Lesson 294: PreAnesthetic Assessment of the Patient With Hereditary Angioedema

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Read this article, reflect on the information presented, then go online and complete the lesson post-test and course evaluation before the termination date below. (CME credit is not valid past this date.) You must achieve a score of 80% or better to earn CME credit.

TIME TO COMPLETE ACTIVITY: 2 hours
RELEASE DATE: October 1, 2011
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Needs statement

Hereditary angioedema (HAE) is a condition with important anesthetic consequences; surgery and airway manipulation are recognized triggers, and attacks involving laryngeal edema may lead to a compromised airway that is life‐threatening. Recent drug developments have expanded the modalities available for acute treatment and long‐term management of these patients. Clinical experience with these agents has been described in journals not generally read by anesthesiologists.
Learning Objectives

At the end of this activity, the participant should be able to:

1. Summarize the epidemiology and pathophysiology of HAE.
2. Recognize signs and symptoms that support the diagnosis of HAE.
3. List laboratory tests that can be used to confirm the diagnosis of HAE.
4. Manage the symptoms in patients presenting with acute HAE attacks.
5. Tabulate common triggers for HAE attacks and indications for short-term prophylaxis.
6. Identify medications used for short-term prophylaxis against HAE attacks and explain their respective mechanisms of action.
7. Review the side effects and contraindications associated with commonly used HAE prophylactic therapies.
8. Discuss options available for long-term management of patients with HAE.
9. Describe how to monitor patients with HAE who are receiving long-term prophylactic drug therapy.
10. Name new drugs currently available for HAE acute therapy and prophylaxis.

Case History

A 13-year-old girl was brought to the emergency department by her parents after developing progressive swelling of the face, lips, and tongue. Her parents explained that over the course of the afternoon, the child’s voice had become increasingly hoarse, and she began to complain of difficulty in swallowing. Earlier that day, she had been to the dentist for routine dental cleaning. She had been well at the time, and the visit itself was uneventful.

On physical examination, there was marked edema of the perioral region. Her tongue was severely enlarged such that she had difficulty keeping her mouth closed and controlling her saliva. She resisted lying down, preferring to sit in a forward-leaning position. No other constitutional symptoms, including rash or urticaria, were apparent. Vital signs included blood pressure, 100/60 mm Hg; heart rate, 88 beats per minute; oxygen saturation, 96%; and temperature, 97.2°F.

Hereditary angioedema (HAE) is a genetic disorder that results in deficiency in functional C1 inhibitor (C1-INH) due to mutations of its gene (SERPING1) on chromosome 11.1,2 The absence of functional C1-INH leads to excess bradykinin, a potent vasodilator that causes edema formation. The main mode of inheritance is autosomal dominant.

Angioedema is a general term defined as localized, self-limited swelling of subcutaneous and submucosal tissue caused by the release of vasoactive mediators that temporarily increase capillary permeability. Many etiologies—both acquired and inherited—are associated with angioedema, and different mediators are responsible for edema formation depending on the underlying diagnosis. Two main types of angioedema are distinguished: mast cell–mediated, which involves histamine and other vasoactive substances released from mast cells, and bradykinin-mediated.1

Hereditary angioedema (HAE) is a genetic disorder that results in deficiency in functional C1 inhibitor (C1-INH) due to mutations of its gene (SERPING1) on chromosome 11.1,2 The absence of functional C1-INH leads to excess bradykinin, a potent vasodilator that causes edema formation. The main mode of inheritance is autosomal dominant.

The prevalence of HAE is estimated to be 1 in 10,000 to 1 in 50,000. Symptoms usually begin within the first 2 decades of life, but a definitive diagnosis often is delayed because clinical suspicion is lacking.
The average time from symptom onset to diagnosis is estimated to be nearly a decade.\textsuperscript{3,4}

Clinical manifestations of HAE include recurrent, spontaneous attacks of subcutaneous and submucosal nonpitting edema without pruritus or urticaria. The severity and frequency of HAE attacks vary dramatically, even among those who share the same genetic mutation.\textsuperscript{4} Attacks can occur anywhere on the body but usually involve the skin—particularly the face and extremities—or the bowel wall. Abdominal attacks are associated with diffuse pain, vomiting, and diarrhea and may result in significant hypovolemia or shock.

In most cases, symptoms develop gradually over a period of 12 to 36 hours and subside without intervention in 48 to 72 hours.\textsuperscript{4} Some patients experience a prodrome of tingling in the extremities and a flat, nonpruritic serpiginous rash (erythema marginatum).\textsuperscript{5} Attacks affecting laryngeal tissue are uncommon (estimated at 0.9% of all HAE attacks), but up to 50% of patients with HAE experience at least 1 episode in their life that involves globus sensation, throat tightness, or dysphagia.\textsuperscript{4,6}

Before the advent of therapy, mortality from HAE attacks with laryngeal edema was as high as 30%, primarily caused by airway compromise.\textsuperscript{6} Even with therapeutic intervention, temporary airway protection including intubation or tracheostomy may be required until edema resolves.

Pathophysiology

HAE is a disorder caused by dysregulation of the kinin-generating system.\textsuperscript{5,7} Kinins are a poorly understood group of polypeptides that circulate in the bloodstream and play a role in inflammation, blood pressure regulation, and coagulation. The most important kinins are kallidin and bradykinin, potent vasodilators that act on many cell types including the vascular endothelium. Kinins circulate in pre-cursor forms called kininogens, which are activated by the serine protease enzyme kallikrein. Kallikrein itself exists in a dormant form called prekallikrein and is activated by factor XIIa (Hageman factor).

C1-INH is a serine protease enzyme (serpin) that was discovered and named for its ability to inactivate the complement factor C1. It has since been discovered to play a role in the regulation of coagulation and fibrinolysis and to be the main downregulator of the kinin-generating cascade.\textsuperscript{8} In addition to inactivating C1, C1-INH also is responsible for inactivating factors XIa and XIIa, plasmin, tissue plasminogen, and kallikrein. The absence of functional C1-INH leads to excess kallikrein, which in turn results in excess bradykinin. A series of proteins degrade bradykinin, including angiotensin-converting enzymes (ACE). Thus, symptoms of HAE are often exacerbated when patients are prescribed ACE inhibitors.

There are 2 main subtypes of HAE.\textsuperscript{2,4} Nearly 85% of patients have type I HAE, which is caused by a genetic mutation that results in absent or very low levels of C1-INH. Type II HAE, which represents about 15% of cases, is characterized by a mutation in the same gene that results in production of a C1-INH protein in a normal quantity, but a nonfunctional form.

A third variety of HAE (sometimes called type III HAE) is a very rare subtype originally thought to occur only in women but subsequently diagnosed also in men. Patients with this type of HAE have normal C1-INH levels and function. In a subset of cases, this form of HAE results from a functional mutation in the factor XII gene that leads to excess kallikrein enzyme activation and subsequent bradykinin formation.
Very little is known about the management of patients with this rare form of HAE. However, estrogen therapy seems to promote attacks, and the initiation of estrogen-containing medication is sometimes a precipitant to diagnosis.²,⁴ The remainder of this lesson pertains to the care of patients with HAE types I and II.

**Diagnosis**

HAE should be suspected in any patient with a history of recurrent edema of the face and extremities without urticaria who is nonresponsive to antihistamine or corticosteroid therapy. HAE also should be considered in patients who present with acute abdominal pain or upper airway obstruction when no other underlying pathology is identified. A positive family history is suggestive, but its absence should not rule out consideration of the diagnosis; in approximately 25% of HAE cases, the genetic defect occurs de novo.⁶

The short half-life of bradykinin makes its measurement as a diagnostic aid impractical. The most cost-effective method to screen for HAE is by measurement of C4 levels.⁹,¹⁰ Although C4 is not directly involved in the pathology of HAE, it serves as a marker of C1-INH activity because C4 is normally cleaved by C1. In patients with HAE, the absence of functional C1-INH leads to excess C1, which in turn results in increased degradation of C4 and characteristically low C4 levels. Normal C4 levels virtually rule out the diagnosis of HAE, although in some patients (about 2%), C4 levels are near normal between attacks.

Further diagnostic evaluation of suspected cases includes quantification of C1-INH antigen and functional C1-INH assay results. Low levels of C4, C1-INH antigen, and functional C1-INH are indicative of type I HAE. Low levels of C4 and functional C1-INH with normal or elevated C1-INH antigen support the diagnosis of type II HAE. Measuring C1q complement factor levels can help distinguish hereditary from acquired C1-INH deficiency. The latter is a rare condition marked by increased protease inhibitor consumption usually related to autoantibodies against C1-INH and C1q. C1q levels are low in 75% of patients with acquired forms of C1-INH deficiency but only in 25% of patients with a hereditary deficiency. Using this algorithmic approach, genetic testing is not necessary to confirm the diagnosis of type I or type II HAE (Figure).⁹,¹⁰

Although HAE is an autosomal dominant disorder, patients with the condition usually have C1-INH levels significantly below 50% normal; laboratory biomarkers are useful for diagnosis but do not correlate well with symptom severity.²,³ Similarly, although many treatments for HAE are intended to increase C1-INH levels, C1-INH assays are not helpful in monitoring treatment efficacy.
Short-term Prophylaxis

Short-term prophylactics were the first drugs approved to treat patients with HAE, and prevention remains the mainstay of management (Table). Prophylaxis is indicated in anticipation of any event that may trigger an HAE attack. Such procedures include surgery, dental manipulations, endoscopic procedures, and particularly stressful events or severe illnesses. Intubation and oral and dental surgeries are especially strong triggers. Although there is no way to gauge treatment adequacy, C1-INH levels of at least 40% of normal appear to confer effective prevention against serious attacks.²
Table. *Treatments for HAP*

<table>
<thead>
<tr>
<th>Medication*</th>
<th>Usual Adult Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute attacks</td>
<td></td>
</tr>
<tr>
<td>C1-INH concentrate</td>
<td>20 U/kg IV</td>
</tr>
<tr>
<td>Kallikrein INH (ecallantide)</td>
<td>30 mg SC, divided into 3 separate 1-ml injections; may be repeated within 24 h if required</td>
</tr>
<tr>
<td>Bradykinin-receptor antagonist (icatibant)</td>
<td>30 mg SC</td>
</tr>
<tr>
<td>Short-term prophylaxis</td>
<td></td>
</tr>
<tr>
<td>C1-INH concentrate</td>
<td>1,000 U IV, given as close to procedure as possible (1-6 h); additional doses should be available</td>
</tr>
<tr>
<td>17-a. Alkylated androgens</td>
<td></td>
</tr>
<tr>
<td><em>Danazol</em></td>
<td>2.5-10 mg/kg/d (maximum, 600 mg/d) started 5 d before and continued for 2 d after procedure date</td>
</tr>
<tr>
<td><em>Stanozolol</em></td>
<td>4-6 mg/d started 5 d before and continued for 2 d after procedure date</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>10 mU/kg (24 U) IV given as close to procedure as possible</td>
</tr>
<tr>
<td>Maintenance therapy</td>
<td></td>
</tr>
<tr>
<td>17-a. Alkylated androgens</td>
<td></td>
</tr>
<tr>
<td><em>Danazol</em></td>
<td>50-200 mg PO QOD to BID (goal, ≥200 mg/d)</td>
</tr>
<tr>
<td><em>Stanozolol</em></td>
<td>1-5 mg PO QOD to BID (goal, ≥2 mg/d)</td>
</tr>
<tr>
<td><em>Oxandrolone</em></td>
<td>2.5-10 mg/d PO (goal, ≥5 mg/d)</td>
</tr>
<tr>
<td>Anti fibrinolytics</td>
<td></td>
</tr>
<tr>
<td><em>Tranexamic acid</em></td>
<td>0.5-1.5 g PO QOD to TD</td>
</tr>
<tr>
<td><em>e-Aminocaproic acid</em></td>
<td>4-8 g/d PO, divided into 2 or 3 doses</td>
</tr>
<tr>
<td>C1-INH concentrate</td>
<td>1,000 U IV up to 1 mg/week (or self-administered by patient at first sign of an attack)</td>
</tr>
</tbody>
</table>

BD, twice daily; HAE, hereditary angioedema; INH, inhibitor; IV, intravenous; PO, by mouth; QOD, every other day; SC, subcutaneous; TD, 3 times daily; U, units

a Adapters from references 4, 10, and 12.
b Several medications are not currently available in the United States for the treatment of acute HAE attacks. Ecallantide is currently available only in Europe. For short-term, preprocedural prophylaxis, C1-INH concentrate is the drug of choice. Androgens may be used but must be started several days in advance or a procedure because of their delayed onset of action. Fresh frozen plasma can be administered if C1-INH concentrate is not available and contraindications or other constraints do not preclude the use of androgens. Before the development of C1-INH concentrate, patients with HAE requiring long-term prophylaxis were usually treated with androgens. Antifibrinolytics were less frequently used because of their reduced efficacy and associated risks. Home self-infusion with C1-INH concentrate is not an additional option for long-term maintenance therapy.

Attenuated androgens, specifically 17-o-alkylated agents such as danazol, stanozolol, and oxandrolone, were the first drugs approved for HAE prophylaxis. The mechanism of action of androgens is not fully understood but is presumed to result from enhanced liver synthesis of C1-INH. In some studies, androgens have been shown to increase the levels of enzymes responsible for bradykinin degradation, including aminopeptidase P, which also may account for their effectiveness.
Lesson 294: PreAnesthetic Assessment of the Patient With Hereditary Angioedema

For short-term prophylaxis, androgens must be started several days before a procedure, as the onset of action is delayed. Current guidelines recommend initiating therapy 5 days prior to the procedure and continuing for 2 to 5 days after. Androgens are not advised in prepubescent children, as the drugs may cause premature closure of the epiphyseal plates. Androgens also are contraindicated in pregnancy because they can interfere with fetal sexual development. Despite these cautions, short courses of androgen therapy have been used safely in pediatric patients and in women in the last trimester of pregnancy. The most commonly used drug is danazol, administered orally in a dose of 2.5 to 10 mg/kg per day (maximum, 600 mg per day). An alternative drug is stanozolol, 4 to 6 mg per day. Despite the availability in Europe for several years of a human plasma–derived, nanofiltered C1-INH concentrate for prevention of HAE attacks, it was not until 2008 that the FDA approved the first formulation in the United States. C1-INH is now the drug of choice for short-term prophylaxis.

C1-INH infusions tend to be well tolerated. The most common adverse side effects are sinusitis, rash, headache, and upper respiratory infection. Although thrombotic events have been reported, treatment does not appear to systematically increase thrombotic risk. Rigorous donor screening, pasteurization, and nanofiltration virtually eliminate the possibility of infectious transmission. However, the drug is a blood product; therefore, in theory its use carries a risk for bloodborne disease transmission. The recommended dose of C1-INH is 1,000 U administered IV 1 to 6 hours before the start of a procedure, with additional doses available intraoperatively or post-operatively if needed.

Before the availability of C1-INH concentrate and in cases when androgen therapy was contraindicated or considered impractical, the administration of fresh frozen plasma (FFP) 1 to 12 hours before the start of a procedure was a frequent treatment strategy. The usual dose was 2 U (400 mL) for adults and 0.05 U/kg (10 mL/kg) in children. Plasma administration restores C1-INH levels and therefore helps to reduce bradykinin generation.

Antifibrinolytics such as tranexamic acid (TA) and ε-aminocaproic acid (EACA) also have been used in short-term prophylaxis, although they are not FDA-approved for this use and are effective in only about 30% of patients with HAE. Antifibrinolytics presumably act to spare C1-INH by inhibiting plasmin activity, thereby blocking complement activation and C1-INH consumption. For adults, the suggested oral dose of TA is 20 to 50 mg/kg per day split into 2 or 3 doses (maximum, 3-6 g per day). The suggested oral dose of EACA is 6 to 12 g per day in 3 or 4 divided doses. Because of reduced efficacy and side effects, these agents are rarely employed today.

In cases of minor manipulation (eg, routine dental cleaning) and when C1-INH concentrate is immediately available, the decision to withhold prophylaxis may be considered. Nevertheless, because attacks are unpredictable, patients with HAE should undergo any procedures in monitored settings where appropriate emergency care is available.

Management of Acute Attacks

Until recently, the only way to manage acute attacks of HAE was with supportive care, primarily pain control and hydration for abdominal attacks with hypovolemia. Corticosteroids, antihistamines, and epinephrine—although frequently administered—are of no value (except to exclude other diagnoses). Androgens and antifibrinolytics are not effective during acute attacks because of their delayed onset of action. Successful use of FFP was at times reported in the literature; however, its utility remains
controversial because in addition to increasing C1-INH levels, FFP also increases concentrations of other complement factors and kinins that may potentiate edema formation. Nevertheless, when newer effective therapies are not available, FFP is still administered.

In 2009, the first human plasma–derived C1-INH concentrate was approved for acute treatment of HAE abdominal or facial attacks. Although not approved for use in children, experience supports the efficacy and safety of C1-INH concentrates in this population. The FDA-approved dose is 20 U/kg.

Ecallantide (DX-88) is a kallikrein inhibitor that blocks release of bradykinin. In 2009, it was approved by the FDA for use in moderate to severe HAE attacks in patients aged 16 years or older. Ecallantide is a recombinant protein produced in yeast. A significant benefit of ecallantide is its ability to be administered either subcutaneously or IV. It is generally well tolerated, but hypersensitivity reactions have occurred. For the treatment of acute HAE attacks, the recommended dose of ecallantide is 30 mg administered subcutaneously in 3 separate 1-mL injections. If symptoms persist, an additional dose may be administered within 24 hours. Ecallantide has a short half-life and is therefore not expected to be useful as a prophylactic agent.

Maintenance Therapy

Among patients with significant quality-of-life issues, frequent HAE attacks (generally considered to be more than 1 severe attack per month), or a history of laryngeal edema, maintenance drug therapy should be considered. Three options are available: androgens, antifibrinolytics, and C1-INH concentrates.

In addition to the short-term, preprocedural use of androgens, they also have been used for decades as long-term prophylactics in patients with HAE. Approximately 95% of these patients improve with androgen therapy, but only about one-fourth become symptom free. Danazol is the most effective and readily available of the androgens and is therefore the drug most commonly used. Stanozolol is an alternative but must be specially compounded. In addition, because of its strength as an anabolic agent, it has been abused by athletes and as a result is considered illegal in competitive sports. Oxandrolone has minimal virilizing effects; although it is less effective than danazol, it is often chosen when androgens are used in pediatric patients.

Long-term androgen use is associated with significant side effects, such as menstrual irregularities, myalgias, and weight gain that may result in self-discontinuation of therapy in as many as 25% of patients. In addition, long-term androgen therapy has several negative consequences, such as hypertension, hyperlipidemia, accelerated atherosclerosis, and increased thromboembolic risk. Hepatotoxicity and liver neoplasms also have been reported, and because androgens are metabolized in the liver, they are not recommended in patients with preexisting liver disease. Androgens also exhibit multiple interactions with other drugs, including potentiating the effects of anticoagulants and decreasing insulin requirements.
It is advised that all patients on long-term androgen therapy be monitored with liver function tests, complete blood count, lipid profile, and urinalysis every 6 months. An annual liver-spleen ultrasound also is recommended. For patients receiving daily doses of more than 200 mg of danazol and those of prepubescent age, liver-spleen ultrasound is advised every 6 months along with annual measurement of α-fetoprotein levels.6,9,10

Although less reliable than androgens, antifibrinolytics have been used since the 1970s on an off-label basis, especially in patients with contraindications or intolerance to androgens.1 Both EACA and TA are available as oral preparations. The typical oral dose of EACA is 6 to 12 g per day given in 3 or 4 divided doses. The recommended oral dose of TA is 20 to 50 mg/kg per day split into 2 or 3 doses.2,6,10

Antifibrinolytics should be used with caution in patients with a history of thromboembolic disease and are not advised in patients with preexisting glaucoma. Side effects include myalgias, fatigue, hypotension, and visual disturbances.10 Since the advent of newer drug therapies, antifibrinolytics are used infrequently today.

Clinical trials in which C1-INH concentrate was used in long-term prophylaxis found that most patients experienced at least a 50% reduction in attack rates compared with placebo therapy.14 Home self-infusion programs in which patients learn to self-administer drug at the first sign of an attack have been successful. If episodic treatment fails, a standing dose of 1,000 U administered every 3 to 7 days is advised.1,14 As expected, the cost of prophylaxis with C1-INH concentrate is far higher than that of androgens (approximately $150,000 vs approximately $1,000 per year).9 To date, only the human plasma–derived C1-INH product is approved for HAE prophylaxis.

Emerging Therapeutic Options

Several clinical trials are under way investigating new agents for treating HAE and are destined to change the management paradigm of these patients.

Icatibant is a competitive synthetic bradykinin β2-receptor antagonist that mitigates the effect of excess bradykinin released during HAE attacks.1,10,11 Overall, the drug is well tolerated; in 2 Phase II trials, approximately 90% of patients required a single dose to achieve symptomatic relief. Hypersensitivity reactions have not been reported, even in patients who have been subjected to multiple exposures of the drug. In 2008, icatibant was approved in Europe for treatment of acute attacks of HAE, and received FDA approval in August 2011 for use in the United States.5,9,11

More recently, a recombinant human C1-INH derived from rabbit milk (rh-C1-INH) has been formulated. Phase II and III trials supported the drug’s efficacy and safety at doses of 50 U/kg and 100 U/kg IV.9,10,11 The European Union recently approved its use for acute treatment; it is currently under FDA review in the United States. The half-life of recombinant C1-INH is shorter than that of the plasma-derived protein; therefore, it is expected to be more useful in the treatment of acute attacks than as prophylaxis. The only definite contraindication is in patients with a clear history of rabbit allergy.11 The benefits of rh-C1-INH include eliminating the risk for bloodborne pathogen transmission and controlling drug production.
Management of the Case Presented

IV access was established in the patient. Hydrocortisone 100 mg IV, diphenhydramine 12.5 mg IV, and nebulized albuterol were administered to her on the presumptive diagnosis of anaphylaxis—although the girl’s parents reported no recent ingestions of new foods or medications and no environmental exposures to potential allergens. After 20 minutes without therapeutic response, the patient began to exhibit inspiratory stridor. The emergency department physician paged the on-call anesthesiology team based on a concern about impending airway compromise.

The decision was made to transport the patient to the operating room for urgent intubation in a controlled setting with an otolaryngologist available to establish a surgical airway if endotracheal intubation was unsuccessful. Midazolam 1 mg was administered IV, and standard monitors were applied. Inhalational induction with sevoflurane was performed, maintaining spontaneous ventilation. Fiber-optic laryngoscopy revealed significant swelling of the pharyngeal tissue and a severely narrowed glottic opening; however, a 7.0-mm endotracheal tube was successfully placed under direct visualization.

Meanwhile, an immunologist was consulted who suggested the possible diagnosis of HAE, although there was no family history of the disorder. Blood was drawn and sent for measurement of C4, C1-INH, and C1q. The immunology laboratory informed the primary team that these specialty tests were performed at an outside facility, and results would not be known for at least 2 to 3 business days. Consequently, the pharmacy was solicited to help procure C1-INH concentrate on an emergency basis, because this medication was nonformulary and would have to be obtained from the hospital’s distributor or the drug manufacturer.

Within 18 hours, C1-INH was located and delivered to the hospital, and the patient was treated with an IV dose of 20 U/kg. After 40 minutes, significant improvement in facial and oropharyngeal edema was evident. Within 2 hours, the patient’s symptoms had almost completely resolved. Her trachea was electively extubated while an anesthesiologist and otolaryngologist were at the bedside. The patient exhibited no signs of respiratory distress after extubation.

The laboratory tests ultimately revealed a quantitative deficiency in C1-INH and normal levels of C1q. The diagnosis of type I HAE was established. The family was counseled about the diagnosis and referred to a pediatric allergist for outpatient consultation. The patient was discharged home and had no negative sequelae from the incident.

Dr. Elizabeth A.M. Frost, who is the editor of this continuing medical education series, is clinical professor of anesthesiology at The Mount Sinai School of Medicine in New York City. She is the author of Clinical Anesthesia in Neurosurgery (Butterworth-Heinemann, Boston) and numerous articles. Dr. Frost is past president of the Anesthesia History Association and former editor of the journal of the New York State Society of Anesthesiologists, Sphere. She is also editor of the book series based on this CME program, Preanesthetic Assessment, Volumes 1 through 3 (Birkhäuser, Boston) and 4 through 6 (McMahon Publishing, New York City).
REFERENCES


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**Post-test**

1. Edema formation in patients with hereditary angioedema (HAE) is mediated primarily by:
   a. bradykinin
   b. histamine
   c. kallikrein
   d. plasmin

2. Low levels of which complement protein are often used as a screening test for HAE?
   a. C1
   b. C2
   c. C3
   d. C4

3. Which drugs are of most benefit in the treatment of acute HAE attacks?
   a. α-Adrenergic antagonists
   b. Bradykinin-receptor antagonists
   c. Histamine-receptor antagonists
   d. Plasmin inhibitors

4. A common side effect of androgen therapy that leads to patient self-discontinuation is:
   a. nausea
   b. hypotension
   c. rash
   d. weight gain

5. The preferred therapy for prophylaxis against HAE attacks during pregnancy is:
   a. androgens
   b. antifibrinolytics
   c. C1-inhibitor (INH) concentrate
   d. fresh frozen plasma
6. **Transmission of HAE occurs primarily via which genetic pattern?**
   a. Autosomal dominant
   b. Autosomal recessive
   c. X-linked recessive
   d. Spontaneous mutation

7. **Which of the following laboratory findings best support the diagnosis of type I HAE?**
   a. Low C4 and low C1-INH
   b. Low C4 and normal C1-INH
   c. Low C4 and low C1q
   d. High C4 and low C1-INH

8. **Cases of HAE in which C1-INH level and function are normal are often found to be caused by a defect in which serum protein?**
   a. Factor II
   b. Factor X
   c. Factor XII
   d. Kallikrein

9. **One of the presumed mechanisms of action responsible for the effectiveness of androgens as a long-term prophylactic against HAE attacks is:**
   a. bradykinin receptor blockade
   b. increased C1-INH synthesis
   c. kallikrein inhibition
   d. reduced plasminogen activation

10. **Ecallantide is FDA-approved for which HAE indications?**
    a. Treatment of acute attacks
    b. Short-term prophylaxis
    c. Long-term prophylaxis
    d. All of the above