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## Angioedema: Review and Novel Updates

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## Disclosures

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- Research Support: Shire
- Advisory Board: Shire, Alnylam, CSL, Salix

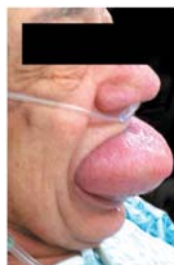


## Objectives

- Define and review different types of angioedema encountered in clinical practice
- Propose an algorithm for evaluation of angioedema based on recent recommendations
- Discuss management options for patient presenting with recurrent episodes of angioedema without urticaria

## Angioedema

- Rapid swelling below the surface of the skin
- Self-limited and localized
- Results from extravasation of fluid into interstitial tissues
- Non-pitting



## Definition

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- It results from a temporary increase in vascular permeability caused by the release of vasoactive mediators
- May occur alone, with urticaria, or as part of an allergic reaction



## Angioedema vs. Edema

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Swelling	Angioedema	Edema
Symmetric	No	Yes
Dependent	No	Yes
Pitting	No	Yes
Mechanism	Increased permeability	Hydrostatic



## Clinical Presentation

- 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 and spontaneous resolution in hours to a few days
  - Asymmetric distribution
  - Tendency **not** to involve gravitationally-dependent areas
  - Association of some forms of angioedema with other signs and symptoms of allergic reactions or anaphylaxis

## Pathophysiology of Angioedema

- Mast cell degranulation
  - Allergic reactions to foods or insect stings
  - Signs and symptoms include urticaria, flushing, generalized pruritus, bronchospasm, throat tightness, and/or hypotension
  - Angioedema may also be histamine-mediated (histaminergic) without clear evidence of mast cell degranulation and often termed idiopathic angioedema
- Activation of kinin-generating pathways (called bradykinin-mediated)
  - **Not** associated with urticaria, bronchospasm, or other symptoms of allergic reactions
  - Prolonged time course, usually developing over 24 to 36 hours and resolving within two to four days
  - In this type of angioedema, the relationship between the trigger and the onset of symptoms is often not apparent

## Angioedema: Bradykinin vs. Histamine

	Bradykinin	Histamine
Severity of swelling	Greater	Lesser
Duration of swelling	Longer	Shorter
Risk for fatal airway obstruction	Appreciable	Exceedingly low
Abdominal attacks	Very common	Rare
Response to antihistamines, corticosteroids, epinephrine	Poor	Excellent

Contact dermatitis involving the facial and periorbital skin



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### Erysipelas involving the buttock



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### 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



## Scleredema



## Blepharochalasis



The patient had recurrent bouts of upper lid swelling. Chronic changes of distended and thinned "cigarette-paper" skin remain.

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## Superior vena cava syndrome and tumors

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- Edema of the face, neck, or upper extremities, accompanied by venous engorgement, is observed with 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



## Hypothyroidism

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- 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





## Granulomatous cheilitis

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## Idiopathic edema

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- Persistent, recurrent episodes of edema of face, hands, trunk, and limbs due to fluid retention, in menstruating women
- No apparent cardiac, renal, or other disease
- Looks like peripheral edema
- Theories about pathogenesis include:
  - Some type of limited capillary leak
  - A form of refeeding syndrome (patients are often very conscious about weight and have unusual eating behaviours)
  - Paradoxical response to diuretic use



## Disorders resembling laryngeal edema

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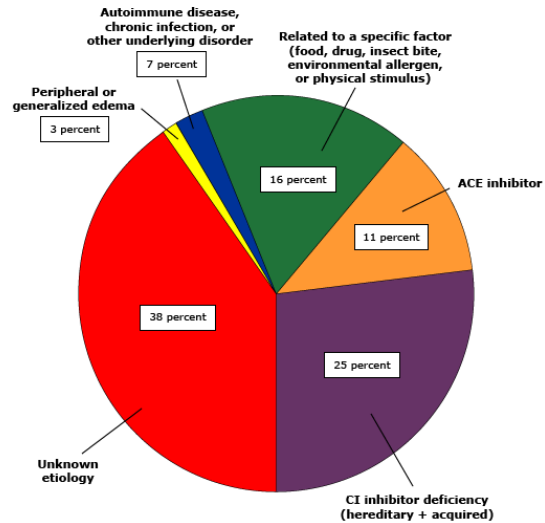
- The differential diagnosis of laryngeal edema includes tonsillitis, peritonsillar abscess, and pharyngeal foreign body
- Historical information should differentiate these entities from angioedema, as infectious causes should have accompanying fever and other signs of illness
- The diagnosis of a pharyngeal foreign body can be difficult, however, particularly in the preverbal infant

## Other causes of bowel wall edema

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- Mesenteric infarction
- Vasculitis
- Intramural hemorrhage
- Inflammatory bowel disease, acute ileitis (Yersinia, Campylobacter infections)
- Peritoneal carcinomatosis
- Inflammatory conditions adjacent to the bowel wall

### Etiologies of angioedema in referral populations



### Angioedema without Urticaria: Clinical Survey

- Tertiary level center where patients are referred mostly by specialists
- Reviewed all patients with angioedema without urticaria between January 1993 and December 2003
- Identified 929 patients and 776 patients completed the full work up



## Evaluation

- Clinical history and physical examination
- CBC, SPEP, CRP, ESR, LFTs, TSH, ANA
- C4, C1 inhibitor level and function, C1Q
- Stool studies
- Urinalysis
- Sinus and dental x-rays

**If evaluation was negative, antihistamine treatment for one month was initiated**



**Table 1:** Classification of angioedema without urticaria according to clinical or etiopathogenetic characteristics, *n* = 776

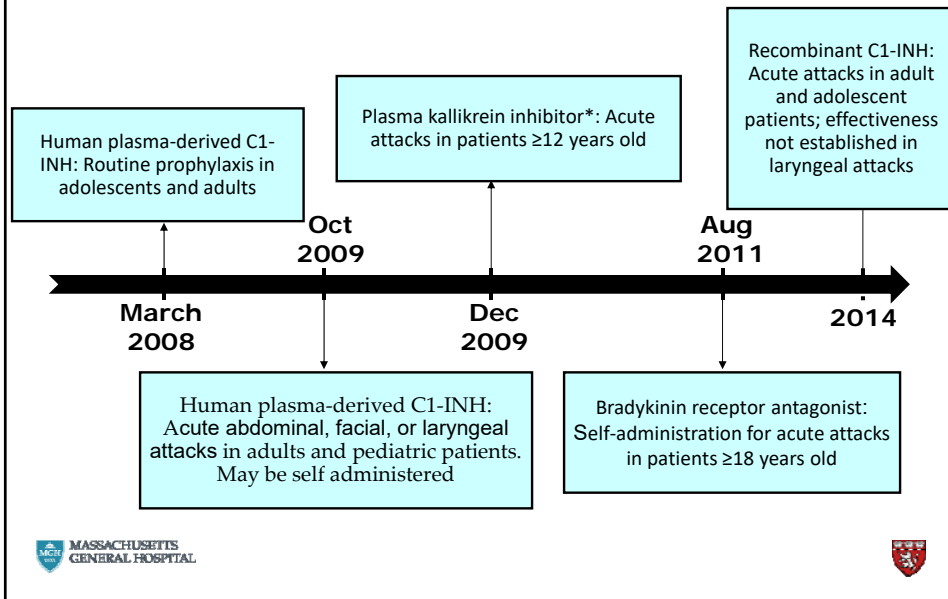
	Patients		M:F ratio	Age at onset, yr	
	No.	%		Median	Range
Related to a specific factor*	124	16	0.51	39	13-76
Autoimmune disease/infection	55	7	0.62	49	3-78
ACE inhibitor-related	85	11	0.93	61	32-84
C1-inhibitor deficiency	197	25			
Hereditary	183		0.88	8	1-34
Acquired	14		1.8	56.5	42-76
Unknown (idiopathic) etiology	294	38			
Histaminergic	254		0.56	40	7-86
Nonhistaminergic	40		1.35	36	8-75
Peripheral/generalized edema	21	3	0.17	—	

Note: M = male, F = female, ACE = angiotensin-converting enzyme.

\*A food, drug, insect bite, environmental allergen or other physical stimulus.



## Current Treatments for HAE in the U.S.



**Table 1:** Classification of angioedema without urticaria according to clinical or etiopathogenetic characteristics,  $n = 776$

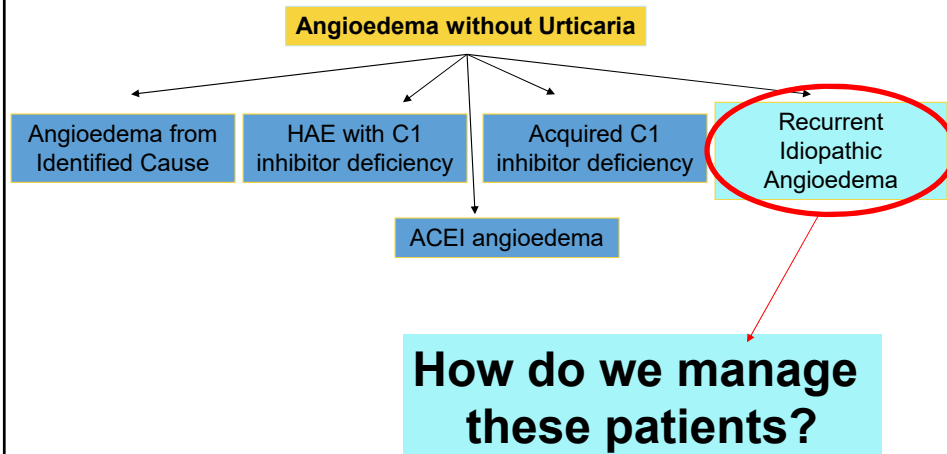
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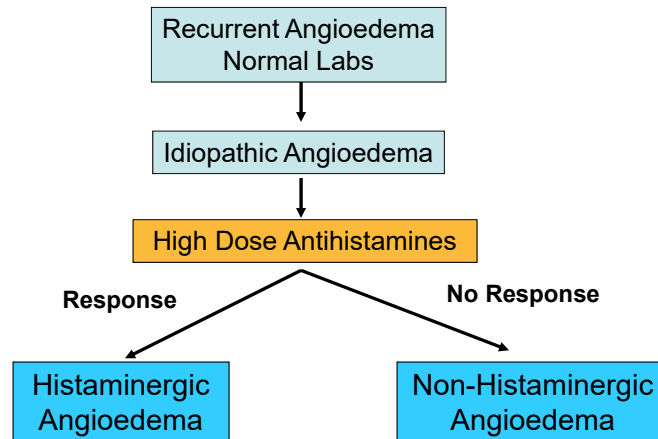
## Recurrent Idiopathic Angioedema



## Idiopathic Angioedema: Definition

- Defined as three or more episodes of swelling in a period of 6–12 months without a clear etiology after a thorough evaluation
- Critical to rule out all of the known causes of angioedema before labeling a patient as having idiopathic angioedema
- To date, the frequency of this type of angioedema is unclear as epidemiologic studies are lacking

## Idiopathic Angioedema



## Idiopathic Histaminergic Angioedema

Table 1: Classification of angioedema without urticaria according to clinical or etiopathogenetic characteristics,  $n = 776$

	Patients		M:F ratio	Age at onset, yr	
	No.	%		Median	Range
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Peripheral/generalized edema	21	3	0.17	—	

Note: M = male, F = female, ACE = angiotensin-converting enzyme.  
\*A food, drug, insect bite, environmental allergen or other physical stimulus.

- Initial evaluation completely normal
- 254 (86%) patients responded to antihistamine therapy



## What is a high dose of antihistamines?

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- The mechanism by which histamine release is initiated in this disorder is not fully understood
- Expert opinion suggests that 4 times the typical dose is accepted as high dose

## Idiopathic Histaminergic Angioedema

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- Most common form of idiopathic angioedema
- Clinical history
  - Age for onset variable
  - No family history of angioedema
  - Develops rapidly reaching maximum in 4-6 hours
  - Gastrointestinal and laryngeal mucosa are spared
  - Death has not been reported
- No precipitating factors identified
- Respond to corticosteroids and epinephrine as acute treatment



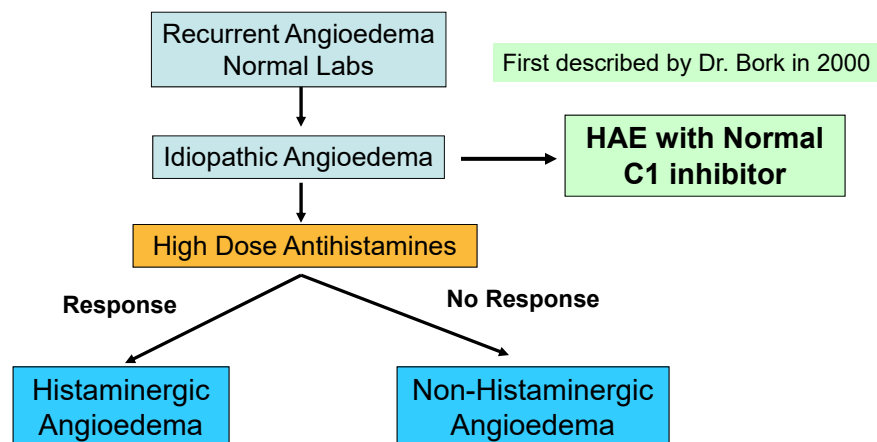
## Treatment for Idiopathic Angioedema: Histaminergic

- High dose antihistamines (4x standard doses)
- **Epinephrine should be considered for treatment of severe symptoms in the acute setting**
- C
- Immunosuppressants
- Xolair

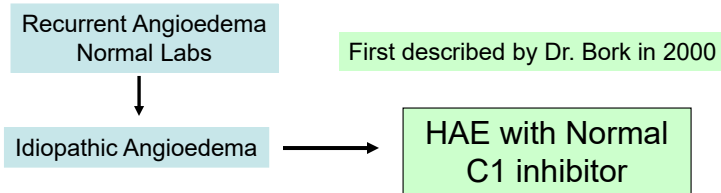
Similar to refractory cases of idiopathic urticaria and angioedema



## Idiopathic Angioedema



## HAE with Normal C1 Inhibitor



- Recurrent angioedema without hives
- Normal C4, C1-INH antigen, and C1-INH function
- Plus one of the following:
  - Factor XII mutation associated with the disease
  - A family history of angioedema and lack of response to high-dose antihistamine therapy

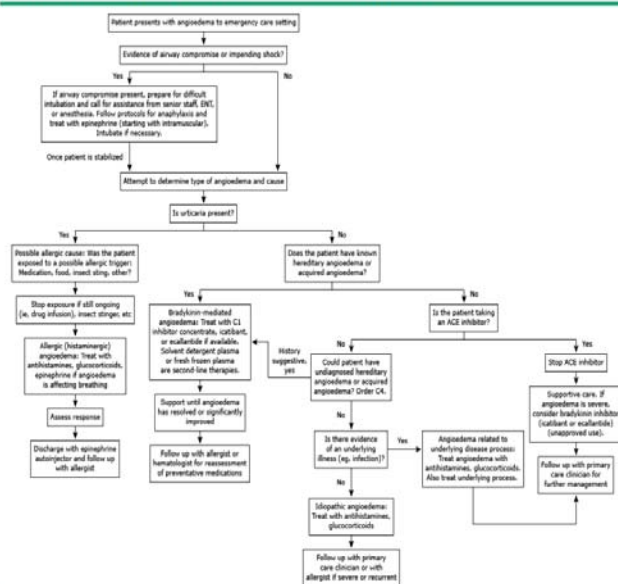
## Treatment for HAE with Normal C1INH

- No randomized prospective clinical trials conducted
- Observations suggest disorder does not involve histamine or mast cell degranulation
- Drugs that are effective for HAE with C1INH deficiency appear to be helpful in HAE with normal C1INH
- Avoid estrogens and ACE inhibitors

## Summary: Idiopathic Angioedema

- Diagnosis of exclusion
- Bradykinin or histamine can be the key mediator
- Majority of patients respond to high dose antihistamine therapy
- Therapeutic trials are helpful in differentiating causes

### Algorithm for evaluation and management of angioedema in the urgent care setting



## Summary

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- Angioedema is a localized, self-limiting swelling of the skin and/or submucosa with or without urticaria
- Large differential diagnosis to consider in angioedema without urticaria
  - Requires thorough history and evaluation
- Treatment of histaminergic angioedema will depend on its cause
  - During the acute phase, treatment will involve antihistamine, corticosteroid and, in severe cases, epinephrine