INTRODUCTION
Hereditary angioedema (HAE) is a rare genetic disorder caused by a deficiency or impaired function of C1 esterase inhibitor (C1-INH), resulting in potentially fatal episodes of edema in the skin and submucosa. Attacks of edema in the gastrointestinal tract can cause significant pain and may mimic other acute abdominal conditions such as appendicitis. Difficulties in interpretation of current imaging technologies can lead to misdiagnoses of HAE attacks as acute appendicitis, resulting in unnecessary surgery. In the 2 cases presented, individualized action plans and access to early on-demand therapy could have prevented unnecessary surgery.

CASE STUDY 1
A 9-year-old female with diagnosed HAE and a confirmed history of peripheral attacks presented to the emergency department (ED) with a 10-hour history of emesis, anorexia, and periumbilical pain. Abdominal examination revealed severe pain in the right upper and lower quadrants with mild guarding. Initial laboratory results showed an elevated white blood cell count of 17.7 K/μL. MRI showed edema in the third portion of the duodenum and proximal jejunal loops, free fluid in the pelvis and paracolic gutters, and an enlarged appendix with associated thickening of the conal fascia (Figures 1A and B). These findings were interpreted as being consistent with appendicitis. In preparation for surgery, the patient received 1000 units of C1-INH ~1 hour prior to appendectomy. Surgical report described her appendix as slightly injected at the tip, but otherwise normal, and pathology showed no other abnormalities.

“...This clinical presentation may make HAE attacks difficult to distinguish from other causes of acute abdominal pain, including appendicitis.”

CASE STUDY 2
An 11-year-old female with a confirmed diagnosis of HAE without a history of any previous attacks presented to the ED with a 2-day history of biliary emesis, right lower quadrant abdominal pain, and diarrhea. Abdominal examination revealed diffuse tenderness with mild rebound tenderness. Laboratory tests showed an elevated white blood cell count of 12.2 K/μL. CT scan was positive for mesenteric edema, many lymph nodes, and free peritoneal fluid (Figure 1C). After 24 hours of observation, the patient received 1000 units of C1-INH in preparation for surgery and underwent diagnostic laparoscopy with appendectomy. Surgical pathology showed no evidence of appendicitis.

DISCUSSION
Gastrointestinal involvement is common in HAE, often presenting as severe, crampy abdominal pain. However, symptoms can vary significantly between attacks and patients. In one study of 153 patients with HAE, many had additional nonspecific symptoms during abdominal attacks, including nausea (87% of abdominal attacks), vomiting (73%), diarrhea (41%), dizziness (90%), and loss of consciousness (2.2%). This variation in clinical presentation may make it difficult to distinguish an acute HAE attack from other causes of abdominal pain.
Although the average age of onset for abdominal attacks in patients with HAE is 14 years old, many patients' first attack may be delayed into puberty or even late adulthood, which may cause clinicians to discount HAE as a potential diagnosis.\(^{3}\) Additionally, abdominal attacks can be the first or only symptom for some patients with HAE, preceding any peripheral or laryngeal attacks.\(^{1,2,4}\) Failure to recognize this association may result in delayed diagnosis and/or unnecessary surgeries.

While advances in technology have increased the utility of CT and MRI in diagnosing acute abdominal symptoms, typical findings of HAE may still be misinterpreted as appendicitis (Table).\(^{5-8}\) HAE attacks may be characterized by findings of bowel wall edema, thickening, and dilation, although these may regress rapidly within 24 hours.\(^{9-11}\) Ascites and free peritoneal fluid are also common and may last for several days after the initiation of an attack.\(^{11,12}\) Therefore, the utilization of imaging studies as early as possible in the acute phase of an attack would increase the likelihood of detecting HAE-specific findings.

Table. Reported Sensitivity and Specificity Values for CT and MRI Scans in the Diagnosis of Acute Appendicitis or Bowel Wall Edema

<table>
<thead>
<tr>
<th></th>
<th>Appendicitis, %</th>
<th>Bowel Wall Edema, %</th>
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</thead>
<tbody>
<tr>
<td><strong>CT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity(^2,3):</td>
<td>91-93</td>
<td>Sensitivity(^5):</td>
</tr>
<tr>
<td>Specificity(^2,3):</td>
<td>90-96</td>
<td>Specificity(^5):</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity(^4):</td>
<td>85</td>
<td>Sensitivity(^5):</td>
</tr>
<tr>
<td>Specificity(^4):</td>
<td>97</td>
<td>Specificity(^5):</td>
</tr>
</tbody>
</table>

The 2 cases presented are examples of misdiagnosed HAE attacks resulting in unnecessary surgeries that could possibly have been prevented. The World Allergy Organization (WAO) 2012 global Guidelines for the Management of Hereditary Angioedema propose 20 specific recommendations to help decrease morbidity, mortality, absenteeism, and impairment of productivity and quality of life for patients with HAE.\(^{13}\) The Guidelines specifically recommend that all patients with a confirmed diagnosis of HAE have individualized action plans and carry an identification card. Action plans detail how to recognize an attack, how to self-administer therapies, and where to seek help in the event of an attack. If patients cannot see their allergist during an acute attack, having an established action plan and identification card may help guide ED physicians in their treatment. In these 2 cases, the prior diagnosis of HAE was known to both the
patient and the ED staff. However, neither patient had an established action plan. Rescue medications were not considered in the initial management and were delayed for many hours, only to be administered in preparation for surgery.

The Guidelines also recommend that patients with HAE be prescribed and carry at least 2 doses of on-demand therapy with them at all times.13 For adults, C1-INH, ecallantide, and icatibant are suitable on-demand therapies. For children, plasma-derived C1-INH is the recommended on-demand therapy. All patients who are provided with on-demand treatment licensed for self-administration should be taught to self-administer. Self-administration early in the course of an attack may help to decrease its severity and duration along with any associated morbidity and mortality. This is an especially important first step in management, given that most EDs in the United States still do not have specific HAE therapies readily available. In these 2 cases, following the WAO Guidelines in the administration of home or self-therapy would have significantly benefited both patients. Administering therapies to patients with HAE at the first sign of abdominal pain will not only help to determine whether the pain is from an HAE attack or other etiology, but also could prevent an attack in the setting of acute illness and/or surgery. It should be emphasized that because upper airway attacks may progress and have the potential to be fatal, patients should still seek emergency care for all attacks of the face or larynx, regardless of administration of on-demand therapy at home.

CONCLUSIONS
Symptoms of gastrointestinal HAE attacks may be nonspecific and overlap with other acute abdominal conditions. Misdiagnosis of such attacks can prolong the period of pain and discomfort during an attack, and may result in unnecessary surgery. Therefore, all patients with HAE, including those with no history of attacks, should be provided with an individualized action plan and prescribed on-demand therapy for home or self-administration. Therapies such as C1-INH should be used as first-line treatments in the setting of acute abdominal pain. These simple steps can prevent significant morbidity and mortality in the event of a suspected attack.

REFERENCES
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