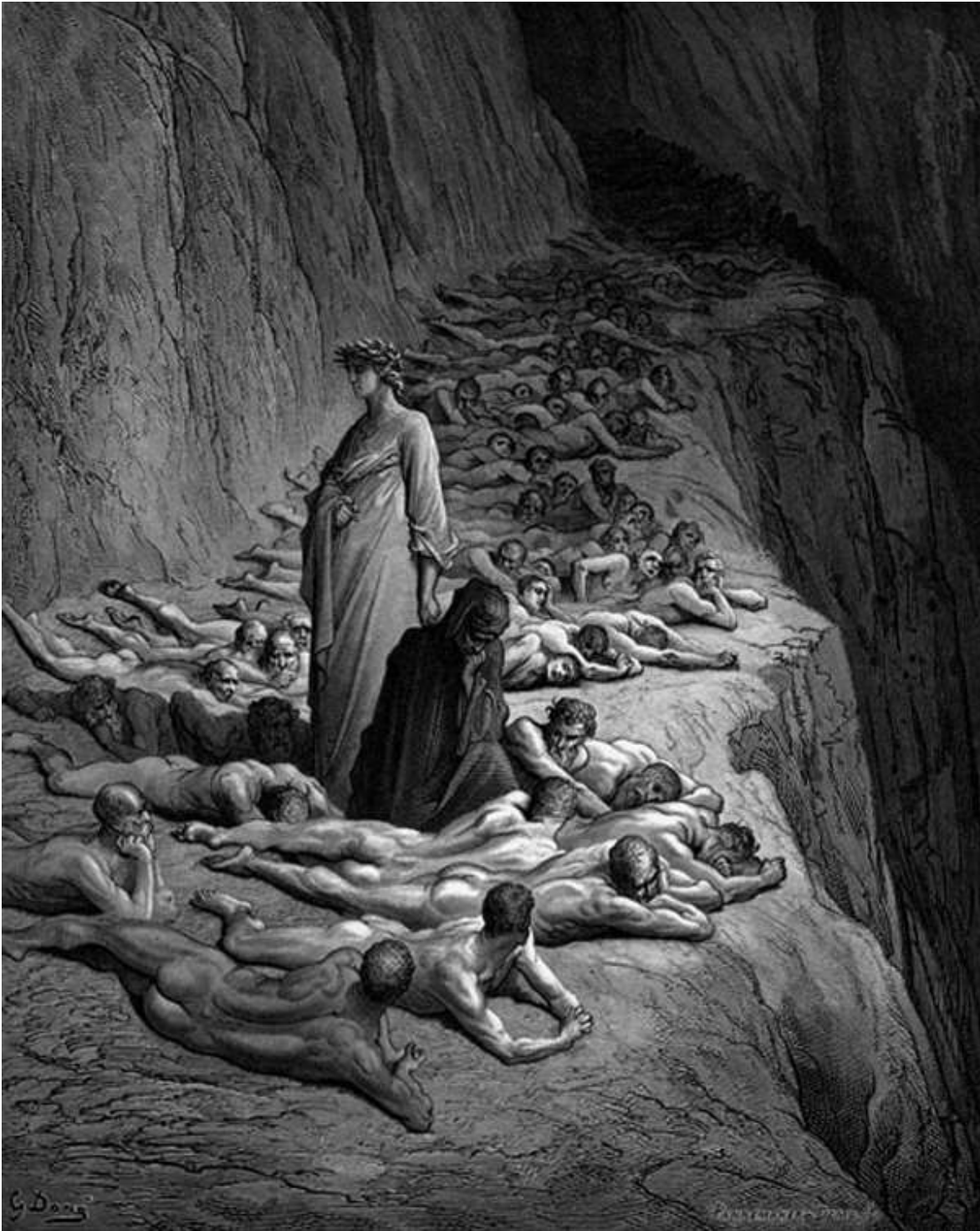


ANGIOEDEMA



Dante kneels to Pope Adrian V who he is astonished to find among the shades of the avaricious on the Fifth Terrace of Purgatory, Woodcut print, Gustave Dore, 1867

*When I was free to do what I desired I
drew away and stood above that soul
whose words had made me first aware of
him,*

*saying, "Spirit in whom weeping ripens
that without which there is no return to
God, for my sake just a while neglect
your greater care.*

*"Tell me who you were and why you lie
face down and whether there is
something I might do for you back there,
where I set out alive".*

*And he to me; "Why Heaven turns our
backs against Itself, that you shall know,
but first know that I was a successor to
St. Peter.*

*"Between Sestri and Chiavari there runs
down a lovely stream and with its name
the title of my line has marked its shield.*

*"In a month and little more I learned
how heavy the mantle weighs on one
who keeps it from the mud, making any
other burden seem a feather.*

*"My conversion, alas, came late - when
I was made the Roman shepherd, I
discovered a life of lies.*

*"I saw that there the heart was not at
peace, nor was preferment possible in
that life, and for this higher state my
love was kindled.*

*"Until that moment I was a wretched
soul, cut off from God, and filled with
avarice. Now, as you see, I am punished
for that here.*

*"The work of avarice is here proclaimed
in the purging of the down-turned souls,
and the mountain gives no punishment
more bitter.*

*"Just as we failed to lift our eyes on high
because they were fixed on earthly
things, so justice here has turned them to
the earth.*

*"As avarice quenched our love of worthy
things, wasting our chance to do good
works, so justice here has bound us fast.*

*"Securely tied are our hands and feet.
As long as it shall please the righteous
Lord so long shall we, unmoving lie here
prone".*

*I had kneeled and was about to speak,
but as soon as I began and he perceived,
only by listening, that I did him
reverence,*

*"Why", he asked "did you bend down
that way?" And I: "Because the dignity
of Your high office stung my conscience
as I stood erect".*

*"Straighten you legs, stand up, brother",
he replied, "make no mistake. I am a
fellow servant with you, and with the
others, of a single Power.*

*"if ever you did understand the holy
passage in the gospel where it says "nor
do they marry" you may well perceive
just why I saw this.*

*"Now go your way. I would not keep you
longer, for your being here impedes the
tears with which I ripen that of which
you spoke.*

*"On earth I have a niece who is called
Alagia - she is still virtuous if indeed
our house has not by its example made
her wicked, and she alone is left to me
back there".*

**Dante Alighieri, Purgatorio XIX, 88-
145 (1306-1317)**

Dante and Virgil now find themselves on the Fifth Terrace of Purgatory, wherein they find the shades of those punished whose sins in life were of avarice and of prodigality. These souls are forced to lie face down with their faces in the dirt for eons, "Just as we failed to lift our eyes on high because they were fixed on earthly things, so justice here has turned them to the earth". Dante hears one shade weeping, and out of pity goes up to speak with it, "Tell me who you were and why you lie face down". The spirit answers, "know that I was a successor to St. Peter". Dante is shocked that he is speaking to no less than a Pope! It seems that this Pope spent his life on earth in a constant state of greed, and the only reason that he is not in Hell (with quite a number of other Popes) is that he repented of his sins shortly after his accession to the throne of St. Peter. Dante, by reflex, kneels reverently before him. But in a severe and urgent admonishment the Pope angrily responds not in elegant Latin this time, but in the rough Italian vernacular of the age - "get up off your knees brother, I am a fellow servant with you, and with the others, of a single Power!" In God's kingdom no one is any more special than anyone else! At least it appears that Adrian has insight and is truly repentant - a good sign that perhaps his torment in Purgatory will not be too much protracted. The Pope explains that despite the exalted office he once held in life, in Purgatory it now makes no difference whatsoever, all are equal before the greater power.

Literary scholars and historians have long pondered the identity of the pope Dante placed into the Fifth Terrace of Purgatory. References to two towns on the Ligurian coast, Sestri and Chiavari, as well as a reference to a stream which runs between these towns and which decorates the coat of arms of a prominent family of the region, leave scholars in little doubt that the identity of the shade is Adrian V, an obscure Thirteenth century Pope who when elected was already unwell and reigned for just five weeks before he died. The line "...in a month and a little more", defines a five week reign, and further confirms the identity of the Pope, as Adrian V who was elected on July 11, 1276 and who died August 18 1276, just five weeks later. When his kindred came to congratulate him on his election he replied with words to the effect that he would rather be a cardinal in good health than a dying Pope. Dante had no hesitation in placing Popes into Hell - we find a number of them there. Adrian V is the first saved Pope we meet in the afterlife - though only just saved - he must spend time in Purgatory first to atone for his earthy sins. His penance on the Fifth Terrace is miserable and protracted.

We know very little about this Pope - but historians cannot find any hard evidence of his having been particularly avaricious, or even of mending his ways in the very brief time after he had become Pope. Perhaps Dante, far more of a contemporary, knew very much more about the short lived Pope than what we now know of him now over eight centuries later. Dante asks what he can do to help - Adrian can name only a single person, his niece Alagia, who might pray for his soul - prayers being able to mitigate but not change a punishment. He can think of none else, indicating that perhaps either all of his relatives are worldly and avaricious themselves without the slightest regard for him or that perhaps none would even think him worthy of their prayers.

Fascinatingly we know that Alagia was married to a certain Moroello Malaspina who had shown Dante hospitality in Lunigiana during the first desperate and lonely years of his political exile from Florence. Dante would therefore have known Alagia and it is clear he thought well enough of her enough to present her in a good light in the Divine

Comedy. And knowing Alagia almost certainly meant he knew something of Adrian V as well. It was Adrian's misfortune that Dante would know of him. If he had not known him he would have been utterly unknown to the world, just simply a name and no more in a long list of St Peter's successors. But Dante did know him, or at least, knew of him, and in consequence Adrian is remembered to posterity always as one of the shades of the avariciousor, to put it into modern Australian vernacular....a "greedy bastard".

When we treat a case of angioedema our immediate reflex response mirrors that of Dante on the Fifth Terrace of the Avaricious, we instantly kneel to the traditional treatments - steroids, antihistamines and adrenaline. Yet not all angioedema is of the same causation. If it is induced by ACE inhibitors then our standard treatments will do no good here, all are equally useless. We must get off our knees and look for another way, in this case the agent icatibant is what will assist us.



Dante and Virgil among the avaricious, Gustave Doré woodcut print, 1867

*We made our way with scant slow steps,
my attention fixed upon those weeping shades
as I listened to their piteous lamentations.*

Dante Alighieri, Purgatorio XX, 16-18 (1306-1317)

ANGIOEDEMA

Introduction

Angioedema is the result of *subdermal and submucosal* edema due to the action of unopposed vasoactive mediators.

This is in distinction to **urticaria** which consists of circumscribed lesions consisting of raised areas of erythema and edema of the *superficial dermis*, (**see separate document**).

The difference between the two is primarily one of degree.

Urticaria and angioedema can occur together in the same patient at the same time or they may occur separately.

Angioedema can involve many areas of the body, but the most serious manifestation will be involvement of the oropharyngeal and tongue mucosal surfaces. In severe cases this may lead to death by airway obstruction.

Pathophysiology

Angioedema involves vessels in the layers of the skin *below* the dermis, while urticaria involves vessels within the *superficial* dermis. ¹

There is an inflammatory response mediated by vasoactive mediators, including:

- Histamine
- Serotonin
- Kinins (mainly **bradykinin**).

The subdermal source of angioedema results in regions of well demarcated, localized, **non-pitting** edema.

Urticaria is localized to the superficial portion of the dermis and consists of circumscribed wheals with raised erythematous borders and central blanching. These may coalesce to form larger wheals.

These conditions can occur together or separately.

Recurrent episodes of one or both conditions for **less than 6 weeks duration are considered acute**, whereas attacks lasting **longer than 6 weeks are considered chronic**.

Causes:

The causes of angioedema, (with or without urticaria) include:

1. True allergic reactions:

This may be part of:

- A true IgE mediated *anaphylactic* reaction.

Foods or drugs will be the most common causes here.

2. Hereditary (**HAE**):

- Hereditary angioedema (HAE) is a rare genetic autosomal dominant disorder characterized by a C1 esterase inhibitor deficiency.
- Associated urticaria is **not** a feature of HAE. ²

See separate document for this condition.

3. Acquired C 1 esterase inhibitor deficiency:

The same enzyme defect that is seen in HAE can be acquired occur in:

- Some malignancies:
 - ♥ Lymphomas
- Some types of autoimmune disease
 - ♥ Systemic Lupus Erythematosus (SLE).

The clinical picture will be much the same as seen in HAE

4. Drug induced:

In particular:

ACE inhibitors:

- Around 1/200 people will get symptoms within the first few months of treatment, but sometimes the onset can be delayed for months to years.
- Sometimes angioedema only appears when the dose is increased.
- Why some people seem to get reactions and others don't is unknown, but simply switching to another brand or type of ACE inhibitor doesn't seem to help.
- Swellings are not itchy or painful, usually occur around the face, tongue and throat and are not accompanied by urticaria (hives).

- Strictly speaking, these are not allergic reactions and can't be proven by any skin or blood allergy test.
- If the drugs are stopped, and the symptoms settle, the diagnosis is considered confirmed.

Note that current expert opinion does *not* attribute angioedema to Angiotensin II receptor blockers.

tPA:

- Angioedema is an uncommon, but well documented complication of tPA.
- The mechanism is thought to be related to plasmin activation of bradykinin. The reaction is more likely to occur if the patient is taking concomitant ACE inhibitors as this also predisposes to increased levels of bradykinin, (**see Appendix II below**).
- Airway threatening angioedema in a patient who has just been given tPA, represents a particularly challenging scenario in the ED, in view of the possible need for a surgical airway!

5. Infection:

- This is one of the most common causes of urticaria (hives) and angioedema, particularly in young infants.

6. Idiopathic:

- Unfortunately, in the **majority** of cases, a cause is not found.

Complications:

Oropharyngeal complications include:

1. Dysphonia.
2. Dysphagia
3. Airway compromise, which may be lethal.

Clinical Features

Clinical features include:

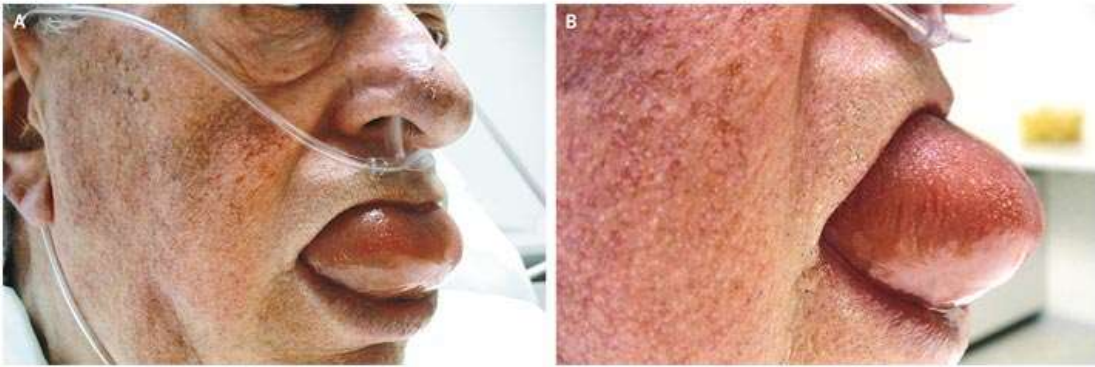
1. Airway compromise:

- This is the most immediate and serious manifestation of angioedema.
 - Oropharyngeal involvement can range from mild edema of the uvula to extreme edema leading to airway compromise, as shown above.
2. Angioedema may be part of a wider systemic anaphylactic reaction.
 3. GIT involvement:
 - Angioedema of the intestine may cause abdominal pain.
 4. Other cutaneous involvement:
 - Other single or multiple regions of skin may be involved including the face, periorbital region, lips, dorsa of feet and hands, and genitalia.
 - Individual lesions resolve over hours to several days.

Important points of history:

1. Symptoms:
 - The timing of onset and the rapidity of symptom development.
2. Has there been any recent local trauma or surgery or dental work?
 - In HAE angioedematous lesions may be precipitated by trauma including surgery or dental work.
3. Allergies:
 - Especially of past anaphylactic reactions.
4. Medications:
 - In particular **ACE inhibitors**
5. Past history:
 - Previous episodes, including whether or not a specific diagnosis of HAE has been made.
 - Any associated known malignant or autoimmune disease.
6. Family history:
 - There may be a family history of HAE.

Important points of examination:



Severe angioedema of the tongue leading to airway compromise, (NEJM July 20 2006)

1. Airway and respiratory assessment:

- Check vital signs
- Oxygen saturation
- Drooling
- Stridor
- Ability to talk
- Paradoxical respiration in extreme cases.

2. Other features of anaphylaxis:

- Hypotension, wheezing and generalized rash.

3. Look for the presence or absence of urticaria:

When angioedema occurs without urticaria the pathogenesis of the swelling is generally the same as when urticaria is present.

However, this syndrome should prompt consideration of **two other forms** of angioedema caused by raised levels of **bradykinin** rather than histamine: ²

- Angioedema associated with angiotensin converting enzyme (ACE) inhibitors
- C1 esterase inhibitor deficiency, (hereditary or acquired)

See also Appendix 1 below for distinguishing features of different types of angioedema.

Investigations

1. C1 esterase inhibitor levels:
2. Complement levels.
3. Lateral neck radiology:
 - This may assist in some cases in assessing the degree of airway obstruction.

Further specialized investigations may be undertaken by an Allergist / Clinical Immunologist

Management

General measures:

1. Airway:

The most immediate concern will be the airway and respiratory status:

- Oxygen may be provided by nasal prongs, even if the oropharynx is severely obstructed, (see above).
- All cases should have IV access
- In extreme case an emergency needle cricothyroidotomy or other surgical airway may be necessary.

Even if not immediately required the equipment to do this should be readily at hand.

- Patients should be closely observed in a resuscitation cube.

2. Adrenaline:

- IM adrenaline if true anaphylaxis is suspected, (**see also anaphylaxis guidelines**).
- 4 mls of 1:1000 nebulized adrenaline may give some benefit towards airway improvement in cases of allergic induced angioedema.

3. Steroids:

- Dexamethasone 10mg IV

Or

- Hydrocortisone 200 mg IV.

4. Antihistamines:

- These are *no longer* recommended for cases of angioedema or anaphylaxis.³

Specific measures:

5. Cases of diagnosed **hereditary angioedema**:²

Definitive treatment consists of:

- **Infusion of C1 esterase inhibitor concentrate**
 - ♥ Fresh frozen plasma may be used if specific C1 esterase inhibitor concentrate is not available, but is much less effective.

Or

- **Subcutaneous injection of icatibant.**

Note that systemic adrenaline, corticosteroids and antihistamines are of little benefit in this form of angioedema.

See separate guidelines for HAE.

6. Angioedema caused by ACE inhibitors:

- **Icatibant:**

ACE inhibitor induced angioedema, has traditionally been treated with steroids/ antihistamines/ adrenaline in severe cases but with limited/ no success.

Recently a study showed good effectiveness of icatibant for the treatment of ACE inhibitor induced angioedema.⁴

Case reports exist of emergency intubations being avoided by the use of icatibant.⁶

Give 30 mg SC. This dose can be repeated twice at 6 hourly intervals if required.

It should be noted that whilst icatibant is an expensive drug, (as of February 2015 it is around 2,500 AUD a syringe), it can potentially save a patient from catastrophic airway compromise.

It should not be used for minor peripheral swellings, (though a patient should still be monitored closely).

It should be used for any tongue, neck, oropharyngeal, laryngeal swellings, and given its lag time of several hours to maximal effect, it should be given **early**.

Experience with cases of HAE also says that the earlier its use the more effective icatibant is, (*personal communication Professor Connie Katelaris February 2015*)

If it is a known case of ACE inhibitor induced angioedema or HAE then icatibant should be given early for any potential airway problem.

If it is a de novo presentation then an initial trial of adrenaline first is indicated but if there is no response and increasing swelling, then it is reasonable to give empirical icatibant.

See also separate document on icatibant (in Drugs folder).

7. Angioedema caused by tPA:

- Icatibant on theoretical grounds could be a treatment for this.

Prevention:

Angioedema is a contraindication to the future use of ACE inhibitors.

Only very rarely will patients experiencing angioedema with an ACE inhibitor also experience this complication with an angiotensin II receptor blocker.

ACE inhibitor should never be used in patients with C1 esterase inhibitor deficiency.

Disposition:

All patients with airway compromise must be admitted and observed closely for any sign of further deterioration.

Patients should be discussed with ICU. Admission to ICU will be necessary in severe cases.

Milder cases may be appropriate for a period of observation in a Short Stay Unit.

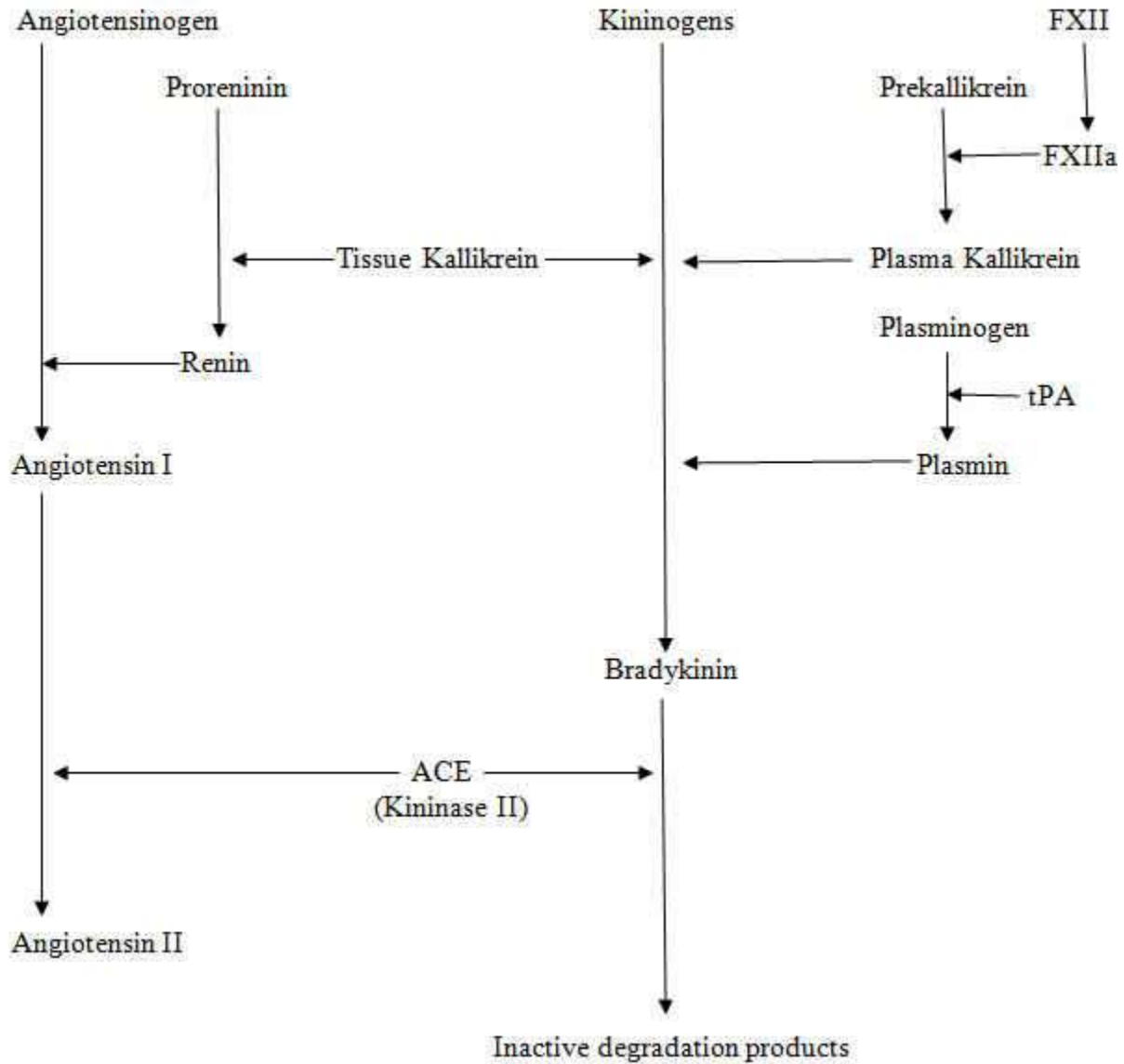
All patients should be referred to an Allergy specialist or Clinical Immunologist on discharge.

Appendix 1

Features distinguishing HAE from other forms of angioedema^[10]

<u>Symptom/Sign</u>	<u>HAE</u>	<u>Acquired</u>	<u>Allergic/IgE Mediated</u>
Angioedema	Yes	Yes	Yes
Urticaria	No	No	Usually
Age of onset (most frequent)	6-20	> 50	Anytime
Family history	Usually	No	Variable
Underlying disease	No	Yes	No
Location of swelling	All	All	Especially face and lips
Precipitation by trauma	Yes	Yes	No
Duration of swelling, hr	48-72	48-72	2-48
Response to treatment with epinephrine, antihistamine, corticosteroids	No	No	Yes

Appendix 2



Biochemical pathways, demonstrating some of the relationships between tissue plasminogen, bradykinin and ACE, in the pathogenesis of angioedema.

References

1. **Professor Connie Katelaris et al.** “Position Paper on Hereditary Angioedema”, Australasian Society of Clinical Immunology and Allergy (ASCIA), Revised March 2011.

See also ASCIA Website for more general information on Angioedema.

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4. Murat Bas et al. A Randomized Trial of Icatibant in ACE Inhibitor Induced Angioedema NEJM 372 (5) January 29 2015.
5. Giuseppe Molinaro et al. Biochemical Basis of Angioedema Associated With Recombinant Tissue Plasminogen Activator Treatment An In Vitro Experimental Approach. *Stroke*. 2002; 33:1712-1716.
6. Phillippa A Pucar et al. Successful treatment of ACE inhibitor-induced angioedema with icatibant, a bradykinin B2 receptor antagonist. MJA 202 (11) 15 June 2015. doi: 10.5694/mja14.01015

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