

C1 Inhibitor Deficiency

and

Anesthesia

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C1 inhibitor

C1 esterase

Hereditary angioedema (HAE)

Hereditary angioneurotic edema (HANE)

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I. Introduction

Hereditary angioedema (HAE) is a condition that is characterized by episodic and sometimes lifethreatening airway edema. HAE represents one of the most serious genetic abnormalities involving the complement system. In 1882, Heinrich I. Quincke¹ published the first detailed description and three years later Strubing used the term "angioedema" to describe this disorder for the first time. By 1888 Osler demonstrated the hereditary nature of the clinical presentation.² The pathophysiologic basis of HAE, deficiency of C1 esterase inhibitor which is also called C1 inhibitor (C1 INH), was postulated in the early 1960s.^{3, 4} In 1972, an acquired form of C1 INH deficiency was first reported.⁵ Lack of C1 INH leads to uncontrolled activation of the classical pathway of complement and is thought to result in the release of "C2 kinin" or perhaps bradykinin⁶⁻¹⁰ which then causes increased vascular permeability and edema of the airway, trunk and extremities, and gastrointestinal tract.^{11, 12}

The term angioedema describes deep swelling of the dermis that is seen in a variety of disorders, including: 1) HAE; 2) acquired C1 INH deficiency; 3) common, idiopathic angioedema; and 4) angiotensin converting enzyme inhibitor (ACE) induced angioedema. Although these conditions share this one characteristic, angioedema, only the first two are caused by a complement abnormality. This review will focus upon them.

HAE and acquired C1 INH deficiency are especially important to anesthesiologists because patients with these disorders are prone to develop massive swelling of the aerodigestive tract (especially the oral cavity, pharynx and larynx) and lifethreatening airway obstruction. Angioedema may occur throughout the body and has a propensity to occur in the extremities and gastrointestinal tissues as well as the head and neck.^{12, 13}

II. Pathophysiology

A full understanding of C1 INH deficiency requires brief review of the serum complement system (figure 1).^{12, 14-16} This system consists of about 20 proteins, many circulating as inactive enzyme precursors, with two pathways for activation: the classical pathway and the alternate pathway. The former pathway is activated by antigen-antibody complexes. In contrast, the alternate pathway is activated by naturally occurring substances such as bacterial cell walls and yeast walls.^{17, 18} Complement activation by either pathway may result in opsonization,¹⁹ lysis,²⁰ anaphylatoxin activity,^{21, 22} chemotactic activity,²³ and immune complex clearance.²⁴ Activation of the classical complement pathway is generally well regulated and focused upon the substances which activate it.¹⁴ In contrast, the alternate pathway is among the first defenses against invading microorganisms and is thought to be older phylogenically than the classical pathway.²⁵

C1, the first component of the classical pathway of complement, exists in serum as a macromolecular complex containing one C1q, two C1r, and two C1s.²⁶ Activation of this pathway begins to occur when antibody in antigen-antibody complexes engages two of the six heads of the C1q subcomponent.²⁷ Then, C1q undergoes a tertiary change in structure allowing autocatalytic cleavage of C1r to C1r̄.²⁸ Although no fragment is released from C1r, it in turn cleaves C1s to C1s̄, again without the release of a fragment. C1s is called C1 esterase and may also be activated directly by interaction with plasmin.²⁹ A small amount of classical pathway activation occurs naturally and may be increased by a wide variety of substances and events such as inflammation, C reactive protein, DNA and even trauma.³⁰⁻³²

C1s̄ may then act on C4 and C2 to produce C4b2a in the fluid phase or on the cell, cleaving C4 and C2. It is thought that this reaction may produce a "C2 kinin".⁸ C4b2a is an enzyme complex, called the classical pathway C3 convertase, that may cleave C3 to C3a (an anaphylatoxin) and C3b (leading to opsonization if C3b is deposited on a particle). C3b may

then interact with C4b2a to form C4b2a3b, the classical pathway C5 convertase, which may then lead to activation of the terminal pathway, also called the membrane attack complex, with subsequent lysis if these events occur on or in the vicinity of suitable cells such as erythrocytes.

Control proteins limit the amount of complement activation that occurs. C1 INH is a single chain, highly glycosylated alpha-2-globulin, serine protease inhibitor (SERPIN) that contains 478 amino acids and specifically inhibits the spontaneous activation of the first component of complement.^{3, 4, 15} C1 INH binds stoichiometrically (in a 1:1 ratio) to C1 \bar{r} and C1 \bar{s} and less well to their inactivated precursors, C1r and C1s.³³⁻³⁶ Individuals who lack sufficient C1 INH are not able to control adequately the activation of C1 leading to the consumption of C4 and C2 with subsequent generation of "C2 kinin" and other biologically active products of activation.^{8, 37} "C2 kinin" alone or perhaps in conjunction with bradykinin or other substances may then cause increased vascular permeability and subcutaneous and mucosal swelling characteristic of HAE.^{3, 15}

C4b2a formation and decay is controlled by complement receptor 1 (CR1, CD35) and C4 binding protein (C4BP) as well as Factor I, preventing C3 levels from decreasing as a result of C1 INH deficiency.¹⁴ Unfortunately, C1 INH is the only known control protein that regulates the consumption of C4 and C2.

C1 INH also has the capacity to inhibit activated Hageman factor (Factor XIIa), plasma thromboplastin antecedent (Factor XIa), and plasma kallikrein.³⁷ Furthermore, C1 INH has been shown to inhibit plasmin and tissue plasminogen activator.⁷ C1 INH is encoded by a gene on chromosome 11.³⁶ The C1 INH gene consists of 8 exons and 7 introns and is approximately 1.7×10^4 base pairs in length.^{37, 38} Androgens may enhance the expression of C1 INH *in vivo* while γ interferon, α interferon, tumor necrosis factor α , interleukin 6 (IL-6),

and monocyte colony stimulating factor (M-CSF) have been shown to do so *in vitro*.³⁹⁻⁴¹ Most C1 INH is synthesized in the liver and blood monocytes.⁴² Amino acid composition, physical characteristics, purification and assays have been described in great detail.^{37, 39, 43, 44}

The etiologies of HAE and acquired C1 INH deficiency are quite different. HAE is caused by a defective C1 INH gene that produces either no C1 INH or dysfunctional C1 INH, which is measurable for antigen but is inactive. In both types of HAE, less than 50% of normal C1 INH is produced and this is insufficient for health. In contrast, acquired C1 INH deficiency is caused by consumption of C1 INH or autoantibodies directed against C1 INH.¹⁶

In Type I HAE, the region of the gene rich in *alu* repeats often contains the defective gene.³⁸ In Type II HAE, the defect is usually at or near the active site, ARG 444, in exon 8. This explains why Type I patients do not produce normal antigenic levels of C1 INH; their abnormal gene does not allow antigenic C1 INH to be expressed. Type II patients express protein that is not functional.

III. Types and laboratory diagnosis

The cardinal feature of Type I HAE is decreased antigenic and functional levels of C1 INH.¹² Type I, the predominant form of HAE, is characterized by C1 INH which is present at less than 40% of the normal amount of C1 INH.⁴⁵ C4 and C2 levels are low as a result of consumption.^{15, 46} Type II HAE is characterized by normal or increased antigenic levels of C1 INH, half of which is dysfunctional.⁴⁷ The type II form afflicts about 15% of patients with HAE.¹⁵ C1 levels are normal in both of the hereditary forms.

A C4 level is a rapid screening test for C1 INH deficiency in both hereditary and acquired forms.^{15, 46, 48, 49} Normal levels during an acute attack tend to rule-out the diagnosis

whereas decreased levels of C4 warrant assay for C1 INH. Both hereditary and acquired forms of C1 INH deficiency are characterized by low or absent levels of C4, C2, and C1 INH during and between attacks. Low C1 and C1q levels suggest acquired C1 INH deficiency rather than HAE.^{13, 49}

It is important to note that C1 INH levels do not necessarily correlate with level of disease. For example, C1 INH may be very low and patients may still remain unaffected throughout life,⁴⁷ whereas higher levels may be seen in patients with massive angioedema.

In summary (table I), both HAE and acquired C1 INH deficiency are characterized by low levels of C1 INH, C4, and C2. A distinguishing laboratory feature is that C1 levels are normal in HAE but remain markedly depressed in acquired C1 INH deficiency.

IV. Natural history, manifestations, clinical presentation

The importance of recognizing HAE cannot be overemphasized. Frank reported that the interval between onset of symptoms and diagnosis is about 20 years¹³ probably because HAE is an uncommon disorder. It is reasonable to speculate that taken as a whole in the United States HAE has a prevalence of approximately 1:50,000 to 1:150,000, although there are tremendous regional differences related to the presence of afflicted families in certain parts of the country. Acquired C1 INH deficiency is probably less common than HAE but its prevalence is unknown. Compounding the rarity of the processes is the wide variety of presenting symptoms. Therefore, the natural history and clinical manifestation of C1 INH deficiency deserve careful attention.

As described above HAE is an autosomal dominant disorder and most patients do have a family history of this disorder.¹³ Age of onset is not helpful in making the diagnosis. Although one half of patients with HAE are symptomatic by age 7, and two thirds by 13⁵⁰

presentation after age 50 has been reported.¹³ Presenting signs are usually cutaneous edema, abdominal pain, vomiting, and edema of the laryngeal or retropharyngeal area. Attack duration typically ranges from about 24 hours to several days. Minor trauma or emotional upset are the most consistent and frequent precipitators of attack. Trauma may be the trigger of one-half of exacerbations.¹³ Manipulation of pimples, venipuncture, nail puncture, typing, horseback riding, sexual intercourse, dental extraction, menses, emotional stress, prolonged standing, piano playing, and pregnancy may all trigger attacks.

Compared to HAE, acquired C1 INH deficiency is associated with onset at an older age and absence of family history. In addition, acquired C1 INH deficiency may be associated with a lymphoproliferative disorder such as lymphoma or with systemic lupus erythematosus.⁴⁹ 51-53

Again, it is important to note that HAE and acquired C1 INH deficiency are both characterized by the presence of angioedema and are not clearly distinguishable from each other on this basis.⁴⁹ The swelling involves the deep dermis and is nonpruritic, nonerythematous, circumscribed, cutaneous, and asymmetric.^{3, 47, 54} Nearly one-fourth of patients have a nonpruritic rash accompanying attacks of HAE, described as erythema marginatum.^{13, 55} Although urticaria (erythematous, pruritic, cutaneous elevations of the skin which blanch with pressure) can occur in patients who have C1 INH deficiency, urticaria that is always associated with angioedema suggests a diagnosis other than HAE.^{12, 56}

The angioedema of C1 INH deficiency characteristically involves the extremities, face, airway, and gastrointestinal tract. In the series reported by Frank et al, 96% had swelling of extremities, 93% had recurrent abdominal pain, 85% had angioedema of the face, and 64% had oropharyngeal involvement.¹³

Attacks involving the airway present the greatest threat. Obstruction generally begins slowly with voice change and dysphagia. Often it is preceded by peripheral swelling¹³ but facial edema has also been reported as the initial presenting sign.⁵⁷ Although the differential diagnosis of airway and extremity swelling is quite extensive (table II), sudden airway compromise leading to the death of a relative should raise suspicion of HAE. HAE may also cause swelling during head and neck or dental surgery so the diagnosis should be made before these procedures are performed. Abdominal and orthopedic procedures may not trigger an attack unless the patient is also intubated, whereas dental surgery is more likely to provoke obstructive laryngeal edema in patients with C1 INH deficiency.^{13, 50, 58} Frank et al reported life-threatening pharyngeal swelling following dental surgery in many untreated HAE patients.¹³

Along with swelling of the extremities and airway, the gastrointestinal tract is also vulnerable to the swelling characteristic of HAE. Osler wrote, "Associated with the oedema, there is almost invariably gastrointestinal disturbance: colic, nausea, vomiting, and sometimes diarrhoea."² Unexplained, episodic edema that occurs in a patient with recurrent abdominal pain or even ascites should raise suspicion of HAE.⁵⁹ Unfortunately, as noted above, the diagnosis is often missed as exemplified by the case of one middle aged woman who underwent almost 50 extensive evaluations for unexplained abdominal pain occurring almost bimonthly. It was not until HAE was diagnosed in her grandson during a military entrance examination that the etiology of her problem was finally determined.⁶⁰ One 52 year old man experienced 3 to 4 attacks per year of intermittent abdominal pain for 40 years before HAE was diagnosed. Three exploratory laparotomies for presumed bowel obstruction had been performed during this period.⁵⁷ It should be emphasized that recurrent abdominal pain can be the sole manifestation of HAE.⁶¹ G.I. "distress" may easily be misinterpreted as representing an acute abdomen and HAE may be present in patients with a history of multiple negative abdominal operations.^{57, 61, 62} Unexplained abdominal pain has historically led to narcotic use and dependence, as

well as psychiatric diagnoses. The traditional name hereditary “angioneurotic” edema (HANE) reflects this presumed psychiatric component. However, major psychiatric illness may not be more frequent in HAE.⁵⁰

The abdominal pain caused by HAE is best characterized as crampy, colicky, and often excruciating.^{13, 47} Usually patients have diffuse abdominal tenderness characterized by normal to high-pitched bowel sounds without rigidity and peritoneal signs.¹² The pain may be secondary to intestinal obstruction caused by localized swelling⁶⁰ and the radiographic appearance is of “stacked-coins” or a “thumbprint”.⁶³ Loss of fluid from the gut wall into the lumen may result in vomiting and copious accompanying watery diarrhea often late in the course of attack.^{12, 50} Diarrhea can be so severe as to cause hemoconcentration, hypotension, and shock.⁶⁴ Significant extraluminal, intraperitoneal fluid sequestration can also develop.⁶⁴ Leukocytosis may or may not be present.^{12, 62}

Although attacks of HAE during pregnancy are unpredictable, the risk of an attack appears to decrease after the first trimester and during delivery.¹³ When attacks do occur, they are often accompanied by acute abdominal pain mimicking acute appendicitis or peritonitis. HAE should be considered in the differential diagnosis of acute abdominal pain in pregnant patients when no other cause is apparent.^{50, 65} Most women do not experience improvement at menopause.^{13, 66} Female patients with HAE may also have cystic ovaries (polycystic or multifollicular).⁶⁷

V. Airway involvement

Airway involvement, especially perioral and oropharyngeal, has been the central concern regarding HAE since early reports of this disorder. This is largely because airway

obstruction is the most common cause of mortality. Thus, it is important to differentiate C1 INH deficiency from other causes of uvular and pharyngeal swelling such as localized injection (i.e. Quincke's disease), trauma, and neoplasms.^{68, 69} Airway swelling caused by HAE may progress slowly over many hours from hoarseness, pooling of secretions, and dysphagia to complete airway obstruction. Unfortunately, one should not assume airway compromise caused by HAE will either resolve or take a slow and deliberate course because airway compromise can also occur quickly and be deadly. Osler described five generations affected by HAE: "In one instance, possibly two, death resulted from a sudden oedema glottidis."² Landerman studied 358 cases of HAE in 36 families and found that most deaths occurred from acute laryngeal edema; of 119 deaths, 92 (77 percent) were secondary to acute laryngeal edema. The average age of death was 35 (range 14 months to 70 years).⁷⁰ In some affected kindred studied by Donaldson, the fatality rate from acute airway obstruction was as high as 25%.⁴⁴ Ohela reported seven families afflicted with HAE in Finland; six individuals died from acute airway edema and each had a triad of paroxysmal abdominal pain, peripheral edema, and laryngeal edema.⁷¹ Overall, approximately two thirds of patients with HAE experience an episode of airway compromise and 14-33% may die from laryngeal edema.⁵⁰

A similar spectrum of laryngeal symptoms occurs in both hereditary and acquired forms of C1 INH deficiency: fullness in the mouth, dysphagia, facial tightness, hoarseness, stridor, laryngeal edema, and/or laryngospasm.¹³ Pruet et al reported on 89 patients with HAE at the National Institutes of Health; 85% had occurrences of head and neck edema. Intubation was required in only 5 (6%), although symptoms of airway compromise were present in over half. Again, airway obstruction was reported to proceed rapidly.⁷² We have also seen airway obstruction progress very rapidly over 5 minutes, to the brink of respiratory arrest; if resuscitative treatment with C1 inhibitor concentrate described below had been unsuccessful, the patient would likely have died.

Neither laryngoscopy and attempted intubation nor tracheostomy are necessarily benign. Airway trauma during intubation may worsen laryngeal edema and necessitate emergent tracheostomy.⁵⁰ A patient described in an early case report required at least two tracheotomies for HAE and eventually succumbed to complete airway obstruction.⁷³ In seven of twelve families studied by Donaldson and Rosen, one or more members died of acute airway obstruction. In one family, six individuals spanning three generations died as young adults of airway obstruction. One man kept a scalpel in the house for possible use by his wife to facilitate tracheostomy. The marriage did not survive.⁴⁷ Whether the patient eventually died from an attack of HAE is not known.

VI. Management of C1 INH deficiency

A. Drug therapies available to treat C1 INH deficiency

The anesthesia literature provides only limited guidance regarding management of patients with C1 INH deficiency.⁷⁴⁻⁸³ In this section, we describe briefly the major therapies that have been used to treat HAE. In subsequent sections, we describe how these medications are used under specific circumstances. Finally, we conclude this part of the review with speculation about new and experimental forms of therapy that are being evaluated today.

EACA, an antifibrinolytic agent which inhibits plasminogen activation and plasmin activity, was once thought to be useful in long-term therapy of HAE.^{13, 84, 85} This drug probably acts primarily by limiting the formation of plasmin, which can activate C1. EACA is not used commonly today because it may cause muscle ache, fatigue, postural hypotension, and thromboembolic events.^{13, 86} Tranexamic acid, another inhibitor of plasminogen activation and of plasmin has also been used in the prophylaxis of HAE.^{87, 88} It too may limit the activation of C1 but is rarely used.^{46, 50}

In 1960, Spaulding demonstrated that chronic therapy with methyltestosterone may be useful in the long-term treatment of HAE.⁸⁹ Androgens such as methyltestosterone, danazol, and stanozolol are thought to act by increasing the synthesis of C1 INH by liver.^{46, 90} Attenuated androgens are clearly effective in preventing attacks, but may cause serious adverse events, including weight gain, headaches, myalgias, menometrorrhagia, amenorrhea, alopecia, acne, altered libido, liver disease, hirsutism, and virilization.⁵⁰ These events have limited androgen use, especially use of methyltestosterone. Danazol may also be hazardous in pregnant patients and children secondary to gonadal effects.¹³ Currently, stanozolol is the therapeutic mainstay (2 mg/kg per day initially and then 0.5-6.0 mg/kg/day) as required to control attacks. In general, the final dose of androgen that is selected prevents serious attacks but still allows mild attacks (such as mild swelling of an extremity) to occur occasionally.

FFP contains C1 INH but also contains the kinins and substrates (including uncleaved C2 and C4) which may fuel complement activation (see below). FFP therapy also presents a risk of infection by blood borne pathogens.

Although anabolic steroids and FFP are currently the chief therapies for C1 INH deficiency, purified C1 INH concentrate is one of the most promising therapies for the future. C1 INH has been available commercially only in Europe since the 1980s (C1-Inactivator HS, Behring, Marburg, Germany). From its use there we know that lyophilized C1 INH concentrate can effect partial resolution of symptoms within one hour and complete resolution within 24 hours. C1 INH is obtained from pooled human plasma and the usual dose is 25 units/kg. Appropriate administration can increase C1 INH levels by 50% in adults over 15 minutes.⁸⁵

C1 INH concentrate offers specific, rapid therapy and can be used to treat acute attacks. C1 INH concentrate may also be used for acute prophylaxis, where the efficacy of other

treatments is more problematic. Disadvantages include lack of availability in the United States, expense, and that it must be given intravenously and not transmit hepatitis or HIV. C1 INH concentrate has not been approved by the FDA for use in the United States and is only available on an investigational basis.⁸³ Following infusion, C1 INH concentrate can be effective within 15 minutes and may be protective for about 2 days⁸⁵, or perhaps longer. Its efficacy during the induction of labor and for tonsillectomy have recently been described.^{81, 83}

B. Chronic prophylaxis

Prophylactic therapy is given to prevent airway obstruction or when the frequency of attacks is greater than once or twice per month and is sufficiently severe as to require treatment.⁸⁵ Danazol and stanozolol maintenance therapy have clearly been shown to prevent attacks. Typically an adult takes stanozolol, 2 mg/d, or danazol, 600 mg/day. Acquired C1 INH deficiency may necessitate a much higher dose than is given to patients with HAE.

C. Prophylaxis before elective surgical procedures

Prior to elective surgical procedures HAE patients may be given stanozolol (Winstrol),⁸³ fresh frozen plasma,^{13, 77, 91} or C1 INH concentrate.^{83, 92, 93} Stanozolol has been used alone or in combination with other therapies.⁸³ Stanozolol is typically given 4 mg four times a day for 5-7 days before scheduled surgery. FFP may be given before dental procedures when C1 INH concentrate is not available. In one report, dental procedures precipitated serious or lifethreatening swelling in 5 of 6 untreated patients but when prophylaxis with 2 units of FFP was undertaken one day prior to dental extraction no swelling was observed immediately postoperatively.¹³ FFP causes an increase in C1 INH serum levels only transiently. C1 INH levels decrease to subnormal levels within days. FFP obviously presents infectious risks and should be reserved for situations where stanozolol has not been effective and C1 INH concentrate is not available. Given its cost, C1 INH concentrate when approved for use in the

United States will probably be reserved in the elective situation for those cases in which stanozolol is ineffective or contraindicated.

D. Prophylaxis before emergency procedures

The best option for prophylaxis prior to an emergency surgical procedure is C1 INH concentrate, although as noted above this is an investigational drug in the United States, not currently approved by the FDA. Alternatively, two units of FFP may be given prior to an emergency procedure. However, when FFP is given in this setting a mild attack may worsen, perhaps because FFP contains C2 and C4 kinins. Glucocorticoids, antifibrinolytic agents, epinephrine, and antihistamines have not been shown to be efficacious when given prior to an emergency procedure.^{13, 94}

E. Treatment of acute attacks

Acute attacks do not respond to treatment with anabolic steroids, glucocorticoids, antifibrinolytic agents, epinephrine, or antihistamines. Treatment options in this setting are limited but it is important to be prepared for possible intubation.⁴⁶ The most effective therapy appears to be C1 INH concentrate.⁹⁵⁻⁹⁷

F. New and experimental therapies

Hopefully C1 INH will soon be licensed for use in the United States. In the interim, patients with HAE must be treated with supportive care to minimize risk from an attack. Patients with a history of severe disease (previous airway obstruction) should be enrolled in a protocol study so that C1 INH concentrate can be available to treat lifethreatening attacks.

Other therapies are also being evaluated. It has been known since the 1920's that heparin has the capacity to inhibit complement *in vitro*, acting on both the classical and alternative pathways of complement.⁹⁸ More recently heparin has been shown to augment

activity of C1 INH in vitro⁹⁹ and even perhaps in vivo.^{100, 101} Studies are ongoing to determine the safety and efficacy of inhaled and subcutaneously administered heparin in preventing attacks of HAE.

G. Special anesthetic considerations

Anesthesiologists must be prepared to manage the airway of patients with HAE in three settings: electively when the airway is not compromised; urgently when mild or moderate airway edema is present; and emergently when airway swelling is lifethreatening. Medical treatment with FFP and C1 INH concentrate are described above. Other anesthetic considerations, particularly those involving the airway are also important.

In the elective surgical setting, either monitored, regional, or general anesthesia can be performed safely.⁷⁴ The presence of angioedema does not influence drug choices for the induction of either general or regional anesthesia or the use of muscle relaxants, including succinylcholine.⁷⁴ There are no known constraints regarding the use of any of the volatile anesthetics.

It is important to avoid manipulation of the airway as much as possible by relying upon regional or inhalation techniques. These obviate the need for the pressure and traction resulting from laryngoscopy and eliminate one important "trigger" for an attack. Abada and Owens, for example, reported successful use of spinal anesthesia for a urologic procedure⁷⁶ and Schar reported a mask inhalation technique utilizing no form of artificial airway.⁷⁸

Regional and mask inhalation techniques are certainly safe and offer some theoretical advantage. However, endotracheal intubation is not necessarily contraindicated nor, under proper circumstances, hazardous.⁷⁴ When intubation is necessary, so is heightened awareness and perhaps some form of prophylaxis should also be given. There are no universally accepted

guidelines but the administration of anabolic steroids for 5-7 days before surgery, as described above, and C1 INH concentrate (or fresh frozen plasma if concentrate is not available) immediately before surgery are most often utilized.

These treatments make intubation generally safe but may not be completely protective. This was suggested recently by a mild, generalized flare of angioedema in a 15-year old male with HAE following tonsillectomy who had been treated prophylactically the week prior to surgery with stanozolol (4 mg four times daily) and then intravenous C1 INH just prior to surgery. This underlines the notion that patients with HAE can usually be safely intubated but require close observation even after prophylactic premedication with stanozolol and C1 INH concentrate.⁸³ Unless the surgical procedure dictates surgical intensive care, this is not generally necessary.⁷⁴

Patients with HAE who are hemodiluted and undergo cardiopulmonary bypass require extra diligence. One case report describes a patient with acquired C1 INH deficiency with a preoperative C1 INH level of 30% of normal who underwent cardiopulmonary bypass. Apparently, hemodilution during surgery reduced these levels even further and the patient died intraoperatively of symptoms related to uncontrolled complement activation.⁷⁹ In contrast, in another similar case the C1 INH level increased after stanozolol therapy preoperatively to about 75% of normal and the patient underwent uneventful cardiopulmonary bypass with a membrane oxygenator.⁸⁰ An acceptable lower preoperative limit for C1 INH is not totally clear but 50% of normal has been suggested.¹⁰²

When HAE attacks involve the airway the anesthesiologist may be called to render care on an emergency basis. In cases of mild airway edema, symptoms can resolve, usually within a few days, without further treatment. Patients should be carefully observed in the hospital. Oxygen therapy may be provided and oxygenation should be monitored with pulse

oximetry. In extreme distress, ventilation by mask followed by immediate intubation is warranted. The use of muscle relaxants is inadvisable as long as the patient demonstrates ability to maintain even marginal oxygenation. When performing emergency laryngoscopy and intubation, the attendance of an otolaryngologist is mandatory should a tracheostomy be necessary. The laryngeal mask airway has no established or demonstrated role in this setting and given the potential for laryngeal distortion secondary to edema, would probably be ineffective in most cases. The presence of severe airway swelling and the demand for acute intervention can greatly limit the effectiveness of fiberoptic intubation. Instrumentation of the airway is best done in the operating room where full resuscitative measures can most readily be undertaken. This may not always be possible and certainly the risk of transport from the emergency room to the operating room must be assessed on the basis of the rapidity of progression of airway compromise. If this risk is deemed unacceptable an emergency tracheostomy should be performed without delay. Airway swelling may become so severe that even tracheostomy may be ineffective in providing a patent airway. Swelling may extend into the airway to such an extent that death is inevitable in the absence of specific therapy (C1 INH replacement).

VII. Summary

Angioedema is a very important disorder for anesthesiologists because it may threaten the airway and cause death. HAE is particularly concerning because it may occur in a patient who has not been fully evaluated and in whom the diagnosis has not been suspected. The angioedema in HAE is episodic and refractory to epinephrine, antihistamines, and glucocorticoids. Acquired C1 INH deficiency may also be the cause of serious angioedema. It is critical for anesthesiologists to recognize and diagnose these disorders so that these patients can be properly treated. One must do so with a full understanding of the potentially lethal nature of the disease process.

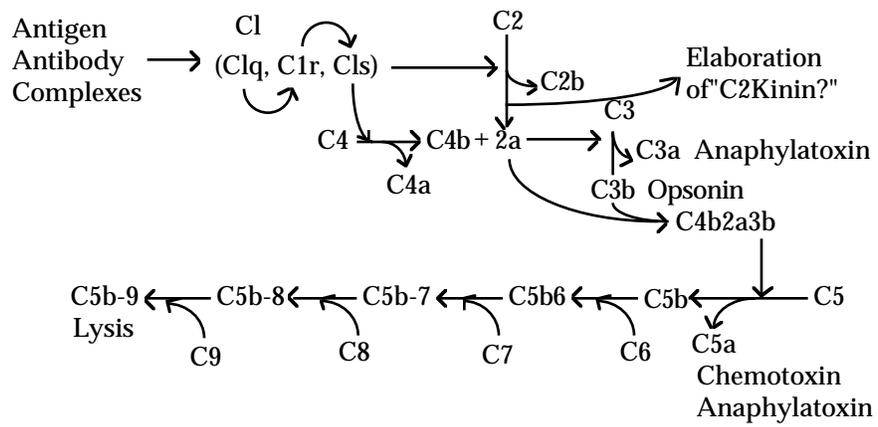


Figure 1
Classic Complement Pathway

TABLE I

Complement Levels in HAE and Acquired C1INH Deficiency

	C1INH Level		C1	C4	C2	C3	CH50
	Ag	Fx					
HAE-I	D	D	N	D	D	N	N*
HAE-II	N	D	N	D	D	N	N*
Acq C1 INH Def	D	D	D	D	D	N*	D
Idiopathic angioedema	N	N	N	N	N	N	N

(*These levels may be decreased in some patients)

TABLE II

Differential Diagnosis of Angioedema

C1 INH deficiency

HAE

Acquired deficiency

Allergic (IgE-mediated)

Inhalants

Bites and stings

Drugs and foreign sera

Foods and food additives

Parasitic infections

Physical causes (cold, exercise-induced)

Direct histamine release

Morphine, codeine, radiocontrast medium

Idiopathic angioedema

Miscellaneous

Aspirin and nonsteroidal anti-inflammatory sensitivity

C3b inactivator (Factor I) deficiency

Carboxypeptidase B deficiency

Cutaneous or systemic mastocytosis

Facial angioedema and eosinophilia

Factitious (Munchausen's) allergic syndrome

Hereditary or acquired vibratory angioedema

Hypocomplementemia urticarial vasculitis syndrome

Serum sickness-like syndrome

Urticaria/angioedema, deafness, and amyloidosis

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