Patients with hereditary angioedema (HAE) present with recurrent, circumscribed, and self-limiting episodes of tissue or mucous membrane swelling caused by C1-inhibitor (C1-INH) deficiency. The estimated frequency of HAE is 1:50,000 persons. Distinguishing HAE from acquired angioedema (AAE) facilitates therapeutic interventions and family planning or testing. Patients with HAE benefit from treatment with attenuated androgen, antifibrinolytic agents, and C1-INH concentrate replacement during acute attacks. HAE is currently recognized as a genetic disorder with autosomal dominant transmission. Other forms of inherited angioedema that are not associated with genetic mutations have also been identified. Readily available tests are complement studies, including C4 and C1-esterase inhibitor, both antigenic and functional C1-INH. These are the most commonly used tests in the diagnosis of HAE. Analysis of C1q can help differentiate between HAE and AAE caused by C1-INH deficiency. Genetic tests would be particularly helpful in patients with no family history of angioedema, which occurs in about half of affected patients, and in patients whose C1q level is borderline and does not differentiate between HAE and AAE. Measuring autoantibodies against C1-INH also would be helpful, but the test is available in research laboratories only. Simple complement determinations are appropriate for screening and diagnosis of the disorder.


**DISEASE SYNOPSIS**

The 2 major types of angioedema are acquired and hereditary. Acquired angioedema (AAE) is most commonly idiopathic, or it may be allergic in nature, related to medication effects, or characterized as an autoimmune or occurring in association with a lymphoproliferative disorder. Hereditary angioedema (HAE) is the result of mutations affecting the C1 inhibitor (C1-INH) gene (SERPING1) resulting in either loss of the C1-INH protein (HAE type I [HAE-I]) or loss of its function (HAE type II [HAE-II]).

An estrogen-dependent form of angioedema is also believed to be hereditary, but it does not have a clear genetic mutation. Patients with HAE present with recurrent, circumscribed, and self-limiting episodes of tissue or mucous membrane swelling. The more common forms of angioedema, with or without urticaria, are allergic or idiopathic.

This article focuses mainly on HAE secondary to C1-INH deficiency, the genetics of HAE, and the mechanisms of and therapy for angioedema. It is currently recognized as a genetic disorder with autosomal dominant transmission that results from deficiency of C1-INH. C1 inhibitor is a member of the serpin superfamily of serine protease inhibitors. C1 inhibitor is mainly produced in the parenchymal cells of the liver; other sites of production include monocytes, fibroblasts, endothelial cells, and microglial cells. It plays a pivotal role in the control of 4 different enzymatic cascades—the complement system cascade, the coagulation cascade, the fibrinolytic cascade, and the kinin system (Figure 1).

Other forms of HAE that are not associated with genetic mutations have also been identified. C1 inhibitor deficiency can be either genetic or acquired. Angioedema due to C1-INH deficiency should be differentiated from the more common allergic and idiopathic angioedema as well as angioedema related to angiotensin-converting enzyme (ACE) inhibitors.

The estimated frequency of HAE is 1:50,000 persons. Despite the identification of multiple mutations in the C1-INH gene (SERPING1), the precise mechanism of angioedema resulting from these mutations remains elusive. The field of HAE investigation progressed slowly during the past few decades, in part because of the small number of patients with this disorder. However, because of the identification of a pivotal role for C1-INH in other diseases or complications, such as endotoxia, coronary artery disease, capillary leak syndromes, and transplant rejection, developments in the field may occur much more quickly than in the past.

**CLINICAL PRESENTATION**

Patients with HAE usually present with a history of recurrent angioedema affecting the face, lips, tongue, genitalia, extremities, or larynx. Some have a history of angioedema...
and present with ascites or bouts of abdominal pain from bowel angioedema.\textsuperscript{37,38} Fifty percent of patients with HAE have laryngeal edema in addition to recurrent angioedema and abdominal pain.\textsuperscript{39,40} Rarely, patients with HAE have cerebral edema,\textsuperscript{41,42} pleural effusions, or symptoms suggestive of bladder involvement.\textsuperscript{43} Some patients have an erythematous rash called erythema marginata associated with attacks of angioedema. This rash may resemble urticaria, and in fact, it can be confused with urticaria, although typical urticaria is not part of HAE. Laryngeal angioedema has the potential of being fatal. Because the therapy for angioedema depends on precise diagnosis, diagnostic criteria for HAE were established by the Third C1 Esterase Inhibitor Deficiency Workshop (Table 1). In our judgment, the main requirements for the diagnosis of HAE (other than history and physical examination) are abnormal results on complement studies, and some patients have abnormal complement results with minimal or no symptoms for years before they become symptomatic.

Several clinical forms of HAE have been described. According to the most recent nomenclature,\textsuperscript{8} the different types are given the designations HAE-I, HAE-II,\textsuperscript{44} and estrogen-dependent or estrogen-associated inherited angioedema (formerly HAE-III). A recent report of a family with angioedema affecting 3 brothers (normal level and function of C1-INH) might represent yet an additional category.\textsuperscript{45} Also, AAE is subtyped as AAE types I and II (AAE-I and AAE-II)\textsuperscript{8} (Table 2).

By far the most common form is idiopathic angioedema, which is not associated with any complement abnormalities or other allergy and is commonly associated with urticaria. The cause remains indeterminate. Cicardi et al\textsuperscript{18} have called this “nonhistaminergic angioedema.” Many patients with idiopathic angioedema that is not associated with urticaria do not respond to antihistamines. Some of these patients respond to tranexamic acid (TA), an antifibrinolytic agent.\textsuperscript{18} Although this article mainly discusses HAE, readers should know that angioedema, with or without urticaria, is common, and often no cause is found.

Identification of the type of angioedema facilitates both therapeutic interventions and family testing or planning. For example, patients with HAE benefit from treatment

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{The role of C1 inhibitor (C1-INH) in modulating the complement, fibrinolytic, kinin, and coagulation cascades. Comparison of the site of action of C1-INH with other serine protease inhibitors and antifibrinolytic agents is demonstrated and marked by the thick lines indicating inhibition of the pathway. ACE = angiotensin-converting enzyme; \( \varepsilon \)-ACA = \( \varepsilon \)-aminocaproic acid; TA = tranexamic acid.}
\end{figure}
Laboratory criteria

Clinical criteria

Diagnosis can be established in presence of 1 major clinical criterion and 1 laboratory criterion

1. C1 inhibitor antigenic levels <50% of normal at 2 separate determinations with patient in basal condition and after the first year of life
2. C1 inhibitor functional levels <50% of normal at 2 separate determinations with patient in basal condition and after the first year of life
3. Mutation in C1 inhibitor gene altering protein synthesis and/or function
4. Family history of recurrent angioedema and/or abdominal pain and/or laryngeal edema

TABLE 1. Criteria for Diagnosis of Angioedema Caused by C1-Inhibitor Deficiency

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Major</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Self-limiting, noninflammatory subcutaneous angioedema without major urticarial rash, often recurrent and often lasting more than 12 h</td>
<td></td>
</tr>
<tr>
<td>2. Self-limiting abdominal pain without clear organic cause, often recurrent and often lasting more than 6 h</td>
<td></td>
</tr>
<tr>
<td>3. Recurrent laryngeal edema</td>
<td></td>
</tr>
</tbody>
</table>

Minor

1. C1 inhibitor antigenic levels <50% of normal at 2 separate determinations with patient in basal condition and after the first year of life
2. C1 inhibitor functional levels <50% of normal at 2 separate determinations with patient in basal condition and after the first year of life
3. Mutation in C1 inhibitor gene altering protein synthesis and/or function
4. Family history of recurrent angioedema and/or abdominal pain and/or laryngeal edema

Diagnosis can be established in presence of 1 major clinical criterion and 1 laboratory criterion

Pathophysiology of Angioedema and the Rationale for Therapy

The mechanism of angioedema in the absence of C1-INH appears to be secondary to increased levels of bradykinin. C1 inhibitor is a serpin that modulates the complement, coagulation, kinin, and fibrinolytic pathways. C1 inhibitor inhibits the formation of activated C1 and the cleavage of C2 and C4. Also, C1-INH inhibits the ability of plasmin to activate C1 and to cause the generation of bradykinin from C2. In the absence or reduced function of C1-INH, the formation of bradykinin is increased, and patients experience angioedema. Another factor that may increase bradykinin through this pathway is tissue-type plasminogen activator (increases level of plasmin), which has also been reported to cause angioedema.

The Role of C1-INH as It Down-Regulates the Generation of Bradykinin. C1 inhibitor is a serpin that modulates the complement, coagulation, kinin, and fibrinolytic pathways. C1 inhibitor inhibits the formation of activated C1 and the cleavage of C2 and C4. Also, C1-INH inhibits the ability of plasmin to activate C1 and to cause the generation of bradykinin from C2. In the absence or reduced function of C1-INH, the formation of bradykinin is increased, and patients experience angioedema. Another factor that may increase bradykinin through this pathway is tissue-type plasminogen activator (increases level of plasmin), which has also been reported to cause angioedema.

The Role of Other Protease Inhibitors and Bradykinin Production. Other protease inhibitors can inhibit some of these pathways as well. Antithrombin III inhibits the formation of hydrogen peroxide and the effect of plasma kallikrein on kininogen, HMWK, and LMWK. Antithrombin III also inhibits the ability of plasmin to induce the generation of bradykinin. Three other protease inhibitors—β2-macroglobulin, α1-antitrypsin, and α1-antiplasmin—inhibit both plasma kallikrein and plasmin. These other antiproteases may have a therapeutic effect on the generation of bradykinin.
Effect118-120 in the absence of C1-INH even though they do not appear to be equipotent.120

Physiology of Other Bradykinin-Modulating Agents. Other factors that affect the cascade previously mentioned include ε-aminocaproic acid (ε-ACA)121,122 and TA.121,123 Both ε-ACA and TA124,125 are antifibrinolytic agents126 that inhibit plasmin; ε-ACA is not a potent inhibitor of activated C1 complement.127,128 Both agents are useful in the treatment of HAE.121,129

Of note, all reported mutations in C1-INH are heterozygous.5,130 Whether this indicates that the complete absence (homozygous trait) of C1-INH is lethal is unknown. The role of attenuated androgens as therapeutic agents becomes apparent, given their ability to increase the level of C1-INH.131 In vitro studies have shown the ability of interferon-γ to stimulate production of C1-INH; however, in vivo, this has not resulted in therapeutic benefit.132

Degradation and Elimination of Bradykinin and Angioedema. Bradykinin is inactivated by carboxypeptidase N,133,134 aminopeptidase P,135 neutral endopeptidase,6 bradykinin receptor binding,6 and ACE.5,6,11,65,136,137 The role of ACE for the degradation of bradykinin is critical.138 Only one report has been published of a patient with familial ACE deficiency who presented with recurrent angioedema.139 Patients taking ACE inhibitors have the propensity to develop angioedema, probably because of an accumulation of bradykinin.137,140 A subgroup of these patients developed angioedema with angiotensin receptor blockers.141 The effect of ACE inhibitors is important not only for patients with HAE and AAE but also for patients who are deficient in other factors that metabolize bradykinin, such as carboxypeptidase N65,133 or aminopeptidase P.135 One patient with carboxypeptidase N deficiency has been reported to develop angioedema,135 probably because of the accumulation of bradykinin.

A question remains about why HAE symptoms are intermittent and the clinical expression of this genetic abnormality is so variable, with some patients having severe symptoms and others having minimal, infrequent, or even no symptoms. Patient observation suggests that stress or minor trauma might precipitate angioedema. Almost all patients with HAE have a low C4 and a low antigenic or functional C1-INH, even though their attacks are intermittent. Rarely, patients exhibit the laboratory abnormalities only during an episode of angioedema.

Therapeutic Interventions

There are 3 approaches to therapy for patients with HAE. The first is immediate therapy during an attack, the second is short-term prophylaxis before dental or surgical procedures, and the third is long-term prophylaxis. Although therapy for HAE and AAE overlaps somewhat, there are clear distinctions, especially in HAE’s acute (life-threatening) stage. The urgent and long-term prophylactic therapy for different forms of angioedema depends on the type. A therapeutic algorithm for HAE is outlined in Figure 2 and Table 3.

Emergency Therapy for Acute Angioedema. The main goal of immediate therapy in an emergency situation (such as laryngeal edema) is to maintain an open airway.40,142 This might require intubation or a tracheostomy and ventilator support. Intubation may not be possible if laryngeal edema is advanced. Therefore, intubation should be considered early in the patient presentation if airway compromise is impending. Abdominal pain from gut edema may require pain control. Therefore, it is important to identify the type of angioedema because patients with HAE respond to C1-INH concentrate.143-147 All other therapies do not abort the attack but might reduce its duration. Most reports are from uncontrolled studies, and some are anecdotal; they describe use of high doses of attenuated androgens49,148-155 fibrinolytic agents121,123 (TA124,125,156-159 and ε-ACA127-129,160), or fresh frozen plasma (FFP).161 Of these modalities, only C1-INH concentrate has proven benefit. The use of FFP in the acute angioedema of HAE remains controversial because it also gives more substrate and may worsen angioedema.1
Treatment with epinephrine for reversal of airway compromise may help patients with allergic angioedema but is of controversial benefit for patients with HAE. Patients with AAE may also benefit from the addition of systemic antihistamines and corticosteroids. Corticosteroids are of little benefit for patients with HAE.

**Short-term and Long-term Prophylaxis Therapeutic Options.**

**Identification and Withdrawal of Precipitating Agent.** Patients with HAE or AAE with a known precipitating factor, such as ACE inhibitors or angiotensin receptor blockers, should discontinue the medication. Patients with estrogen-dependent angioedema and those with HAE made worse by estrogens should discontinue oral contraceptives or hormone therapy. Withdrawal of estrogen therapy helps patients with estrogen-dependent angioedema and might help patients with HAE. Stress may precipitate acute attacks of angioedema.

**Fresh Frozen Plasma.** Fresh frozen plasma has been used for treatment of acute exacerbations and HAE prophylaxis. Patients with severe recalcitrant ACE-induced angioedema have benefited from the administration of FFP. The concern in HAE, however, is that FFP might provide the factors that make the angioedema worse. The use of FFP remains controversial and lacks controlled studies. We have not used it in patients with acute attacks.

**C1-INH Concentrate.** For patients with an acute exacerbation of HAE-I or HAE-II, replacement of the missing enzyme is the ideal therapy. C1 inhibitor concentrate is the preferred therapy for patients with HAE who present with acute laryngeal edema that might otherwise be fatal. C1 inhibitor replacement with the concentrate is of benefit for some but not all patients with AAE-II, possibly due to inadequate dosing.

Long-term prophylaxis with C1-INH is necessary when treatment with other agents is not effective or not tolerated. A pasteurized concentrate of C1-INH administered for 1 year to 1 patient with HAE and for 1 year to another patient with AAE rendered both patients symptom-free without reported adverse effects. C1 inhibitor concentrate is ideal therapy for patients with infrequent attacks, those not fre-
quent enough to warrant long-term prophylaxis. However, the concentrate is not yet available on the US market.

**Attenuated Androgens.** Attenuated androgens are the mainstay of prophylactic therapy for both HAE and AAE. Attenuated androgens are used for short- and long-term prophylaxis.

Multiple androgens such as testosterone, methyltestosterone, fluoxymesterone, and oxymetholone were early therapeutic agents for HAE. They markedly decreased the frequency of attacks of edema without serious adverse effects. Subsequently, more attenuated 17α-alkylated corticosteroids (danazol and stanozolol) also were found to have therapeutic benefit.

Short-term prophylaxis before planned surgery or dental procedures requires a transient increase in the therapeutic dose (Figure 3). For short-term prophylaxis, danazol, up to 600 mg/d, is given for 5 days before surgery. Increased doses of other androgenic agents can also be used. The dosage at which danazol is used for long-term prophylactic treatment ranges from 50 to 600 mg/d (Figure 4). Stanozolol is used at 2 to 12 mg/d, and methyltestosterone at 10 to 30 mg/d. A typical treatment regimen is to start adult patients at the highest dose divided into 3-times-daily doses for the initial 4 weeks, then tapering the dosage every 4 weeks to the minimal effective dose. Another treatment approach starts at lower doses and increases the dose if needed (Figure 4 and Table 3). If the patient has frequent or severe episodes of angioedema, we start with the high dose and taper; however, if the patient has mild or infrequent episodes of angioedema, we choose the lower dose and increase as needed. The minimal effective dose should be used for maintenance therapy. Some patients do well with every-other-day dosing. Danazol doses as low as 200 mg every 2 or 3 days and stanozolol at 2 mg/d (or even every second or third day) have been used successfully to reduce attack frequency. They are effective in preventing attacks at these low doses even though the results of complement studies remain abnormal.

Long-term prophylactic measures are outlined in Figure 4. Long-term use of danazol and stanozolol can cause irregular menstruation, hepatotoxicity, masculinization in women and children (acne, increased hair growth, weight gain, deepening of the voice), behavioral changes (aggression or depression), weight gain, and hypertension. Other adverse effects include alteration of blood lipid levels and coagulation factors and polycythemia. The potential for inducing hepatocellular neoplasms and liver vascular lesions (peliosis hepatica) should alert the physician.
to check levels of α-fetoprotein and to perform liver ultrasonography annually. Other possible risks include prostate adenocarcinoma; therefore, an annual digital rectal examination and a prostate-specific antigen determination are important. Attenuated androgens are relatively contraindicated in children.

Stanozolol is no longer manufactured for use in humans in the United States, although it is still available for veterinary use. Some compounding pharmacies can make it available for human use.

**Antifibrinolytic Agents.** Antifibrinolytic agents (plasmin inhibitors), such as TA and ε-ACA, are also used for prophylaxis against attacks.

**ε-Aminocaproic Acid.** ε-Aminocaproic acid is used clinically as an antifibrinolytic agent. In 1968, ε-ACA was successfully given to a patient after an attack of angioedema. Since then other studies have demonstrated its potential beneficial role in this condition. It has been used for acute therapy as well as short-term and long-term prophylaxis.

ε-Aminocaproic acid, 16 g/d, adequately controls HAE; however, lower doses (7-10 g) taken daily in divided doses might be sufficient. The major adverse effect of ε-ACA is myalgia, with or without rhabdomyolysis. Thrombosis is another potential complication. Muscle weakness, hypotension, and fatigue may also occur with the use of higher doses.

**Tranexamic Acid.** Tranexamic acid is a synthetic antifibrinolytic amino acid that binds plasminogen and blocks its function. It is commonly used for the prevention of excessive bleeding. Treatment of HAE patients with TA reduces the frequency of swelling in 70% of the patients. Because of the virilizing effects of androgens, TA can be used as the first agent of choice in children with HAE. Also, TA is of use in AAE and is safe for use in pregnancy (class B).

On a molar per molar base, TA is 7 times more potent than ε-ACA. Its plasma half-life is about 80 minutes, and it is cleared through the kidney. The usual total dosage of TA is 25 to 75 mg/kg of body weight given in divided doses 2 to 3 times daily. Once the patient is symptom-free, the dose should be tapered to the minimum effective level. The dose could be tapered by 30% every 2 months until the reappearance of symptoms. Therapy reduces the frequency and intensity of symptoms without greatly changing any biochemical parameters.
Tranexamic acid can be used with acute episodes\textsuperscript{183} and for short-term and long-term prophylaxis.\textsuperscript{156} The main adverse effects of TA are nausea, diarrhea, and sensation of laryngeal or pharyngeal dryness.\textsuperscript{19} Arterial thrombosis is one of the potential risks of TA therapy.\textsuperscript{16,193}

**Potential Therapeutic Agents**

Potential therapeutic agents other than C1-INH replacement include agents that would replace the C1-INH function, interfere with major steps in the pathway of bradykinin generation, or block the effector function of bradykinin. Another potential therapeutic modality is gene therapy. The following agents have been studied.

**Plasma Kallikrein Antagonists.** Plasma kallikrein is one of the important mediators in the pathophysiology of angioedema. A plasma kallikrein antagonist DX-88\textsuperscript{120,194,195} is currently under investigation for therapeutic use in patients with HAE and appears promising.

**Bradykinin Antagonists.** Bradykinin is a nanopeptide that appears to be at the center of the pathogenesis of angioedema in patients with HAE\textsuperscript{57,50,60,88} as well as in mouse models of C1-INH deficiency.\textsuperscript{59} The disputed C2 complement kinin likely has similar function.\textsuperscript{55,65-67,196} Bradykinin, however, is involved in the mediation of several other processes. Those processes include inflammation,\textsuperscript{61,76,197} cardioprotection,\textsuperscript{198} bronchoconstriction,\textsuperscript{199-202} blood pressure control,\textsuperscript{203,204} neuroprotection,\textsuperscript{205} and nociceptive (pain) nerve transmission,\textsuperscript{206,207} Therefore, it is logical to consider use of bradykinin antagonists to ameliorate the angioedema in HAE.\textsuperscript{207-211} The B2 bradykinin receptor in a mouse model appears to have a major role in angioedema. To date, 1 bradykinin antagonist, icatibant, has been tested and granted therapeutic orphan drug status showing benefit in both the mouse model and human angioedema.

**Serine Protease Inhibitors.** Several protease inhibitors share some of the functions of C1-INH.\textsuperscript{109} These include antithrombin III,\textsuperscript{107,110,111,113} \(\beta\)-macroglobulin,\textsuperscript{114,115} \(\alpha\)_\textsubscript{1}-antitrypsin,\textsuperscript{116,117} and \(\alpha\)_\textsubscript{1}-antiplasmin.\textsuperscript{116,117} These protease inhibitors and others have a potential use as therapeutic agents\textsuperscript{118-120,212} despite their lower potency.\textsuperscript{120}

**GENETIC BACKGROUND OF HAE**

**C1-INH Deficiency: HAE-I and HAE-II**

Hereditary angioedema is an autosomal dominant disorder associated with mutations in the C1-INH gene. This gene, \textit{SERPING1}, is located in the q12-q13.1 subregion of chromosome 11. The C1-INH gene comprises 8 exons.\textsuperscript{213} Many kinds of mutations have been described; they can occur in the exons or in the regions controlling gene expression. If the mutation results in the loss of production of C1-INH protein, HAE-I develops. If the mutation results in the generation of a nonfunctional mutant protein, HAE-II develops. Anomalies related to this gene result in HAE-I and HAE-II. Other genetic variants of HAE that occur in the presence of completely normal C1-INH level and function have been described.\textsuperscript{214} Only about 50% of patients have a positive family history, suggesting the occurrence of spontaneous mutations.

C1 inhibitor deficiency has 2 major phenotypes: HAE-I and HAE-II. Both have C1-INH function at 5% to 30% of normal instead of the 50% expected if the single normal allele were fully expressed (Table 2). Hereditary angioedema type I (about 85% of C1-INH–associated HAE) is associated with almost absent expression (level and function) of C1-INH.\textsuperscript{215-217} In HAE-II (about 15% of C1-INH–associated HAE), C1-INH is expressed but is not functional (normal or high level but reduced function).\textsuperscript{213,218-220} Each disorder can result from one of many mutations in the \textit{SERPING1}.\textsuperscript{221-223} These include point mutations,\textsuperscript{224,225} deletions,\textsuperscript{226} substitution,\textsuperscript{227} duplication,\textsuperscript{228} frame shift,\textsuperscript{229} premature stop codon,\textsuperscript{230} and many others.\textsuperscript{8,15,130,213-235} Not all \textit{SERPING1} mutations result in clinical disease.\textsuperscript{236} An online database of documented mutations is available at hae.biomembrane.hu.

**Estrogen-Dependent HAE**

This type of HAE was recently described and affects women only in conditions with elevated levels of serum estrogen.\textsuperscript{5,9} Patients present with symptoms identical to patients with HAE-I and HAE-II, but symptoms occur in the setting of normal C1-INH level and function as well as genetic makeup.\textsuperscript{6,214} The inheritance appears to be mendelian autosomal dominant, and these patients appear to have increased sensitivity to estrogen. To date, the genetic anomaly has yet to be identified.\textsuperscript{8} This type should be differentiated from HAE-I or HAE-II because the C1-INH deficiency is exacerbated with hormonal changes.\textsuperscript{10,237,238}

**RATIONALE FOR TESTS IN HAE**

Hereditary angioedema presents in a fashion similar to all other types of angioedema. About half the patients do not have a family history of the disorder. The diagnosis of the type of angioedema is important not only for identification of therapeutic options but also for family planning and counseling. If the family history is positive, the diagnosis is easier to make.

**DIAGNOSIS**

To date, genetic testing for HAE is available only in the research laboratory because of the multitude of different mutations leading to the disorder. Thus, complement stud-
ies are the important diagnostic studies and the only ones readily available. The correct diagnosis is essential for appropriate therapy, management during childhood, management of the acute attack, and during pregnancy.

After a clinical presentation suggestive of a diagnosis of HAE, studies to determine whether the patients fulfill the diagnostic criteria (Table 1) must be performed. Readily available tests are complement studies including C4 and both antigenic and functional C1-INH. These are the most commonly used in the diagnosis. C1q can help differentiate between HAE and AAE. A diagnostic algorithm is presented in Figure 5, and the differential diagnosis is summarized in Table 4.

Laboratory findings in the different types of angioedema are compared in Table 4. Genetic tests would be particularly helpful in patients with no family history of angioedema, which occurs in about half the patients with HAE, and the C1q is borderline and does not differentiate between HAE and AAE. Measuring autoantibodies against C1-INH also would be helpful, but this test currently is done only in research laboratories.

**Family Counseling**

Given the autosomal dominant inheritance of the disorder, family counseling is important. Patients and their families need to be educated about the disease and its inheritance. This may result in appropriate therapeutic interventions for affected family members. Close follow-up of the patients and their families is essential, with appropriate tests performed at regular intervals. Prenatal screening is not yet feasible.

**Methods Overview of Specific Genetic Tests Used in HAE**

**Fluorescence-Assisted Mismatch Analysis.** Appropriate gene regions of the wild-type and the putative mutant allele are simultaneously amplified from genomic DNA by

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**FIGURE 5.** Diagnostic algorithm for patients with angioedema and possible C1-inhibitor (C1-INH) deficiency as suggested by Bowen et al.\(^2^7\)

ACE = angiotensin-converting enzyme; HAE = hereditary angioedema. From J Allergy Clin Immunol,\(^2^7\) with permission from the American Academy of Allergy, Asthma and Immunology.
polymerase chain reaction (PCR) analysis, and large DNA fragments (up to 800 base pairs) are end-labeled with strand-specific fluorophores. Cleavages occurring on opposite strands are detected by denaturing gel electrophoresis using an automated DNA sequencer. The sensitivity of detection is also increased. Automatic superimposition of tracings from different subjects allows mismatch detection even when the mutant chromosome is diluted 10-fold or more compared with the normal chromosome.

Specific PCR Amplification and Real-Time PCR Analysis. Real-time PCR analysis following Southern blot analysis can be used with direct sequencing to study SERPING1, the C1-INH gene. Large deletions can be detected by this technique. Real-time quantitative reverse transcription–PCR analysis has also been used successfully to measure C1-INH messenger RNA levels in peripheral blood mononuclear cells. Also, PCR analysis can be used to measure the level of expression of C1-INH messenger RNA in peripheral blood mononuclear cells. Levels of mRNA can be quantitated by computerized optical densitometry of reverse transcriptase–PCR products. Fluorescent multiplex assay can be constructed to amplify simultaneously 5 exons of C1-INH. Polymerase chain reaction protocols using forward and reverse primers can be optimized for amplicons (size range between 300 and 700 base pairs). Superposing fluorescent profiles of test and control DNA can be done. This technique is suitable for screening the C1-INH gene in patients with HAE before screening for point mutations.

Chemical Cleavage of Mismatches Technology. Selective reactions of mismatched thymine and cytosine base pairs with osmium tetroxide and hydroxylamine, respectively, can be used to separate and identify the resulting fragments after digestion by gel electrophoresis. This method has been used to detect pathogenic SERPING1 mutations and analyze its polymorphism. The efficiency of this technique depends on the mismatch and the stability of the adjacent sequences. Fluorescent probes have been used to develop fluorescence-assisted mismatch analysis.

Chemical Cleavage of Mismatches Technology. Selective reactions of mismatched thymine and cytosine base pairs with osmium tetroxide and hydroxylamine, respectively, can be used to separate and identify the resulting fragments after digestion by gel electrophoresis.

Denaturing High-Performance Liquid Chromatography and Gradient Gel Electrophoresis. This technique uses polyacrylamide gels with linearly increasing concentrations of a denaturing agent for studying the migration of double-stranded DNA. The genomic DNA segments are amplified, identified, and directly sequenced.

Single-Stranded Conformational Analysis. In non-denaturing gel electrophoresis, the mobility of heat-denatured single strands depends on secondary structure formation. This technique is simple, inexpensive, and highly sensitive.

**TABLE 4. Complement Studies in Angioedema**

<table>
<thead>
<tr>
<th>Type of angioedema</th>
<th>Clq concentration</th>
<th>Cl1-INH concentration</th>
<th>Cl1-INH function</th>
<th>C4 concentration</th>
<th>C3 concentration</th>
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<td>Acquired Cl1-INH deficiency type I</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>N/↓</td>
</tr>
<tr>
<td>Acquired Cl1-INH deficiency type II</td>
<td>↓§</td>
<td>N/↓</td>
<td>↓</td>
<td>N/↑</td>
<td>N</td>
</tr>
<tr>
<td>Angioedema in association with sex hormone balance shifts#</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor–induced angioedema</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Other drug-induced angioedema</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Idiopathic angioedema</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

*†High; ‡low; ACE = angiotensin-converting enzyme; Cl1-INH = C1 inhibitor; HAE = hereditary angioedema; N = normal.
†Low Clq concentrations occur in some patients with HAE.
‡A normal C4 concentration was reported in 1 patient.
§At least 1 patient with normal Clq level was reported.
#Female patients and 1 male patient with recurrent angioedema caused by androgen deficiency. Some patients also had urticaria.

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GENETIC TESTS FOR HEREDITARY ANGIOEDEMA


The Genetics in Clinical Practice series will continue in the September issue.