Recognition, Evaluation, and Management of Pediatric Hereditary Angioedema

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Abstract: Hereditary angioedema (HAE) is a rare, often underrecognized genetic disorder caused by either a C1 esterase inhibitor deficiency (type 1) or mutation (type 2). This leads to overproduction of bradykinin resulting in vasodilation, vascular leakage, and transient nonpitting angioedema occurring most frequently in the face, neck, upper airway, abdomen, and/or extremities. Involvement of the tongue and laryngopharynx has been associated with asphyxiation and death. Hereditary angioedema is an autosomal-dominant condition; therefore, there is a 50% chance an offspring will inherit this disorder. Any patient presenting with isolated angioedema should be screened with a C4 measurement, as 25% of cases have no family history of HAE. All patients with HAE will have a functional deficiency of C1 esterase inhibitor. Contributors that delay the diagnosis of HAE include recognition delay by clinicians who confuse this condition with histaminergic angioedema, the disease’s varied presentations, and limitations to timely testing. Pediatric emergency clinicians should be knowledgeable about how to distinguish between bradykinin- and histamine-mediated angioedema, as there are significant differences in the diagnostic testing, treatment, and clinical response between these 2 different conditions. Evidence indicates that early diagnosis and treatment of HAE reduces morbidity and mortality. Clinician recognition of the mechanistically different problems will ensure patients are appropriately referred to an expert for outpatient management.

Key Words: hereditary angioedema, HAE, angioedema, bradykinin, C1 esterase

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TARGET AUDIENCE

This CME review is intended for pediatricians, family medicine physicians, emergency medicine physicians, pediatric emergency medicine physicians, pediatric hospitalists, nurse practitioners, physician assistants, emergency medical services personnel, and other health care workers who care for children and adolescents primarily in the prehospital, office, urgent care, or emergency department setting.

LEARNING OBJECTIVES

After completion of this article, the reader should be better able to:

1. Describe the pathophysiologic differences between various causes of angioedema.
2. Identify, evaluate, and manage acute complications of hereditary angioedema (HAE).
3. Explain the natural history, precipitating events, and chronic management of HAE, including short-term and long-term prophylactic treatments.

BACKGROUND

Hereditary angioedema (HAE) is a rare, often underrecognized genetic disorder caused by either a C1 esterase inhibitor (C1-INH) deficiency (type 1) or mutation (type 2). This leads to overproduction of bradykinin resulting in vasodilation, vascular leakage, and transient nonpitting angioedema occurring most frequently in the face, neck, upper airway, abdomen, and/or extremities.1,2 Involve ment of the tongue and laryngopharynx has been associated with asphyxiation and death.2,3,4

Type 1 HAE is an autosomal-dominant condition; therefore, there is a 50% chance an offspring will inherit this disorder.4 Any patient presenting with isolated angioedema should be screened with a C4 serum measure because 25% of HAE cases have no family history. All patients with HAE will have a functional deficiency of C1-INH. Patients with type 1 HAE will also have a decrease in quantitative C1-INH, whereas patients with type 2 HAE have a normal or increased quantitative C1-INH level.4 Type 1 and Type 2 HAEs are also collectively referred to as HAE-C1-INH. A subtype of HAE with normal complement (HAE-nl-C1-INH), previously labeled type 3, has been recognized. HAE-nl-C1-INH is associated with Factor XII missense mutations. Mutations in plasminogen, kininogenase, or angiopoietin have also been reported.5,6

PATHOPHYSIOLOGY

Acute care clinicians should be knowledgeable regarding the various pathophysiologic mechanisms by which angioedema can manifest, given that the diagnostic workup, management, and prognostic outcome differs widely based on etiology.1 Angioedema, defined as nonpitting edema of the deep dermis or submucosal or subcutaneous tissues is due to different mechanisms of action resulting in increased vascular permeability and extravasation of fluid into the interstitium.1,7–9

Acute histamine-mediated (allergic; histaminergic) angioedema is an allergen-induced, IgE-mediated (type I hypersensitivity reaction) form of angioedema secondary to mast cell degranulation, associated with urticarial wheal-and-flare lesions (ie, hives) in 40% of cases. It involves the mid- and papillary dermis and in some cases can progress to anaphylaxis.9 Approximately 20% of patients with histaminergic angioedema present with isolated angioedema without...
hives. Common precipitating allergens include foods, medications, pollen, dander, and insect stings.

**Bradykinin-mediated angioedema** results from activation of the contact activation system, which is a complex cascade regulated by C1-INH with substrates including Factor XII, high-molecular-weight kininogen, prekallikrein, and kallikrein. Absence of C1-INH results in an increased production of bradykinin, which binds to vascular bradykinin B2 receptors, precipitating vasodilation, and extravasation of fluid causing interstitial edema. The bradykinin-mediated angioedema types include HAE, angiotensin-converting enzyme inhibitor (ACEi)-induced angioedema, and acquired angioedema, the latter 2 of which are exceedingly rare in children and adolescents and will not be discussed in this review.

In addition to histaminergic angioedema and bradykinin-mediated angioedema, non–histamine-/non–bradykinin-mediated angioedema types have been described. These include idiopathic angioedema and pseudoallergic angioedema (including nonsteroidal anti-inflammatory drug–induced), which are relatively rare in children and adolescents and will not be discussed in this review.

**EPIDEMIOLOGY**

Children and adolescents are affected primarily by type 1 and type 2 HAES, with HAE type I accounting for ~85% of cases and HAE type II accounting for the remaining ~15%. The prevalence of HAE is estimated to affect 1:30,000 to 1:50,000 individuals. In a large case series, the mean ± SD age of symptom onset was 11.2 ± 7.7 years; approximately 50% experienced the onset of symptoms in the first decade of life, ~37% in the second decade, and the final ~11% sometime thereafter. There is equal predilection for males and females (Table 1).

Pediatric patients diagnosed with HAE C1-INH often manifest symptomatic attacks requiring acute treatment from puberty down to as early as 6 months of age. Diagnosis is frequently delayed because many patients receive repeated treatment of histaminergic angioedema. Earlier onset of symptoms correlates with delays in diagnosis and may predict a more severe disease phenotype.

**CLINICAL CASES**

**Case 1**

A 19-month-old girl presented with swelling of her hands and feet and abdominal rash that appeared like “ringworm” to her father after amoxicillin treatment for acute otitis media. Her examination was notable for being well-appearing with normal vital signs and few scattered erythematous blanching macules with central clearing on her abdomen, legs, and inguinal region with swelling of hands and feet bilaterally. A diagnosis of serum sickness-like reaction was made. She returned to the emergency department (ED) 1 year later with left-hand swelling, and again 3 months later with a similar rash associated with left hand and ankle swelling without fever. Swelling with each presentation resolved in 1 to 3 days. A referral to rheumatology was made, at which time it was noted that similar episodes occurred 3 to 4 times a year, usually with mild viral-type illnesses. The differential at that time included drug/viral-induced erythema multiforme minor, serum sickness-like reaction and less likely periodic fever syndrome, urticaria vasculitis.

**TABLE 1. HAE Pediatric Cohort Epidemiologic Factors and Clinical Characteristics**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Farkas et al</th>
<th>Nanda et al</th>
<th>Bennett and Craig</th>
<th>Aabom et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>50</td>
<td>21</td>
<td>25</td>
<td>22 (14*)</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>54</td>
<td>29</td>
<td>52</td>
<td>36</td>
</tr>
<tr>
<td>Race, % White</td>
<td>NR</td>
<td>95</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Family history of HAE, %</td>
<td>84</td>
<td>86</td>
<td>84</td>
<td>NR</td>
</tr>
<tr>
<td>Age of symptom onset, median (IQR), y</td>
<td>5 (2.8–10)</td>
<td>5.7 (5–9)</td>
<td>7.7 (NR)</td>
<td>4 (1–11)</td>
</tr>
<tr>
<td>Age of diagnosis, median (IQR), y</td>
<td>8 (4.5–11.5)</td>
<td>5.0 (4–8)</td>
<td>7.2 (NR)</td>
<td>3.4 (1.7–5.7)</td>
</tr>
<tr>
<td>With fam Hx</td>
<td>NR</td>
<td>5.0 (2.0–7.5)</td>
<td>7.2† (NR)</td>
<td>NR</td>
</tr>
<tr>
<td>Without fam Hx</td>
<td>NR</td>
<td>10.0 (5–16)</td>
<td>9.5† (NR)</td>
<td>NR</td>
</tr>
<tr>
<td>HAE type, %</td>
<td>Type I (90%)</td>
<td>NR</td>
<td>Type I (100%)</td>
<td>Type I (86%)</td>
</tr>
<tr>
<td>Presenting complaint at diagnosis, n/N (%)</td>
<td>NR</td>
<td>14/25 (56)</td>
<td>8/14 (57)</td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>NR</td>
<td>NR</td>
<td>14/25 (32)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Abdominal pain/edema</td>
<td>NR</td>
<td>NR</td>
<td>9/25 (35)</td>
<td>6/14 (43)</td>
</tr>
<tr>
<td>Genitourinary edema</td>
<td>NR</td>
<td>NR</td>
<td>1/25 (4)</td>
<td>NR</td>
</tr>
<tr>
<td>None (presymptomatic)</td>
<td>NR</td>
<td>5/21 (24)</td>
<td>3/25 (12)</td>
<td>8/14 (36)</td>
</tr>
</tbody>
</table>

Adapted from Pattanaik and Leiberman. *Only 14 of 22 patients had symptoms at/before the time of diagnosis. †Reported as mean. ‡Reports varied from the location of total cohort attacks during study period (Farkas et al) to lifetime attacks (Nanda et al) to individual history of personal attack experiences ever (Aabom et al).

NR indicates not reported; HAE, hereditary angioedema; No, number; IQR, interquartile range; Hx, history.
and juvenile idiopathic arthritis. Care was established at age 3 years with allergy. During her fourth year of life, symptom frequency and severity worsened, presenting as monthly episodes of fever and associated swelling of the extremities and face—periodic fever syndromes were suspected. A serum C4 was obtained and was decreased at <5.5 mg/dL (normal range, 11.8–39.0 mg/dL). C3 was normal. Low serum C1-INH quantitative (4.8 mg/dL; normal range, 21.0–39.0 mg/dL) and serum C1-INH functional percent (37%; normal value, >67%) were subsequently obtained, establishing the diagnosis of type I HAE. The previous associated rash was retrospectively believed to have been erythema marginatum, which is a prodromal rash seen before HAE attacks in a large percentage of patients. She was started on plasma-derived C1-INH (Berinert, King of Prussia, Penn) as an on-demand therapy for acute attacks. Both parents were tested for HAE and showed normal results. Because there was no family history of HAE noted, it was believed that this case represented a de novo mutation.

**Case 2**

A 16-year-old boy with a known diagnosis of type I HAE presents with allergy during follow-up. Family history was notable for the father and multiple relatives having type I HAE. At 5 years of age, he began experiencing symptoms of intermittent hand, feet, and genitalia swelling; abdominal pain and vomiting; and a lacy reticular rash. His attacks occurred 4 to 5 times a year. The attacks were triggered by minor physical trauma, and he responded well to plasma-derived C1-INH (Berinert). At age 10 years, he was enrolled in a trial for on-demand icatibant, a bradykinin-2 receptor antagonist therapy. At age 12 years, his facial swelling attacks increased in frequency with 6 episodes in 2 months triggered by trauma, stress, and weather changes (20°F–30°F swings in either direction). Each attack had prodromal rash of 24 hours consistent with erythema marginatum. His treatment was changed to the on-demand kallikrein inhibitor, ecallantine. His attack frequency continued to progress to monthly episodes at age 13 years, and cognitive behavior therapy to reduce stress was initiated. At age 14 years, because of the increased attack frequency and waning response to ecallantine, the patient was enrolled in a trial investigating lanadelumab (Takhzyro, Lexington, Mass), a long-acting kallikrein inhibitor administered subcutaneously every 2 weeks. By age 15 years, the patient experienced near-complete resolution of attacks irrespective of triggers like stress, weather changes, and trauma. He was eventually able to space the injections to once a month per the research protocol. He is now currently enrolled in the trial per the research protocol. He is now currently enrolled in the trial.

**Table 2. Differentiating Histaminergic from Bradykinin-Mediated Angioedema**

<table>
<thead>
<tr>
<th>Histaminergic</th>
<th>Both</th>
<th>Bradykinin-Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria</td>
<td>Swelling of lip/tongue</td>
<td>Erythema marginatum</td>
</tr>
<tr>
<td>Rapid onset</td>
<td>Pruritis</td>
<td>Subacute prograde</td>
</tr>
<tr>
<td>(minutes to hours)</td>
<td>Facial swelling</td>
<td>(hours to days)</td>
</tr>
<tr>
<td>Response to epinephrine</td>
<td>Laryngeal swelling</td>
<td>Abdominal swelling/obstruction</td>
</tr>
<tr>
<td>Hypotension/shock</td>
<td>Abdominal pain</td>
<td>Peripheral swelling</td>
</tr>
<tr>
<td>Wheeze</td>
<td>Nausea</td>
<td>Genitourinary swelling</td>
</tr>
<tr>
<td>Resolution in &lt;12–24 h</td>
<td>Vomiting</td>
<td>Resolution in several days</td>
</tr>
</tbody>
</table>

Adapted from Bernstein et al.15

**Differential Diagnosis**

Clinician suspicion of primary angioedema will help in reducing the large differential often associated with upper airway obstruction, abdominal pain syndromes, and joint or extremity pain, swelling, and rash (Table 3, Supplemental Digital Content 1, http://links.lww.com/PEC/A710).33 This is important because all 3 of those symptoms or signs may not manifest in a single episode of HAE. Differential diagnosis will vary depending on age and sex of the patient, geographic location, and presenting signs and symptoms.

**Diagnosing Testing in the ED**

In the ED, children with new-onset or recurrent angioedema or unexplained, recurrent abdominal pain should have a screening C4 level to assess for HAE. C4 is typically low during and between attacks, but normal in HAE-nl-C1-INH, ACEi-induced angioedema, and histamine-mediated anaphylaxis.1,15 A normal C4 level in a patient highly suspected to have HAE should be repeated during an attack. Tryptase has utility only in patients presenting with symptoms suggestive of anaphylaxis.15 Other diagnostic importance for clinicians to recognize the difference between bradykinin-mediated and histaminergic swelling.2

A history of recurrent episodes of angioedema or colicky abdominal pain should raise suspicion for HAE (Table 1).1,17–20 Hereditary angioedema can be varied in its initial or recurrent presentation with significant overlap of signs and symptoms with histamine-mediated angioedema and anaphylaxis (Table 2).1,15,26

Prodromal symptoms, present in 50% to 95.7% of cases, can be present hours to days before onset of an angioedema attack.31 The most common prodromal symptoms include pruritis (42%), erythema marginatum rash (42%), gastrointestinal pain/pressure (39%), and nausea (33%), and, to a lesser extent, fatigue, extremity tingling, anorexia, and myalgias.31

Clinical factors more suggestive of histaminergic urticarial/angioedema or IgE-mediated anaphylaxis, respectively, are rapid onset of hives with angioedema in minutes to hours, without or with wheezing, hypotension, nausea/vomiting, and response to antihistamines, glucocorticoids, or epinephrine, particularly with exposure to a known trigger with resolution within the first 12 to 24 hours of onset.14 In contrast, HAE attacks tend to peak at up to 12 to 24 hours from onset and may persist up to several days.15

Unlike histamine-mediated angioedema, bradykinin-mediated angioedema is not associated with urticarial lesions; however, erythema marginatum, a characteristic nonpruritic prodromal rash easily confused with hives, is common as observed in case 1.1,14,15,31

**Clinical Characteristics**

Severity and frequency of HAE attacks can vary within and between individuals on a spectrum ranging from severe weekly attacks to mild annual attacks.8,24–31 Attacks typically manifest as swelling of the face or lips, tongue, larynx, extremities, or genitalia and/or painful bowel wall edema that can lead to intestinal obstruction.15,17–20 Attacks can last several days without treatment and be incapacitating.32 Upper airway angioedema can lead to asphyxiation and death if the airway is not properly monitored and secured to prevent deterioration of ventilation. Up to 50% of patients with HAE report at least one laryngeal swelling episode in their lifetime, and a single episode of laryngeal angioedema has been reported to be fatal in children as young as 9 years.3,25

In contrast to anaphylaxis, HAE attacks do not respond to epinephrine, H1-antihistamines, or glucocorticoids, emphasizing the
testing should be dictated by the patient's clinical presentation. Consultation with an allergist with HAE expertise is recommended.

**GENERAL MANAGEMENT**

General management strategies for HAE focus on a well-designed rescue plan for acute attacks with early recognition and on-demand rescue treatment. There should be a patient-specific prevention plan with attention to patient education, trigger avoidance, and care coordination, which should include patient and family preferences for both short-term and long-term prophylactic treatments. Emergency department pharmacies should keep at least one on-demand therapy like icatibant or C1-INH replacement therapy on formulary for emergent treatment of an HAE attack.

Effective, targeted therapies developed over the past 2 decades have reduced morbidity and mortality for patients with HAE. Antifibrinolytic therapies (tranexamic acid and ε-aminocaproic acid) and androgens were historically used for prophylaxis, but have been replaced with safer and more effective therapies.14

**On-Demand Treatment for Acute Attacks**

Several Food and Drug Administration (FDA)-approved pediatric HAE therapies are now available (Table 3). Onset of treatment effect may take up to 60 minutes, and complete resolution of an attack may take several hours.1,14,36

**Short-Term Prophylaxis**

Short-term prophylaxis (STP) is indicated for well-known “stressors,” including medical, surgical, and dental procedures, given the increased potential risk of precipitating an attack. Short-term prophylaxis significantly reduces, but does not eliminate, the risk of acute attack. Plasma-derived C1-INH (Berinert) or recombinant C1-INH (Ruconest, Leiden, the Netherlands; not FDA labeled for this use) delivered intravenously 1 to 2 hours before the procedure is the preferred STP method. If these agents are not available, and the patient is not old enough for other on-demand therapies, fresh-frozen plasma can be used.1,14,40 Patients without a history of angioedema attacks induced by trauma or on prophylactic therapy that is preventing attacks may not always require short-term prophylaxis, but on-demand therapy should be readily available in case of postprocedure swelling. A second dose of on-demand therapy should also be available in the event initial STP is ineffective.14

**Long-Term Prophylaxis**

The decision to implement long-term prophylaxis (Table 3) should involve individual patient factors including severity, frequency, and location of attacks after discussion with patient and family members.14

**ED MANAGEMENT**

After assessing the severity of angioedema and ensuring airway patency, the next step is to determine if the swelling is histaminergic or nonhistaminergic in order to select the appropriate treatment pathway. When nonhistaminergic angioedema is suspected, workup should be initiated to determine if the patient has HAE. In the ED setting, this workup can be challenging because quantitative C4 is unlikely to result in the time necessary to make management decisions. Institutions may also not have HAE on-demand therapies on their formularies. Previously diagnosed patients with HAE or those with a strong family history of HAE should receive on-demand therapy as soon as possible after initiation of attack to stop progression. Rarely, a second on-demand dose may be required. In the circumstances of an acute abdominal attack requiring a second dose, it is recommended to avoid premature diagnostic closure and to assess for other causes of an acute abdomen. Recommended observation time after medication administration in the ED is between 2 to 6 hours to ensure no further progression.15

For attacks involving the upper airway, airway management is essential to prevent progression to complete airway obstruction. In general, angioedema behind the teeth (ie, lingual, posterior oropharyngeal, and laryngeal) is more likely to progress to airway obstruction than preoral angioedema. Any evidence of impending upper airway obstruction, including respiratory distress or failure, stridor, hoarseness, or drooling, should prompt the activation of institutional critical/difficult airway teams experienced in fiber optic–guided intubation and surgical airways, where available. Because supraglottic devices are unlikely to be successful, 2-hand bag-valve-mask ventilation may be required, ideally with in-line ETCO2 monitoring.15 Neuromuscular paralysis should be avoided.

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**TABLE 3. FDA-Approved Pediatric Therapies for HAE**1,15,19,34,35

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>FDA Approval Indication</th>
<th>Approved Ages</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma-derived C1-INH (protein replacement)</td>
<td>Berinert (King of Prussia, Penn)</td>
<td>Acute attacks, short-term prophylaxis</td>
<td>All ages</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Recombinant human C1-INH (protein replacement)</td>
<td>Ruconest (Leiden, the Netherlands)</td>
<td>Acute attacks</td>
<td>13 y and up</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Ecallantide (plasma-kallikrein inhibitor)</td>
<td>Kalbitor (Lexington, Mass)</td>
<td>Acute attacks</td>
<td>12 y and up</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Icatibant (bradykinin-2 receptor antagonist)</td>
<td>Firazyr (Lexington, Mass)</td>
<td>Acute attacks</td>
<td>18 y and up</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Plasma-derived C1-INH (protein replacement)</td>
<td>Cinryze (Lexington, Mass)</td>
<td>Long-term prophylaxis</td>
<td>6 y and up</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Plasma-derived C1-INH (protein replacement)</td>
<td>HAEGARDA (King of Prussia, PA)</td>
<td>Long-term prophylaxis</td>
<td>12 y and up</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Lanadelumab (monoclonal antibody inhibitor of plasma kallikrein)</td>
<td>Takhzyro (Lexington, Mass)</td>
<td>Long-term Prophylaxis</td>
<td>12 y and up</td>
<td>Subcutaneous</td>
</tr>
</tbody>
</table>

Adapted from Bennett and Craig.19

C1-INH indicates C1 esterase inhibitor.
and sedation that allows for intact neuromuscular reflexes and spontaneous ventilation is recommended. Fiber optic nasotracheal intubation is considered the criterion standard of care, but video oral tracheal laryngoscopy is an acceptable alternative.\textsuperscript{32–34} Preparation and use of experienced proceduralists is encouraged to avoid multiple intubation attempts given the risk of exacerbating airway angioedema from direct trauma. Ensure cessation of offending agents, including exogenous estrogens or ACEi therapy, as both can worsen HAE.\textsuperscript{1} Intestinal attacks may warrant rehydration therapy and pain control. If ED discharge is deemed appropriate, patients should be prescribed refills for their on-demand agent. Referral to an HAE expert is key. Admission is indicated for patients who relapse after on-demand therapy, or, when there is concern for upper airway closure, pain control is inadequate, or patients are unable to tolerate oral intake.

**OUTCOMES**

Despite recent advances, diagnostic delay for HAE worldwide remains longer than 10 years from onset of the first clinical symptoms, resulting in inappropriate, ineffective treatment medications.\textsuperscript{22} Although a lifetime diagnosis, attack frequency and severity can be well controlled with on-demand and preventative therapies. Before effective therapies, up to one-third of patients died of asphyxiation.\textsuperscript{43} Despite newer, very effective on-demand and prophylactic therapies, long-term follow-up is necessary to ensure against complications like asphyxiation and death, as previous studies reported a mean ±SD age at asphyxiation of 40.6 ± 14.3 years (range, 9–78 years).\textsuperscript{3} Mortality is overall higher in undiagnosed patients and patients with psychiatric disorders who are nonadherent with treatment recommendations, with death occurring, on average, 31 years earlier.\textsuperscript{3}

**SUMMARY**

Hereditary angioedema, a bradykinin-mediated angioedema, is an underrecognized disease that carries a significant risk of morbidity and mortality. Highly variable natural history of disease, symptom overlap with histamine-mediated angioedema, and limitations in timely referral and testing contribute to delayed diagnosis. Recent advances in pathophysiologic understanding have spurred the development of several effective on-demand and prophylactic therapies with improvement of outcomes. Emergency providers should be able to distinguish bradykinin-mediated from histaminergic angioedema, initiate appropriate diagnostic workups and on-demand therapies for acute attacks, and counsel patients and parents on expected response to therapies and outpatient monitoring. Arranging consultation with an HAE expert, which is usually an allergist and less commonly a hematologist, is critical to ensure effective outpatient management and follow-up.

**REFERENCES**


