US HAE Association Consensus Document:
An Approach to the Diagnosis and Treatment of HAE

US HAEA Medical Advisory Board 2012

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BACKGROUND:

- HAE is a rare disease characterized by episodic unpredictable swelling that may be associated with significant morbidity and mortality.
- There are several newly approved medications to treat acute attacks and to prevent HAE attacks, necessitating that patients and physicians carefully consider a variety of approaches to HAE treatment.

GENERAL APPROACH:

HAE is characterized by substantial variability between patients with regards to severity, provoking factors, impact of co-morbid conditions, and response to treatment. Additionally, the medications available to treat HAE have very different modes of action, methods of administration, and risk to benefit profiles. Due to this variability, it is critical that physicians and patients work together to design individualized treatment plans that optimize care for each patient.

Therapeutic approaches for HAE include both on-demand treatments to stop angioedema attacks as well as prophylactic treatment to prevent attacks. For some patients, on-demand treatment alone is sufficient; for other patients, prophylactic treatment is indicated as first-line treatment together with on-demand treatment; and in other patients, prophylactic treatment may be added to existing on-demand treatment. It should be recognized that HAE severity may wax and wane over time, and that the physician needs to periodically review and potentially refine the treatment plan.

Recognizing that no single set of recommendations can cover all possible patient situations, the HAEA Medical Advisory Board (MAB) proposes general guidelines regarding the on-demand and prophylactic treatment of HAE.

GOALS OF HAE TREATMENT

1) Reduce morbidity and mortality

2) Achieve early and accurate diagnosis of affected patients

3) Restore a normal quality of life to the patient

To achieve these goals, all patients should have a defined management plan in place. The following aspects of a management plan are recommended:

- Coordination of disease management with health care providers familiar with HAE
- Treatment of HAE patients individualized based on patient-specific factors and preferences.
- Education of patients and other health care providers of potential HAE triggers and coordination in prevention of attacks under these circumstances
- Education and understanding of HAE by other medical staff caring for a patient during an attack

TREATMENT OF ATTACKS OF ANGIOEDEMA IN PATIENTS WITH HAE DUE TO C1-INH DEFICIENCY

The goal of acute treatment in HAE is to prevent morbidity and mortality from an angioedema attack. The results of Phase III randomized placebo-controlled double-blind studies regarding the safety and efficacy of 5 separate medicines for the treatment of HAE have been published (see Table). Specific and effective medicines to treat acute attacks of angioedema in HAE patients are now available to most physicians. Based on these studies, the HAEA MAB makes the following recommendations:

- All patients with HAE due to C1-INH deficiency should have access to at least one of these specific effective medicines for treatment of acute attacks "on-demand".
- Patients should have an existing management plan in place with easy access to their health care provider during an acute attack. The management plan should include either home administration (either self treatment, treatment by a family member, or treatment by a home health care provider) or pre-arranged access to a medical facility or health care provider.
- On-demand treatment of attacks may be most effective when administered early in the attack at a time when the swelling is mild. Patients who self-administer treatment should seek medical care if their response to self-treatment is ineffective.
- All attacks, irrespective of location, should be considered for treatment as soon as they are clearly recognized.
- Patients who experience symptoms of laryngeal, tongue or throat swelling should seek emergency medical care as soon as possible, even after initial self-treatment.

PROPHYLACTIC TREATMENT OF HAE DUE TO C1-INH DEFICIENCY

In addition to treating acute attacks of angioedema, patients with HAE due to C1-INH deficiency may require prophylactic treatment. The goal of prophylactic treatment is either to reduce the likelihood of swelling in a patient undergoing a stressor or procedure likely to precipitate an attack (short-term prophylaxis) or to decrease the number and severity of angioedema attacks (long-term prophylaxis). The decision on when to use prophylactic treatment cannot be made on rigid criteria but should reflect the needs of the individual patient. The HAEA MAB makes the following recommendations regarding prophylactic treatment:

- Short-term prophylaxis is indicated prior to medical, surgical, or dental procedures. Dental surgery is associated with swelling of the oral cavity that can progress and cause airway obstruction
- 17-alpha-alkylated androgens should not be used for long-term prophylaxis when the patient does not tolerate them, in patients under the age of 16, or in pregnant or breastfeeding women. Caution should be exercised if the dose exceeds the equivalent of 200 mg danazol/day as side effects are dose-related.
- Patients on a prophylactic treatment regimen must also have access to effective on-demand treatment of acute attacks
- Prophylactic medications should be used at the lowest effective dose that controls disease activity

TABLE: FDA APPROVED DRUGS FOR TREATMENT OF HAE

Name (generic, trade)	FDA Indications	Dosage	Mechanism	Anticipated Potential Side Effects
Newer Drugs				
Plasma-derived C1 INH (Cinryze; ViroPharma)	Approved for prophylaxis in Adults and Adolescents	1000 U intravenous twice/week	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	**Rare:** risk of anaphylaxis **Theoretical:** transmission of infectious agent
Plasma-derived C1 INH (Berinert, CSL Behring)	Approved for acute attacks in Adults and Adolescents	20 U per kg intravenous	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	**Rare:** risk of anaphylaxis **Theoretical:** transmission of infectious agent
DX-88 (Ecallantide, Dyax)	Approved for acute attacks in Pts ≥16 yrs age	30 mg subcutaneous	Inhibits plasma kallikrein	**Uncommon:** risk of anaphylaxis (must be administered by healthcare professional)
HOE-140 (Icatibant, Shire)	Approved for acute attacks in Pts ≥18 yrs age	30 mg subcutaneous	Bradykinin B2 receptor antagonist	**Common:** discomfort at injection site **Theoretical:** worsening of an ongoing ischemic event
Older Drugs				
Danazol (Danacrine, Sanofi-Synthelabo)	Approved for prophylaxis in Adults	200 mg/day or less	17-α-alkylated androgen, mechanism of action unknown	**Common:** weight gain, virilization, acne, altered libido, muscle pains and cramps, headaches, depression, fatigue, nausea, constipation, menstrual abnormalities, increase in liver enzymes, hypertension, and alterations in lipid profile **Uncommon:** decreased growth rate in children, masculinization of the female fetus, cholestatic jaundice, peliosis hepatis, and hepatocellular adenoma

Adapted from Zuraw, BL NEJM 2008