HES) and Gleich syndrome.

  - Approximately 15 percent of patients with the HES have angioedema, and this diagnosis should be considered in patients with dramatic elevations in peripheral eosinophil counts (eg, ≥1500 eosinophils/microliter) [46,47]. The mechanisms of the angioedema in this disorder may involve the direct release of vasodilatory mediators from eosinophils or may reflect the activation of cutaneous mast cells by eosinophil-derived mediators. (See "Hypereosinophilic syndromes: Clinical manifestations, pathophysiology, and diagnosis".)

  - The entity of episodic angioedema with eosinophilia (Gleich syndrome) is characterized by recurrent episodes of angioedema, urticaria, pruritus, fever, weight gain, elevated serum immunoglobulin M (IgM), and leukocytosis with marked blood eosinophilia [48-51]. The level of blood eosinophilia parallels disease activity. The etiology of this syndrome is unknown but has been associated with upregulation of C5a receptors on eosinophils during episodes of disease [52]. Gleich syndrome is now considered a type

of HES, although the absence of cardiac damage or other end-organ involvement and the episodic nature of the symptoms distinguish this condition from other forms of HES. (See "Hypereosinophilic syndromes: Clinical manifestations, pathophysiology, and diagnosis", section on 'Episodic angioedema with eosinophilia (Gleich syndrome)'.)

- **Urticarial vasculitis** – Angioedema may be observed in patients with hypocomplementemic urticarial vasculitis, in which immunoglobulin G (IgG) anti-C1q is often identified [53,54]. The urticarial lesions of urticarial vasculitis are variably painful, ecchymotic, and purpuric and often leave residual bruising upon resolution. Systemic disease and fever may be present. (See "Urticarial vasculitis".)

CHILDREN

There are very few studies of angioedema in children (other than hereditary angioedema [HAE]), and isolated angioedema (ie, without urticaria or anaphylaxis) appears to be uncommon in this age group. One study reported on 95 children referred to an allergy clinic and followed prospectively [24]. Most had more than one episode. In 51 percent, no cause could be identified. In the remaining one-half, the most common associations were common infections (21 percent), followed by various allergic disorders (14 percent), the presence of thyroid autoimmunity with normal thyroid function (8 percent), and nonsteroidal antiinflammatory drugs (NSAIDs; 6 percent). One-third of the children required ongoing treatment with antihistamines, and all improved with this intervention. (See 'Infections' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Urticaria and angioedema (excluding hereditary 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 education: Angioedema (The Basics)" and "Patient education: Angioedema caused by ACE inhibitor medicines (The Basics)")

SUMMARY

- **Definition and pathogenesis** – Angioedema is self-limited, localized swelling of the skin or mucosal tissues. The presence of inflammatory mediators leads to a loss of vascular integrity, which allows fluid to move into the interstitial tissues. Angioedema may occur in isolation, accompanied by urticaria, or as a component of anaphylaxis. (See 'Pathogenesis' above.)

- **Three groups of etiologies** – The causes of angioedema can be divided into three groups based on the underlying mechanism (table 1) (see 'Causes' above):

  - **Mast cell mediated** – Mast cell-mediated angioedema, such as that seen in allergic reactions and reactions to nonsteroidal antiinflammatory drugs (NSAIDs). (See 'Mast cell-mediated etiologies' above.)

  - **Bradykinin mediated** – Bradykinin-mediated angioedema, such as that induced by angiotensin-converting enzyme (ACE) inhibitors or hereditary or acquired C1 inhibitor (C1INH) deficiency. (See 'Bradykinin-mediated etiologies' above.)

  - **Unknown mechanism** – Causes with unknown mechanisms, such as idiopathic angioedema and angioedema associated with viral infections in children. (See 'Etiologies of unknown mechanism' above.)

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REFERENCES

1. Lin RY, Cannon AG, Teitel AD. Pattern of hospitalizations for angioedema in New York between 1990 and 2003. Ann Allergy Asthma Immunol 2005; 95:159.
2. Commins SP, Satinover SM, Hosen J, et al. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-alpha-1,3-galactose. J Allergy Clin Immunol 2009; 123:426.
3. Romano A, Viola M, Guéant-Rodriguez RM, et al. Imipenem in patients with immediate hypersensitivity to penicillins. N Engl J Med 2006; 354:2835.
4. Zembowicz A, Mastalerz L, Setkowicz M, et al. Safety of cyclooxygenase 2 inhibitors and increased leukotriene synthesis in chronic idiopathic urticaria with sensitivity to nonsteroidal anti-inflammatory drugs. Arch Dermatol 2003; 139:1577.
5. Fontaine C, Bousquet PJ, Demoly P. Anaphylactic shock caused by a selective allergy to celecoxib, with no allergy to rofecoxib or sulfamethoxazole. J Allergy Clin Immunol 2005; 115:633.
6. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy 2014; 69:868.
7. Maurer M, Church MK, Marsland AM, et al. Questions and answers in chronic urticaria: where do we stand and where do we go? J Eur Acad Dermatol Venereol 2016; 30 Suppl 5:7.
8. Agah R, Bandi V, Guntupalli KK. Angioedema: the role of ACE inhibitors and factors associated with poor clinical outcome. Intensive Care Med 1997; 23:793.
9. Gandhi J, Jones R, Teubner D, Gabb G. Multicentre audit of ACE-inhibitor associated angioedema (MAAAA). Aust Fam Physician 2015; 44:579.
10. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008; 358:1547.
11. van Rijnsoever EW, Kwee-Zuiderwijk WJ, Feenstra J. Angioneurotic edema attributed to the use of losartan. Arch Intern Med 1998; 158:2063.
12. Abdi R, Dong VM, Lee CJ, Ntoso KA. Angiotensin II receptor blocker-associated angioedema: on the heels of ACE inhibitor angioedema. Pharmacotherapy 2002; 22:1173.
13. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. Ann Intern Med 1992; 117:234.
14. Dykewicz MS. Cough and angioedema from angiotensin-converting enzyme inhibitors: new insights into mechanisms and management. Curr Opin Allergy Clin Immunol 2004; 4:267.

15. Berkun Y, Shalit M. Hereditary angioedema first apparent in the ninth decade during treatment with ACE inhibitor. Ann Allergy Asthma Immunol 2001; 87:138.
16. Ricketti AJ, Cleri DJ, Ramos-Bonner LS, Vernaleo JR. Hereditary angioedema presenting in late middle age after angiotensin-converting enzyme inhibitor treatment. Ann Allergy Asthma Immunol 2007; 98:397.
17. Byrd JB, Woodard-Grice A, Stone E, et al. Association of angiotensin-converting enzyme inhibitor-associated angioedema with transplant and immunosuppressant use. Allergy 2010; 65:1381.
18. Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. Lancet 2000; 356:213.
19. Ottomeyer C, Hennerici MG, Szabo K. Raising awareness of orolingual angioedema as a complication of thrombolysis in acute stroke patients. Cerebrovasc Dis 2009; 27:307.
20. Walls RM, Pollack CV Jr. Successful cricothyrotomy after thrombolytic therapy for acute myocardial infarction: a report of two cases. Ann Emerg Med 2000; 35:188.
21. Agostoni A, Gardinali M, Frangi D, et al. Activation of complement and kinin systems after thrombolytic therapy in patients with acute myocardial infarction. A comparison between streptokinase and recombinant tissue-type plasminogen activator. Circulation 1994; 90:2666.
22. Sabaté-Brescó M, Rodriguez-Garijo N, Azofra J, et al. A Comparative Study of Sex Distribution, Autoimmunity, Blood, and Inflammatory Parameters in Chronic Spontaneous Urticaria with Angioedema and Chronic Histaminergic Angioedema. J Allergy Clin Immunol Pract 2021; 9:2284.
23. Pattanaik D, Lieberman JA. Pediatric Angioedema. Curr Allergy Asthma Rep 2017; 17:60.
24. Ertoy Karagol HI, Yilmaz O, Bakirtas A, et al. Angioedema without urticaria in childhood. Pediatr Allergy Immunol 2013; 24:685.
25. Turcu AF, White JA, Kulaga ME, et al. Calcium channel blocker-associated small bowel angioedema. J Clin Gastroenterol 2009; 43:338.
26. Southward J, Irvine E, Rabinovich M. Probable amlodipine-induced angioedema. Ann Pharmacother 2009; 43:772.
27. Hedner T, Samuelsson O, Lindholm L, et al. Precipitation of angioedema by antihypertensive drugs. J Hypertens Suppl 1991; 9:S360.
28. Romano A, Pietrantonio F, Garcovich A, et al. Delayed hypersensitivity to diltiazem in two patients. Ann Allergy 1992; 69:31.

29. Sadick NS, Katz AS, Schreiber TL. Angioedema from calcium channel blockers. J Am Acad Dermatol 1989; 21:132.
30. Er F, Nia AM, Erdmann E. [67-year-old patient with speech disorder and dysphagia]. Dtsch Med Wochenschr 2008; 133:2463.
31. Fuchs U, Zittermann A, Berthold HK, et al. Immunosuppressive therapy with everolimus can be associated with potentially life-threatening lingual angioedema. Transplantation 2005; 79:981.
32. Mackenzie M, Wood LA. Lingual angioedema associated with everolimus. Acta Oncol 2010; 49:107.
33. Mahé E, Morelon E, Lechaton S, et al. Angioedema in renal transplant recipients on sirolimus. Dermatology 2007; 214:205.
34. Burches E, Garcia-Verdegay F, Ferrer M, Pelaez A. Amiodarone-induced angioedema. Allergy 2000; 55:1199.
35. Krikorian RK, Quick A, Tal A. Angioedema following the intravenous administration of metoprolol. Chest 1994; 106:1922.
36. Sendur OF, Turan Y, Berkit IK, Tastaban E. Angio-oedema in a patient treated with etanercept for rheumatoid arthritis. Basic Clin Pharmacol Toxicol 2009; 104:488.
37. Cooney C, Nagy A. Angio-oedema associated with risperidone. BMJ 1995; 311:1204.
38. Kimyai-Asadi A, Harris JC, Nousari HC. Critical overview: adverse cutaneous reactions to psychotropic medications. J Clin Psychiatry 1999; 60:714.
39. Kinsey CM, Howell M. A 27-year-old woman with a swollen uvula, chest pain, and elevated creatinine phosphokinase levels. Chest 2008; 133:809.
40. Hidalgo Mora JJ, Giménez de Llano E, Sempere Verdú E, Feliú Sagalá M. [Uvular angioedema after intranasal cocaine consumption]. Med Clin (Barc) 2002; 119:438.
41. Kestler A, Keyes L. Images in clinical medicine. Uvular angioedema (Quincke's disease). N Engl J Med 2003; 349:867.
42. Welling A. Enlarged uvula (Quincke's Oedema)--a side effect of inhaled cocaine?--A case study and review of the literature. Int Emerg Nurs 2008; 16:207.
43. Hur GY, Park HJ, Kim HA, et al. Identification of Dioscorea batatas (sanyak) allergen as an inhalant and oral allergen. J Korean Med Sci 2008; 23:72.
44. Micozzi MS, Pribitkin EA. Common herbal remedies, adverse reactions, and dermatologic effects. Skinmed 2010; 8:30.

45. Caiozzi G, Cabrera D, Mardónez JM, Saldías F. [Herbal medicines and severe adverse effects: uvular angioedema caused by Echballium elaterium]. Rev Med Chil 2002; 130:1407.
46. Weller PF, Bubley GJ. The idiopathic hypereosinophilic syndrome. Blood 1994; 83:2759.
47. Fauci AS, Harley JB, Roberts WC, et al. NIH conference. The idiopathic hypereosinophilic syndrome. Clinical, pathophysiologic, and therapeutic considerations. Ann Intern Med 1982; 97:78.
48. Gleich GJ, Schroeter AL, Marcoux JP, et al. Episodic angioedema associated with eosinophilia. N Engl J Med 1984; 310:1621.
49. Lassalle P, Gosset P, Gruart V, et al. Presence of antibodies against endothelial cells in the sera of patients with episodic angioedema and hypereosinophilia. Clin Exp Immunol 1990; 82:38.
50. Bain BJ, Fletcher SH. Chronic eosinophilic leukemias and the myeloproliferative variant of the hypereosinophilic syndrome. Immunol Allergy Clin North Am 2007; 27:377.
51. Florian S, Esterbauer H, Binder T, et al. Systemic mastocytosis (SM) associated with chronic eosinophilic leukemia (SM-CEL): detection of FIP1L1/PDGFRalpha, classification by WHO criteria, and response to therapy with imatinib. Leuk Res 2006; 30:1201.
52. Nakashima K, Sakurada T, Imayama S, et al. A case of episodic angioedema associated with blood eosinophilia: upregulated C5a receptor expression on eosinophils. Allergy 1998; 53:320.
53. Venzor J, Lee WL, Huston DP. Urticarial vasculitis. Clin Rev Allergy Immunol 2002; 23:201.
54. Jara LJ, Navarro C, Medina G, et al. Hypocomplementemic urticarial vasculitis syndrome. Curr Rheumatol Rep 2009; 11:410.

Topic 8099 Version 26.0

GRAPHICS

Causes of angioedema classified by mechanism

Mechanism	Known or presumed pathophysiology	Examples
Activation of mast cells Clinical characteristics – Often associated with pruritus and urticaria. May present as part of an allergic reaction or anaphylaxis.	IgE-mediated mast cell activation (type I hypersensitivity)	Allergic reactions to foods, drugs latex, insect stings, other allergens
	Direct mast cell activation	Opioids, radiocontrast agents
	Perturbations in arachidonic acid metabolism	Aspirin and other NSAIDs
	Immunologic and other non-IgE-mediated mast cell activation	Idiopathic histaminergic angioedema, often associated with chronic spontaneous urticaria or inducible urticaria
Generation of bradykinin Clinical characteristics – **Not** associated with pruritus or urticaria. May present with abdominal symptoms due to bowel wall edema.	Inhibition of enzymes involved in degradation of bradykinin	ACE inhibitors, DPP-4 inhibitors
	Deficiency or dysfunction of complement C1 inhibitor due to mutation	Hereditary angioedema (also known as hereditary C1 inhibitor deficiency or dysfunction)
	Deficiency or dysfunction of complement C1 inhibitor often due to anti-C1 inhibitor antibody or an underlying malignancy	Acquired C1 inhibitor deficiency
	Defects in several genes have been implicated, including those for coagulation factor XII, plasminogen, and angiopoietin-1. Other cases are idiopathic.	Hereditary angioedema with normal C1 inhibitor
Unknown pathophysiology Clinical characteristics – Variable. Sometimes associated with urticaria.		Idiopathic nonhistaminergic angioedema
		Infections (especially in children)
		Drugs – Calcium channel blockers, fibrinolytic agents, herbal medicines, other hypereosinophilic syndrome
		Hypereosinophilic syndrome

		Gleich syndrome
		Urticarial vasculitis

IgE: immunoglobulin E; NSAIDs: nonsteroidal antiinflammatory drugs; ACE: angiotensin-converting enzyme; DPP-4: dipeptidyl peptidase 4

Graphic 97087 Version 10.0

Major causes of mast cell-mediated angioedema

IgE-dependent allergic reactions
Foods
Drugs (antibiotics, local anesthetics, hormones)
Stinging insects
Latex
Contact (fresh fruits and vegetables, animal saliva)
Direct mast cell mediator release
Opiates
Muscle relaxants (succinylcholine, curare)
Radiocontrast agents
Perturbations in arachidonic acid metabolism within mast cells
Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs)

IgE: immunoglobulin E.

Graphic 58834 Version 6.0

Causes of anaphylaxis

Allergens (IgE-dependent immunologic mechanism)
Foods, especially peanut, tree nut, crustacean shellfish, finned fish, cow's milk, hen's egg
Insect stings (eg, Hymenoptera venom) and insect bites (eg, kissing bugs)
Medications (eg, antibiotics, NSAIDs)
Biologic materials, including allergen immunotherapy, monoclonal antibodies, chemotherapy agents, and vaccines*
Natural rubber latex
Food additives, including spices, insect-derived colorants (eg, carmine), and vegetable gums
Inhalants (rare; eg, horse dander, cat dander, grass pollen)
Human seminal fluid (rare trigger of anaphylaxis in women)
Occupational allergens (eg, stinging insects, natural rubber latex)
Immunologic triggers (IgE-independent mechanism)
IgG dependent (rare; eg, to high-molecular-weight dextran, infliximab)
Coagulation system activation (eg, heparin contaminated with oversulfated chondroitin sulfate)
Idiopathic anaphylaxis
Consider the possibility of a hidden or previously unrecognized trigger
Consider the possibility of a mast cell activation syndrome, including systemic mastocytosis
Nonimmunologic triggers (direct activation of mast cells and basophils)
Physical factors (eg, exercise¶, cold, heat)
Medications (eg, opioids, NSAIDs)
Radiocontrast agents
Alcohol (ethanol; may augment, rarely induces)

Any food, insect sting or bite, or medication or biologic can potentially trigger anaphylaxis. Novel or unusual allergen triggers include storage mite-contaminated flour and saliva from kissing bugs. They also include mosquitoes, pigeon ticks, green ants, and pharaoh ants and venoms from jellyfish, scorpions, and snakes. Medications include taxanes, platins, and other chemotherapy drugs, biologic agents, including monoclonal antibodies, such as rituximab, cetuximab, infliximab, and, uncommonly, omalizumab. Some triggers, such as radiocontrast media, insect venoms, and medications (such as NSAIDs) can act through more than one mechanism.

IgE: immunoglobulin E; NSAID: nonsteroidal antiinflammatory drug; IgG: immunoglobulin G.

* Reactions to vaccines are rare and typically involve an excipient, such as gelatin, rather than microbial content.

¶ Often involves a cofactor, such as a food, medication (eg, an NSAID), or exposure to cold air or water.

Graphic 70667 Version 24.0

Gell and Coombs classification of immunologic drug reactions

Type	Description	Mechanism	Clinical features
I Immediate reaction (within one hour)	IgE-mediated, immediate-type hypersensitivity	Antigen exposure causes IgE-mediated activation of mast cells and basophils, with release of vasoactive substances, such as histamine, prostaglandins, and leukotrienes.	Anaphylaxis Angioedema Bronchospasm Urticaria (hives) Hypotension
II	Antibody-dependent cytotoxicity	An antigen or hapten that is intimately associated with a cell binds to antibody, leading to cell or tissue injury.	Hemolytic anemia Thrombocytopenia Neutropenia
III	Immune complex disease	Damage is caused by formation or deposition of antigen-antibody complexes in vessels or tissue. Deposition of immune complexes causes complement activation and/or recruitment of neutrophils by interaction of immune complexes with Fc IgG receptors.	Serum sickness Arthus reaction
IV	Cell-mediated or delayed hypersensitivity	Antigen exposure activates T cells, which then mediate tissue injury. Depending upon the type of T cell activation and the other effector cells recruited, different subtypes can be differentiated (ie, types IVa to IVd).	Contact dermatitis Some morbilliform reactions Severe exfoliative dermatoses (eg, SJS/TEN) AGEP DRESS/DiHS Interstitial nephritis Drug-induced hepatitis Other presentations

IgE: immunoglobulin E; Fc IgG: Fc portion of immunoglobulin G; SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis; AGEP: acute generalized exanthematous pustulosis; DRESS/DiHS:

drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome.

Adapted from: Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. Clin Allergy 1988; 18:515.

Graphic 80466 Version 18.0

Pseudoallergic and allergic reactions to nonsteroidal antiinflammatory drugs (NSAIDs)

Type	Eliciting NSAID	Signs and symptoms	Timing of onset of signs/symptoms	Patient comorbidities
Pseudoallergic NSAID reactions: ▪ Elicited by multiple NSAIDs (including aspirin) in a susceptible patient ▪ Related to the pharmacologic ability of NSAIDs to inhibit COX-1 enzyme				
Type 1	Multiple (including aspirin)	Common: ▪ Severe rhinitis, nasal obstruction ▪ Bronchospasm ▪ Conjunctival injection ▪ Facial flushing Uncommon: ▪ Throat tightness/laryngospasm ▪ Nausea/vomiting ▪ Diarrhea ▪ Hypotension	Delayed: 30 minutes to 3 hours after ingestion or administration	▪ Asthma (present in most but not all patients) ▪ Chronic rhinosinusitis with nasal polyposis (patients usually have extensive sinusitis on CT and often report anosmia) ▪ AERD*
Type 2	Multiple (including aspirin)	Urticaria and/or angioedema	30 to 90 minutes	Chronic urticaria (patients may report being able to tolerate NSAIDs when urticaria is in remission)
Type 3	Multiple (including aspirin)	Urticaria and/or angioedema	30 to 90 minutes	None
Type 4	Multiple (including aspirin)	Symptoms affecting both the respiratory tract and skin. Includes patients with AERD who develop cutaneous symptoms in the context of respiratory reactions.	Variable depending upon the type of reaction: 30 to 90 minutes	▪ Some patients have AERD and experience systemic reactions with

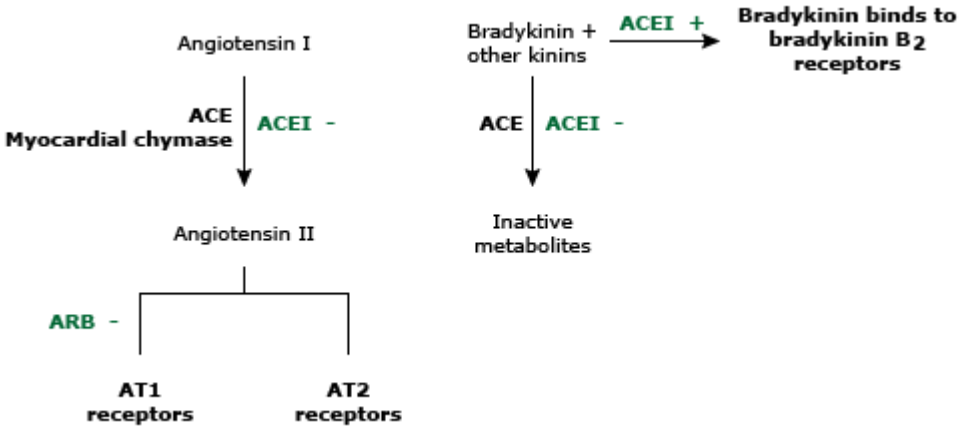
				cutaneous symptoms ▪ Other patient have no underlying conditions
Allergic NSAID reactions: ▪ Elicited by a single NSAID (or rarely by more than one agent with very similar structure) in a susceptible patient ▪ **Not** reported with aspirin ▪ Presumed to be IgE mediated				
Type 5	A single NSAID (not aspirin)	Cutaneous: Urticaria, pruritus, angioedema	Variable: Minutes to a few hours after ingestion/administration	None
Type 6	A single NSAID (not aspirin)	Anaphylaxis (probably a more severe form of type 5)	Variable: Minutes to a few hours after ingestion/administration	None

COX: cyclooxygenase; CT: computed tomography; AERD: aspirin-exacerbated respiratory disease; IgE: immunoglobulin E.

* AERD refers to the triad of asthma, chronic rhinosinusitis with nasal polyposis, and aspirin (or NSAID) induced type 1 pseudoallergic reactions.

Graphic 90304 Version 19.0

Actions of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on angiotensin and kinin pathways



Left side of figure: ACE normally converts angiotension I to angiotension II, and ACE inhibitors (ACEIs) inhibit this reaction.

Right side of figure: In the presence of ACEIs, bradykinin is not degraded and binds to bradykinin B_2 receptors.

ACE: angiotensin-converting enzyme; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

Graphic 67838 Version 4.0