INTRODUCTION — Acquired deficiency of C1 inhibitor (C1-INH), also called acquired angioedema (AAE), is a rare syndrome of recurrent episodes of angioedema, without urticaria, which is associated with B cell lymphoproliferative disorders in some patients [1,2]. Angioedema typically affects the skin or mucosal tissues of the upper respiratory and gastrointestinal tracts. The swelling is self-limited, although laryngeal involvement may cause fatal asphyxiation. Clinically, this disorder is very similar to hereditary angioedema (HAE), although AAE most commonly develops in patients over the age of 40 years, some of whom have associated lymphoproliferative disorders, whereas HAE usually presents in younger patients who are otherwise healthy.

This topic review will discuss the clinical manifestations, epidemiology, pathogenesis, and diagnosis of acquired C1 inhibitor deficiency. The management and prognosis of this disorder are reviewed separately. (See "Acquired C1 inhibitor deficiency: Management and prognosis".)

Hereditary angioedema is discussed separately. (See "Diagnosis of hereditary angioedema" and "Clinical manifestations and pathogenesis of hereditary angioedema" and "Treatment of acute attacks in hereditary angioedema" and "Prevention of attacks in hereditary angioedema".)

EPIDEMIOLOGY — AAE is rare; the precise incidence is not known.

- In the group of 776 patients referred to the author's specialty center in Milan for angioedema without urticaria between 1993 and 2003, only 14 had an acquired C1-INH deficiency [3]. Twenty-one additional patients were identified among referrals during the next six years (2004 to 2009). At one point in time, we estimated that we had diagnosed 46 patients with AAE and 545 patients with HAE, for a ratio of approximately 1 patient with AAE for every 12 with HAE.

- A 2010 literature review identified 168 probable cases [4].

However, AAE is likely underdiagnosed and we have identified several factors that may contribute to this. (See ‘Obstacles to diagnosis’ below.)

CLINICAL MANIFESTATIONS — Acquired angioedema (AAE) is characterized by recurrent episodes of angioedema, without urticaria or pruritus [2]. Attacks are commonly triggered by trauma and psychological stress. As in hereditary angioedema (HAE), swelling episodes in AAE can be characterized into three types: cutaneous, gastrointestinal, or upper airway. The similarities and differences between AAE and HAE are summarized here. A more detailed discussion of each type of attack is found in the topic review of hereditary...
Upper airway edema, frequently involving the larynx, is the most severe and potentially lethal location for both disorders. Around 50 percent of patients with AAE experience upper airway edema, and anoxic brain injury or death from upper airway obstruction can occur [5,6]. (See "Acquired C1 inhibitor deficiency: Management and prognosis", section on 'Prognosis'.)

The most consistent difference between AAE and HAE is the age of onset of the disorder. AAE presents in the fourth decade of life or later [7,8]. In a series of 46 patients with AAE from the author’s center, the earliest age of angioedema appearance was 39 years. In comparison, more than 90 percent of patients with HAE experience their first symptoms before the age of 20 years.

There are other subtle differences between the clinical manifestations of AAE and HAE:

- Gastrointestinal attacks appear to be less frequent in AAE — Angioedema of the gastrointestinal mucosa presenting as recurrent colicky abdominal pain, distention, vomiting and/or diarrhea is reported by nearly 80 percent of patients with HAE, while less than 50 percent of our AAE patients and around 30 percent of those from other centers reported gastrointestinal attacks [5,9].

- Cutaneous angioedema in AAE seems to affect the face more than the limbs, while in patients with HAE, swelling of the extremities is more typical [5]. However, both disorders can cause swellings in both locations.

- Patients may report antecedent changes in the skin (ie, similar in appearance to erythema marginatum) prior to cutaneous or gastrointestinal angioedema episodes, although it is not as prevalent as in patients with hereditary angioedema. Skin findings are described elsewhere. (See "Clinical manifestations and pathogenesis of hereditary angioedema", section on 'General observations'.)

ASSOCIATED DISORDERS — Acquired angioedema (AAE) was first described in two patients with lymphoma [1]. Since this initial report in 1972, the majority of patients diagnosed with acquired angioedema have been found to have an underlying disorder. In particular, there is an association with B cell malignancies (most often non-Hodgkin's lymphoma) and lymphoproliferative disorders [10-14]. Autoimmune disorders are also identified in patients with AAE [15].

- A total of 136 cases of acquired C1 inhibitor deficiency were identified in one extensive review of the literature [11,16]. An underlying disease was identified in 85 percent of patients, including the following disorders:
  - Lymphatic malignancies in 35 percent
  - Monoclonal gammopathy of uncertain significance (MGUS) in 32 percent
  - Autoimmune diseases in 8 percent
  - Adenocarcinoma and other malignancies in 6 percent (NB: Other than lymphoma and adenocarcinoma, no other specific types of malignancies have been reported with regularity)

- In a more recent series, approximately 70 percent of patients with AAE had an identifiable B cell lymphoproliferative disorder [16].

In both studies, about one-half of identified lymphoproliferative disorders were malignant (most often
non-Hodgkin's lymphoma), while the other half were benign (most often MGUS).

PATHOGENESIS — AAE usually arises in the setting of an uncontrolled clonal proliferation of B lymphocytes. However, the mechanism by which clonal B cell disorders lead to depletion of C1-inhibitor (C1-INH) and angioedema remains incompletely understood.

Role of bradykinin — The angioedema of AAE appears to be mediated largely by bradykinin, as in hereditary angioedema (HAE) [17]. Tissue insult or injury normally activates the contact system, leading to the generation of bradykinin and other proinflammatory mediators. Bradykinin, acting through bradykinin 2 receptors, increases endothelial permeability via mechanisms involving nitric oxide, cyclic GMP, and other effector molecules [18,19]. Bradykinin production is normally regulated by C1-INH.

Antibodies to C1-INH — Most (although not all) patients with AAE have identifiable autoantibodies against the C1-INH protein [20-23]. In our patient group, we were able to detect these antibodies in 31 of 42 patients (74 percent) [24]. One theory proposes that pathologic B lymphocyte proliferation results in expansion of a clone that produces antibodies that bind to C1-INH (“neutralizing antibodies”), causing steric hindrance and a functional deficiency of the C1-inhibitor protein.

Normally, C1-INH interacts with its target proteases and is cleaved in the process. The cleaved and inactive inhibitor irreversibly binds to the protease and renders it inactive. However, in the presence of anti-C1-INH antibodies, C1-INH is still cleaved, but it cannot bind the protease, and the protease continues to function, leading to uncontrolled generations of bradykinin and angioedema.

If this theory were correct, then AAE would be predicted to result in essentially the same pattern of complement abnormalities as HAE. However, this is not the case, as most patients with AAE demonstrate profound depletion of components of the classical complement pathway, as evidenced by low C1q (the measurable component of the C1 complex, C1q-r-s), which is not seen in patients with HAE. In addition, not all AAE patients with low C1q values have detectable anti-C1-INH antibodies [24]. (See "Complement pathways").

The relationship between autoantibodies to C1-INH and lymphoproliferative disorders in patients with AAE is not clear either. An early study identified these neutralizing antibodies in otherwise healthy AAE patients and hypothesized that AAE could arise from an autoimmune mechanism, without an associated lymphoproliferative disease [20]. Based on this, two types of AAE were proposed: one paraneoplastic and the other autoimmune [25]. However, subsequent work revealed that patients with and without autoantibodies to C1-INH develop lymphatic malignancies over time and at similar rates, indicating that this distinction is not clinically or prognostically relevant [8,26]. Thus, the division of AAE into these two types has been abandoned [10].

Activation of the classical complement pathway — A second theory proposes that the pathogenesis of AAE involves massive activation of the classical complement pathway by the neoplastic lymphoid tissue or by the abnormal antibodies and subsequent depletion of normally functioning C1-INH [11,27-29]. Evidence includes increased in vivo turnover of radiolabeled C1q and C1-INH with concomitant normal C1-INH production by monocytes of the same patient [28,29]. In this theory, anti-C1-INH autoantibodies are either an aggravating factor or purely an epiphenomenon.

An interesting patient was reported who had HAE and then developed non-Hodgkin's lymphoma [30]. With the appearance of the lymphoma, the patient's angioedema markedly worsened, and depletion of classical pathway complement components was apparent that had not been present before. This patient did not have detectable anti C1-INH antibodies, and the case supports the role of lymphoma tissue as activator of the
classical complement pathway and as the trigger of angioedema symptoms.

**Idiopathic** — We have two patients in our cohort in which we have detected neither an associated disorder nor autoantibodies to C1-INH and in whom the mechanism underlying AAE remains unknown. We can hypothesize that these individuals have antibodies to C1-INH that elude detection in plasma because of a low titer or because they are bound to cell membranes. It is also possible that an entirely different mechanism exists in such patients.

**Other implicated etiologies** — A small number of case reports have implicated infections, especially Helicobacter pylori, in the development of AAE [31-33]. Eradication of H pylori was followed by reversal of the clinical and biochemical symptoms abnormalities of AAE, suggesting the possibility that this infection could have a pathogenetic role in the development of AAE. The author has seen a patient with echinococcus and AAE who improved after treatment of the infection [24]. However, infections are unlikely to be related to pathogenesis in most patients and we do not suggest an exhaustive search for infections unless there are suggestive clinical and laboratory findings.

**DIAGNOSIS** — The diagnosis of acquired C1 inhibitor deficiency (AAE) is based upon a suggestive clinical history and appropriate complement abnormalities.

**Clinical history** — Acquired angioedema (AAE) should be considered in patients with the following:

- Episodes of angioedema affecting the cutaneous tissues and mucous membranes of the upper respiratory and gastrointestinal tracts
- Symptoms beginning in the fourth decade of life or later
- No family history of angioedema

Patients with AAE generally demonstrate all three of the above characteristics. Absence of a family history of angioedema, in isolation, is NOT diagnostic of AAE because more than 25 percent of patients with HAE carry a de novo mutation in C1-INH gene and therefore have no affected ancestors [34]. On the other hand, the presence of a family member with angioedema essentially excludes the diagnosis of AAE.

**Complement studies** — An algorithm for the diagnosis of angioedema due to C1-INH deficiency (acquired or hereditary) was published by an international consensus group ([algorithm](#)) [35]. In patients with isolated angioedema who are suspected of having a disorder of C1 inhibitor, the following tests should be obtained:

- C4 level
- C1 inhibitor antigenic level
- C1q level

Most patients with AAE demonstrate the following:

- Low C4
- Low C1q (usually <50 percent of normal)
- Low or normal C1 inhibitor antigenic (or quantitative protein) level

If the patient demonstrates these laboratory abnormalities, then a test of C1 inhibitor function should be obtained. Low function is required for the diagnosis ([table](#)).

C1q levels are usually <50 percent of normal in patients with AAE. However, about 30 percent of the patients in two large series had C1q levels that were decreased, but >50 percent of normal [7,16]. Finally,
there are rare cases in which C1q levels are normal.

**Additional studies** — Other diagnostic tests are only occasionally required. These include genotyping, detection of antibodies directed against C1-INH, and detection of cleaved C1-INH by SDS PAGE electrophoresis and immunoblotting.

**Genotyping** — In rare cases of AAE in which C1q is normal, the complement findings of AAE are identical to HAE. Genotyping for mutations in the C1-INH gene (SERPING1), which are only found in HAE, would be the only definitive way to differentiate these disorders. However, genetic testing is not widely available. If testing is not available, we recommend screening and monitoring patients who develop HAE over the age of 40 years for the underlying diseases associated with AAE. (See 'Evaluation for underlying disorders' below.)

**Detection of anti-C1-INH antibodies** — The other biochemical finding that is characteristic of AAE is the presence of anti-C1-INH autoantibodies in plasma. By comparison, approximately 30 percent of patients with AAE have these antibodies, as well as 3 percent of normal controls [36]. As with other autoantibodies, no clear cut separation between the background noise of natural autoantibody production in otherwise healthy individuals and significant pathologic levels in AAE patients has been established, and there is no diagnostic titer above which a patient can be determined to have AAE. No commercial assay for measuring these antibodies is available, although an ELISA system can be set up in specialized laboratories and yields reliable results for investigational purposes [23,37]. Therefore, the finding of high titers of anti-C1-INH antibodies in a patient's serum is supportive of the diagnosis of AAE but the absence of these antibodies does not exclude the disorder.

**Electrophoresis for inactive inhibitor** — An additional test that may help to refine the diagnosis of AAE is the detection of cleaved C1-INH by SDS PAGE electrophoresis and immunoblotting [25]. C1-INH normally interacts with its target protease and is cleaved by this interaction. Cleaved C1-INH then irreversibly binds to the protease, rendering it inactive. However, in the presence of anti-C1INH antibodies, C1-INH is cleaved, but cannot bind the protease [38]. The protease then continues to function while cleaved, but inactive C1-INH remains in the circulation. The cleaved, inactive form can be distinguished by electrophoresis [38]. In contrast, the routine quantitative assay for antigenic levels of C1-INH cannot distinguish between cleaved inactive and uncleaved active C1-INH, which explains why patients with AAE can have normal C1-INH antigenic levels and low function with standard complement tests.

**Obstacles to diagnosis** — It is our clinical impression that AAE frequently evades diagnosis for a period of years. We believe there are several obstacles to diagnosis:

- Even among specialists, awareness of the existence of an acquired form of C1-INH deficiency is not widespread, and uncertainties regarding the pathogenesis and laboratory features of the disorder further complicate diagnosis.

- Patients with AAE lack a family history, so cases are not detected through family screenings, as with HAE.

- The diagnosis of a coexisting lymphoproliferative malignancy can overshadow other medical issues, including recurrent angioedema, which may be attributed to a paraneoplastic phenomenon and not evaluated further.

- Because the disorder begins later in life, many patients are taking multiple medications and the episodes of angioedema are attributed to drug allergic reactions. Similarly, patients may have multiple
comorbidities, and the evaluation of angioedema may not take precedence until a severe attack occurs.

- Complement abnormalities may fluctuate between normal and abnormal when the disorder first develops, becoming more consistently abnormal over the ensuing months. For this reason, mild abnormalities associated with a consistent clinical presentation should be followed over time.

**DIFFERENTIAL DIAGNOSIS** — The differential diagnosis of acquired angioedema includes:

- Angioedema induced by ACE inhibitors
- Hereditary angioedema with normal C1 inhibitor or Type III HAE (formerly called estrogen-dependent hereditary angioedema)
- Isolated angioedema as a manifestation of an allergic reaction
- Idiopathic angioedema (ie, angioedema with no associated complement abnormalities)

In each of the above disorders, complement studies are normal.

AAE can also be confused with hereditary angioedema (HAE) type 1 and type 2, which have similar clinical features and complement abnormalities. However, C1q is low in most patients with AAE and normal in those with HAE (table 1). In addition, HAE usually presents in young people who are otherwise healthy, and about 75 percent of HAE patients have a family history of angioedema.

The differential diagnosis of angioedema, in general, is reviewed separately. (See "An overview of angioedema: Clinical features, diagnosis, and management", section on 'Differential diagnosis'.)

**Low C1q levels** — Low levels of C1q are not exclusive to acquired C1 inhibitor deficiency. Autoantibodies to C1q, causing depressed C1q levels, can be seen in hypocomplementemic urticarial vasculitis syndrome (HUVS) and SLE. Levels of C1q less than 30 percent of normal are typical of both conditions. However, HUVS usually includes urticaria, which is not observed with inherited or acquired C1-inhibitor deficiency. The diagnosis of HUVS and SLE are reviewed elsewhere. (See "Urticarial vasculitis" and "Diagnosis and differential diagnosis of systemic lupus erythematosus in adults".)

**EVALUATION FOR UNDERLYING DISORDERS** — All patients with acquired C1 inhibitor disorders should be evaluated for an underlying B cell lymphoproliferative disorder. This evaluation begins with a thorough review of systems and physical examination. Any abnormalities identified should be investigated further. Referral to a clinician trained in hematology can help with this evaluation. (See "Clinical features, laboratory manifestations, and diagnosis of multiple myeloma" and "Clinical presentation and diagnosis of non-Hodgkin lymphoma" and "Initial evaluation and staging of non-Hodgkin lymphoma".)

If the review of systems and physical examination is unrevealing, we usually obtain the following studies:

- Complete blood count (CBC), white blood cell differential, platelet count, and examination of the peripheral smear for the presence of atypical cells.
- Biochemical tests including blood urea nitrogen (BUN), creatinine, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH).
- Urinalysis.
- Serum protein electrophoresis and immunofixation.
- Serum free light chain assay (see "Recognition of monoclonal proteins", section on 'Serum free light..."
• Screening for lymphadenopathy and masses with imaging studies of the chest and abdomen. We usually perform chest x-ray and abdominal ultrasound, although computed tomography (CT) scans are also an option.

• All age-appropriate cancer screening (see "Screening for lung cancer" and "Screening for colorectal cancer: Strategies in patients at average risk" and "Screening for breast cancer") and see other relevant topic reviews.

Monitoring — If no associated condition is identified, then we monitor patients by repeating studies for B cell malignancies annually. Specifically, we obtain CBC with differential, serum protein electrophoresis and immunofixation, chest radiograph, and abdominal ultrasound.

SUMMARY

• Acquired C1 inhibitor deficiency (also called acquired angioedema or AAE) is a rare disorder characterized by recurrent episodes of angioedema, without urticaria or pruritus. Swelling most often involves the subcutaneous tissues of the face and the submucosa of the upper airway and small bowel. AAE presents in the fourth decade of life or later. (See ‘Epidemiology’ above and ‘Clinical manifestations’ above.)

• Approximately 70 percent of patients with AAE are found to have an associated disorder. In one-half of cases, the disorder is malignant (most often non-Hodgkin's lymphoma) and the other half, the associated condition is benign (most often MGUS). (See ‘Associated disorders’ above.)

• Angioedema in AAE is bradykinin-mediated, but the precise pathogenesis is undefined. Most patients have autoantibodies against the C1 inhibitor protein. These autoantibodies may impede the normal functioning of C1 inhibitor and cause a functional deficiency. Alternatively, the antibodies, or perhaps neoplastic tissue in some cases, may cause activation of the classical complement pathway, leading to depletion of normally functioning C1 inhibitor. (See ‘Pathogenesis’ above.)

• Acquired C1 inhibitor deficiency (acquired angioedema, AAE) should be considered in a patient who presents with isolated angioedema (without urticaria) in the fourth decade of life or later, and has no family history of angioedema. (See ‘Diagnosis’ above.)

• Initial testing should consist of levels of C4, C1q, and C1 inhibitor (antigenic level). If C4 and C1q are low and C1 inhibitor antigenic level is low or normal, then C1 inhibitor function should be obtained. Low C1 inhibitor function confirms the diagnosis (algorithm 1 and table 1). Other studies are usually not needed. (See ‘Complement studies’ above.)

• All patients with acquired C1 inhibitor disorders should be evaluated for an underlying B cell lymphoproliferative disorder at the time of diagnosis. If no disorder is found, we recommend repeating an evaluation annually. (See ‘Evaluation for underlying disorders’ above.)

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REFERENCES


1986; 323:722.


Topic 8112 Version 3.0
C1-INH deficiency diagnostic algorithm

Consider Hereditary Angioedema (HAE):
- Recurrent angioedema (without urticaria)
- Recurrent episodes of abdominal pain and vomiting
- Laryngeal edema
- Positive family history for angioedema

Measure: serum complement factor 4 (C4), C1 inhibitor (C1-INH) antigenic protein, C1 inhibitor (C1-INH) functional level if available

C4 and C1-INH protein quantities decreased
- Confirm decreased C4 and C1-INH protein by second measurement
- Family history of angioedema
  - HAE-C1INH-Type I
    - Earlier age of onset and C1q normal
    - Consider Acquired Angioedema
- No family history of angioedema
  - Measure C1q and consider age of onset of symptoms
  - Later age of onset and/or low C1q
  - Consider Acquired Angioedema

C4 quantity low but C1-INH protein normal or elevated
- Determine C1-INH function and repeat C4 and C1-INH protein levels
- C1-INH function normal
  - HAE-C1INH-Type II
    - Family history of angioedema
    - HAE Type III - HAE-FXII - HAE-unknown
    - AE from medications AE idiopathic
- C1-INH function decreased

C4, C1-INH protein normal
- Confirm C4, C1-INH normal during attack

<table>
<thead>
<tr>
<th>Angioedema disorder</th>
<th>C4*</th>
<th>C1 inhibitor level</th>
<th>C1 inhibitor function</th>
<th>C1q</th>
<th>C3</th>
<th>Other tests (not routinely needed for diagnosis)</th>
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<tr>
<td>HAE I</td>
<td>Low</td>
<td>Low</td>
<td>Low (usually &lt;50 percent of normal)</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>HAE II</td>
<td>Low</td>
<td>Normal or elevated</td>
<td>Low (usually &lt;50 percent of normal)</td>
<td>Normal</td>
<td>Normal</td>
<td>Genetic testing</td>
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<tr>
<td>HAE III</td>
<td>Normal</td>
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<td>Normal</td>
<td>Normal</td>
<td>Mutations in gene for factor XII detected in some patients</td>
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<tr>
<td>AAE</td>
<td>Low</td>
<td>Normal or low</td>
<td>Low (usually &lt;50 percent of normal)</td>
<td>Normal or low*</td>
<td>Normal or low</td>
<td>Anti-C1 inhibitor antibodies</td>
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</tbody>
</table>

HAE: Hereditary angioedema (aka hereditary C1 inhibitor deficiency)
AAE: Acquired angioedema (aka acquired C1 inhibitor deficiency)
* In inherited angioedema types I and II, C4 is always low during an attack (with one published exception) and are chronically low in the majority of patients.
  - There are rare forms of acquired angioedema in which C1q levels are normal. See topic review of acquired C1 inhibitor deficiency for details.
Acquired C1 inhibitor deficiency: Management and prognosis

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Disclosures

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INTRODUCTION — Acquired deficiency of C1 inhibitor, also called acquired angioedema (AAE), is a rare syndrome of recurrent episodes of angioedema, without urticaria, which is associated with B cell lymphoproliferative disorders in some patients [1]. Angioedema typically affects the skin or mucosal tissues of the upper respiratory and gastrointestinal tracts. The swelling is self-limited, although laryngeal involvement may cause fatal asphyxiation. Clinically, this disorder is very similar to hereditary angioedema (HAE), although AAE develops in older patients and is associated with underlying disease, whereas HAE presents in younger patients who are otherwise healthy.

This topic review will discuss the management and prognosis of acquired C1 inhibitor deficiency. The clinical manifestations, epidemiology, pathogenesis, and diagnosis of this disorder are reviewed elsewhere. (See “Acquired C1 inhibitor deficiency: Clinical manifestations, epidemiology, pathogenesis, and diagnosis”.)

Hereditary angioedema, which is caused by mutations in the gene for C1-INH, is discussed separately. (See “Diagnosis of hereditary angioedema” and “Clinical manifestations and pathogenesis of hereditary angioedema” and “Treatment of acute attacks in hereditary angioedema” and “Prevention of attacks in hereditary angioedema”.)

ACUTE MANAGEMENT — The management of a patient with AAE involves several components.

- Educating the patient about the potential characteristics of angioedema attacks and ensuring that the patient understands there is a real risk of fatal asphyxiation with attacks involving the upper airway.
- Providing the patient with written instructions about treatment of acute attacks, which can be given to other providers in the emergency setting.
- Management of associated diseases, if present, or monitoring for the development of an associated disease.
- Evaluating the need for prophylaxis to prevent angioedema attacks.

Patient education about laryngeal edema — All patients with AAE must understand what steps to take to get prompt and appropriate treatment in case of angioedema involving the upper airway. Patients should not attempt to manage early laryngeal attacks at home. Instead, they should be taken by ambulance to the nearest emergency department. If therapy is available for self injection it can be initiated, but should not substitute for obtaining emergency care or delay the acquisition of emergency care.
AAE is a rare disorder, and few emergency department providers are familiar with the treatment. Patients can be equipped with a document that briefly explains the patient’s diagnosis, outlines the indicated treatment for acute attacks, and provides contact information for the supervising clinician (form 1).

Laryngeal attacks are the most dangerous type of attack in acquired angioedema because edema can lead to fatal airway obstruction. Upper airway angioedema usually progresses over hours, although it can occur precipitously. Intubation may become very difficult due to distortion of the anatomy of the upper airway.

**Airway management in laryngeal edema** — Assessment and protection of the upper airway is the first and most important management issue in the patient with an acute attack involving any part of the airway, because none of the available therapies, including C1-inhibitor replacement (C1INHRP), icatibant, and ecallantide, can be considered universally effective in all cases. In addition, these agents take time to work, and the patient’s airway must be protected in the interim.

Intubation should be performed immediately if stridor or signs of respiratory arrest are present. A clinician trained in difficult airway management should be summoned if possible, because failed attempts can lead to fatal obstruction. Emergent cricothyroidotomy may be required in rare cases. (See "The difficult airway in adults" and "Emergent surgical cricothyrotomy (cricothyroidotomy")

Once the patient is assessed and either intubated or deemed stable, additional therapies can be considered. Transfer to the intensive care unit should be arranged. Frequent and meticulous monitoring of airway status should continue throughout the course of the attack until complete resolution, and patients should not be discharged until all airway symptoms have resolved.

**Pharmacologic treatment of acute attacks** — The treatment of acquired angioedema (AAE) is extrapolated from that of hereditary angioedema (HAE). No controlled studies have been performed in patients with AAE and no therapies are specifically registered for treatment of this condition. Based on clinical experience, there appears to be some differences in the response of these two disorders to the available therapies, as discussed in this section. The safety, efficacy, and administration of each agent (in HAE) are reviewed in greater detail separately. (See "Treatment of acute attacks in hereditary angioedema".)

**C1 inhibitor concentrate** — The most widely used therapy for acute laryngeal edema is C1 inhibitor concentrate (C1INHRP). C1INHRP became available in the United States in 2009, but has been available in Europe for decades. Clinical experience indicates that C1INHRP is effective in the majority of patients with AAE.

An initial dose of 20 units/kg is suggested, based on data in patients with HAE. The dosing, administration, and adverse effects of C1INHRP are reviewed elsewhere. (See "Treatment of acute attacks in hereditary angioedema", section on 'Medication options'.)

**Resistance** — A small percentage of patients with AAE become less responsive to C1INHRP over time, requiring higher doses to control symptoms [2,3]. As an example, one of our patients required multiple infusions totaling 12,000 units of C1INHRP (the usual initial dose is 1000 units) over a period of two hours to control laryngeal edema. If a patient with AAE fails to improve after an initial dose of C1INHRP, we would suggest administering one of the newer agents discussed below as the next intervention. (See 'Ecallantide' below and 'Icatibant' below.)

The mechanism by which resistance to C1INHRP develops appears to involve extremely rapid catabolism of the inhibitor protein, although this has not been formally demonstrated. In blood samples collected from the patient described above, no significant increase of C1-INH function could be detected at any point during the multiple infusions, while C1-INH antigen normalized due to the increase in cleaved C1-INH. These data
suggest that the infused C1-INH was rapidly bound by the autoantibodies and converted in its cleaved inactive form upon interaction with target proteases. The patient described above had very high levels of anti-C1-INH antibodies.

The newer therapies for bradykinin-mediated angioedema, **ecallantide** and **icatibant**, offer alternatives for the treatment of patients who become resistant to C1INHRP.

**Ecallantide** — **Ecallantide** (Kalbitor®) is an inhibitor of plasma kallikrein. Kallikrein is the enzyme that releases bradykinin, the mediator of angioedema, from high molecular weight kininogen. Ecallantide is approved by US FDA for acute angioedema attacks in patients with HAE [4]. It is only available in the US (at the time of this update).

During the first open label trial we used this drug in two patients with AAE, one of them resistant to C1-INH, and observed a prompt resolution of symptoms [5]. Both patients developed a relapse of angioedema within 12 hours, but the symptoms were mild and resolved spontaneously without need for further treatment.

The dosing, administration, and adverse effects of **ecallantide** are reviewed elsewhere. (See "Treatment of acute attacks in hereditary angioedema", section on 'Kallikrein inhibitor (US only)').

**Icatibant** — **Icatibant** (Firazyr®) is an antagonist of the B2 bradykinin receptor. This drug has been approved in Europe by the European Medicines Agency (EMA) for treatment of acute attacks of HAE (the same indication as **ecallantide** [6]. It became available in the United States in 2011.

The author has successfully used **icatibant** to treat AAE patients who presented with angioedema, including laryngeal edema, and who were not responsive to C1-INH [7].

The dosing, administration, and adverse effects of **icatibant** are reviewed elsewhere. (See "Treatment of acute attacks in hereditary angioedema", section on 'Bradykinin B2 receptor antagonist'.)

**Plasma** — Plasma, in the form of fresh frozen plasma (FFP) in the US, or solvent-detergent treated plasma (S/D plasma) in other countries, has been used in the treatment of acute laryngeal attacks and severe abdominal attacks in both AAE and HAE. Plasma contains an array of complement components, including C1 inhibitor. The efficacy has not been formally investigated.

Two units is the usual initial dose for treatment of angioedema. This dose can be repeated every two to four hours until there is clinical improvement. Once the attack begins to subside, further plasma is not usually required. If a patient has comorbid conditions that increase the risk for volume overload, then dosing of 10 to 15 mL per kg body weight is recommended instead, with monitoring of volume status and cardiopulmonary function.

The administration, infection risks, and adverse effects of plasma are reviewed elsewhere. (See "Treatment of acute attacks in hereditary angioedema", section on 'Plasma'.)

**Antihistamines, glucocorticoids and epinephrine** — Our and others' experience support the view that antihistamines, corticosteroids, and epinephrine are NOT effective in acute treatment of AAE [8]. There are no trials that directly evaluate the use of these therapies in HAE or AAE. We strongly recommend NOT relying on these drugs to treat angioedema in patients with C1-INH deficiency. In one review of 22 patients, investigators concluded that "in the acute setting, high dose corticosteroids with or without subcutaneous epinephrine seem to be effective, depending on the severity of symptoms" [9]. However, they did not provide the data to support statement, and this conclusion is not consistent with our clinical experience. On the other hand, the harm of administering antihistamines, glucocorticoids, and intramuscular epinephrine is probably
minimal, and these therapies should be considered if there is any uncertainty about the patient's diagnosis, because allergic forms of angioedema do respond to these therapies.

**LONG-TERM MANAGEMENT** — Long-term management includes treatment of any associated diseases, monitoring for development of lymphoproliferative disorders, and in some cases, prophylaxis to prevent recurrent angioedema.

**Avoidance of medications that may exacerbate symptoms** — Medications that can increase the frequency and/or severity of attacks in AAE include the following:

- Estrogen-containing medications, such as hormone replacement therapy and contraceptives [10].
- Tamoxifen, a selective estrogen receptor modulator (SERM) that has mixed agonist/antagonist actions on the estrogen receptor. In one reported case, a patient with HAE who developed increased episodes on tamoxifen was successfully treated with the aromatase inhibitor letrozole [11].
- Angiotensin-converting enzyme (ACE) inhibitors [12]. In contrast, the experience of the author is that angiotensin II receptor blockers (ARBs) are well-tolerated.

**Treatment of associated disease** — Treatment of the associated disease in patients with AAE is usually successful in reducing attacks of angioedema, although the degree of improvement is variable. This may be the best initial approach to management, depending upon the nature of the associated condition.

There are scattered reports of partial or complete clinical and/or biochemical remission of AAE upon treatment of different associated diseases [13-18]. In patients with AAE and lymphoma, a variety of therapies, including surgery, chemotherapy, and biologic agents as rituximab, have been reported to be helpful in reducing episodes of angioedema [17,19-21]. Responses to treatment range from partial to complete (and apparently stable) remission.

Alterations in complement abnormalities are also variable following treatment for lymphoma in patients with AAE. C1-INH levels, C1q, and C4 levels may normalize in concert or independently. Disappearance of autoantibodies can also occur. We have observed a wide range of changes in complement studies and autoantibody levels in the patients we manage following treatment for lymphoma, although we have not detected a consistent pattern. One of our patients had complete reversal of clinical and complement abnormalities, but persistence of anti-C1-INH autoantibodies. Such findings highlight the uncertainties regarding the pathogenesis of AAE. (See "Acquired C1 inhibitor deficiency: Clinical manifestations, epidemiology, pathogenesis, and diagnosis", section on 'Pathogenesis'.)

**Monitoring MGUS** — Patients with AAE who are found to have monoclonal gammopathy of uncertain significance (MGUS) must be followed and evaluated regularly, as MGUS can transform to a more serious disorder at a rate of approximately 1 percent per year. It is not known if treatment of MGUS prior to transformation would impact the patient's outcome. The recommendations for monitoring are reviewed separately. (See "Clinical course and management of monoclonal gammopathy of undetermined significance".)

**Prophylaxis to prevent attacks** — Prophylactic therapy to prevent attacks of angioedema in AAE should be considered in patients who are significantly impaired by recurrent episodes resulting in five or more days of disability per month.

The options for prophylactic therapy in patients with AAE are the same as those used in HAE: antifibrinolytic agents, attenuated androgens, or regular infusions of C1-INHRP [2,13,22-24]. However, we have concerns
about the use of C1-INHRP for prophylaxis because AAE patients sometimes become resistant to it (possibly due to anti-C1 inhibitor antibodies) and we prefer to reserve it for treating acute attacks. (See 'Resistance' above.)

Thus, it is the author's approach to start with tranexamic acid (3 grams daily). If the attacks do not decline in number and severity, we then change to danazol (600 mg daily, usually as 200 mg three times daily) for one month with subsequent tapering if symptoms subside to the lowest effective dose.

Anti-fibrinolytics — TA is well tolerated by most patients with AAE, and reduces the frequency and severity of attacks in the majority of patients. As an example, of 13 patients treated with TA in one series, 8 responded very well, and 4 responded partially [2]. Use of TA for the prevention of angioedema, including dosing and monitoring, is discussed in more detail separately. (See "Prevention of attacks in hereditary angioedema", section on 'Anti-fibrinolytics'.)

It is still debated whether or not anti-fibrinolytics carry an increased risk of thrombosis, particularly in patients with associated malignancies. We have not seen this complication in our patients, but the number of individuals treated is sufficiently small that we may not have encountered it yet. Until this question is conclusively answered, we coadminister warfarin therapy (with a target INR between 2 and 3) in patients with increased risk of thromboembolism who also need long-term TA for AAE [25]. In the US, there is limited experience with TA because it was not available in oral form until 2009. Experience with the use of aminocaproic acid in AAE is extremely limited.

Androgens — Attenuated androgens, such as danazol, stanozolol, and others control symptoms in approximately one-half of patients, in our clinical experience [2,13,23,24]. Those who respond well to this therapy sometimes achieve control of symptoms with very low doses and remain on this agent for years. However, in the remaining patients, androgens either do not work from the outset, or become ineffective after a period of time [2]. Use of androgens for the prevention of angioedema is discussed in more detail separately. (See "Prevention of attacks in hereditary angioedema", section on 'Attenuated androgens'.)

PROGNOSIS — There are no published studies that provide information about the long-term prognosis of patients with AAE. Among the 40 to 50 patients we have followed, six have died (two of lymphoma, one of breast cancer, and three of apparently unrelated causes).

The risk of asphyxiation due to upper airway closure remains a real and immediate risk for patients with AAE because of the limited knowledge of this condition on the part of clinicians. We learned of a female patient with known AAE who is in a persistent vegetative state after presenting with "dysphagia" to the emergency department of a local hospital. An infusion of 1000 units of C1-INHRP was started, but during administration, the swelling suddenly progressed to airway closure. Attempts at endotracheal intubation failed because of massive laryngeal edema and permanent anoxic brain damage was already established by the time a tracheotomy was performed. We know of several other patients who have died of laryngeal edema.

SUMMARY AND RECOMMENDATIONS

- Patients should be educated about the risk of fatal laryngeal attacks, and instructed on how to proceed should swelling in the throat develop. Because so few clinicians are familiar with this disorder, equipping the patient with information about proper treatment is critical. A printable form is provided (form 1). (See 'Patient education about laryngeal edema' above.)

- Patients with laryngeal attacks require immediate assessment of the airway. If respiratory distress or stridor is present, preparations to intubate should be made, because even the first line therapies take
approximately 30 minutes or more to begin working. An expert should manage the airway if possible. (See 'Airway management in laryngeal edema' above.)

- First-line therapies for treatment of severe attacks of AAE are:
  - Purified human C1 inhibitor (C1INHRP) (available in many countries)
  - Ecallantide, a kallikrein inhibitor (available in the US)
  - Icatibant, a bradykinin B2 receptor antagonist (available in US, Europe and other countries)

(See 'Pharmacologic treatment of acute attacks' above.)

- Patients with AAE can become resistant to C1INHRP over time. For patients with acute angioedema who do not improve in response to an initial dose of C1INHRP, we suggest administering ecallantide or icatibant instead (Grade 2C).

- If an underlying disorder is identified, treatment of that disorder usually reduces the frequency of angioedema episodes. (See 'Treatment of associated disease' above.)

- For patients with ongoing symptoms resulting in five or more days of disability per month, we suggest prophylactic therapy (Grade 2C). The primary agents for prevention of attacks are attenuated androgens or antifibrinolytic agents. (See 'Prophylaxis to prevent attacks' above.)

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REFERENCES

5. Cicardi M, unpublished data.


Instructions for emergency care of acquired angioedema

Patient’s name: ____________________________

**Diagnosis:** Acquired angioedema

Treating physician’s name and contact information:


Acquired angioedema is a disorder of C1 inhibitor, in which there are recurrent episodes of angioedema (deep tissue swelling) caused by excessive production of bradykinin. Swelling most commonly affects the skin and small bowel, but it can also affect the pharynx and larynx. Swelling in acquired angioedema does NOT respond to intramuscular epinephrine, glucocorticoids, or antihistamines, since it is not an allergic reaction.

**ACUTE SWELLING SHOULD BE MANAGED AS FOLLOWS:**

- Any swelling involving the throat or structures near the throat should be immediately evaluated to determine the status of the airway and then regularly monitored. **LARYNGEAL EDEMA CAN PROGRESS RAPIDLY TO ASPHYXIATION AND CAN BE FATAL!** The patient should be in a setting in which endotracheal intubation or tracheostomy can be performed immediately if necessary, although most attacks resolve without requiring this intervention.

Pharmacologic treatments to reduce swelling include:

- Infusion of C1 inhibitor concentrate (available products include Cinryze or Berinert in the US, Berinert P and Ruconest in the EU).
- Ecallantide (Kalbitor) (available in the US only). This medication blocks production of bradykinin.
- Icatibant (Firazyr). This medication is an antagonist of the bradykinin B2 receptor.

If none of these therapies is available, then plasma may be used:

- In the US: Fresh frozen plasma, 2 units
- In Europe: Solvent/detergent treated plasma