Hereditary angiodema: a current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema

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Background: We published the Canadian 2003 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema (HAE; C1 inhibitor [C1-INH] deficiency) in 2004.

Objective: To ensure that this consensus remains current.

Methods: In collaboration with the Canadian Network of Rare Blood Disorder Organizations, we held the second Canadian Consensus discussion with our international colleagues in Toronto, Ontario, on February 3, 2006, and reviewed its content at the Fifth C1 Inhibitor Deficiency Workshop in Budapest on June 2, 2007. Papers were presented by international investigators, and this consensus algorithm approach resulted.

Results: This consensus algorithm outlines the approach recommended for the diagnosis, therapy, and management of HAE, which was agreed on by the authors of this report. This document is only a consensus algorithm approach and continues to require validation. As such, participants agreed to make this a living 2007 algorithm, a work in progress, and to review its content at future international HAE meetings.

Conclusions: There is a paucity of double-blind, placebo-controlled trials on the treatment of HAE, making levels of evidence to support the algorithm less than optimal. Controlled trials currently under way will provide further insight into the management of HAE. As with our Canadian 2003 Consensus, this 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of HAE was formed through the meeting and agreement of patient care professionals along with patient group representatives and individual patients.

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INTRODUCTION

C1 inhibitor (C1-INH) deficiency (congenital or hereditary angioedema [HAE]) was first described by Quincke in 1882[1]; its inheritance nature was evidenced by Osler in 1888[2] and further defined as autosomal dominant by Crowder and Crowder in 1917. The protein defect was described by Donaldson in 1963.[3] An acquired form (acquired angioedema [AAE]) was described in 1972.[4] The approach to patients who

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present with angioedema without urticaria was recently presented by Zingale et al.[5] The incidence of HAE is estimated at 1:10,000 to 1:150,000, with most authors quoting 1:10,000 to 1:50,000 (with most agreeing that 1:50,000 is the closest estimate), no ethnic group differences have been reported, 25% of patients present with new mutations and no family history, and the *C1-INH* gene maps to chromosome 11q12-q13.1.[5–9] There appears to be little phenotype genotype correlation.[10] The gene for C1-INH has been expressed in recombinant systems, a knockout mouse model created, and much of the pathophysiology of HAE worked out, with the most likely candidate molecule resulting in angioedema being bradykinin.[5,8] Three variants of HAE have been described: HAE type 1, with low C1-INH antigenic protein and functional activity (85% of cases; autosomal dominant); HAE type 2, with normal or elevated protein level but low C1-INH function (15% of cases; autosomal dominant); and the recently described types of HAE (sometimes called HAE type 3 or estrogen-dependent angioedema), with normal C1-INH protein level and function occurring mainly in women, including HAE due to mutations in the coagulation factor XII gene and other defects yet to be identified.[8,11–13] AAE differs from HAE because it has an absent family history, late onset of symptoms, and different response to therapy (sometimes markedly higher doses of C1-INH required with rapid C1-INH catabolism and prophylactic response to antifibrinolytics often better than to androgens) and usually low C1q antigen levels.[5,8] AAE has been found with some B-lymphocyte disorders from monoclonal gammopathies of unknown significance to B-cell malignancies (AAE type 1) and in persons with acquired anti–C1-INH antibodies (AAE type 2).[5,8,14] Angioedema has been seen with some medication use (eg, angiotensin-converting enzyme inhibitors [ACE-Is]).[5] Patients with HAE may experience recurrent edema of subcutaneous tissues (extremities, genitals, face, trunk, or elsewhere); intestinal swellings and abdominal pains, nausea, vomiting, or diarrhea; and life-threatening swellings of the airway.[8] Risk of dying from airway obstruction if left untreated has been estimated at 30%.[10,15]

Approaches to the diagnosis, therapy, and management of HAE vary among countries, with C1-INH replacement therapy being standard in many countries but not available or with limited availability in others (licensed in Germany and Holland, available under the Special Access Program of Health Canada, not available in countries such as the United States). The Canadian Hereditary Angioedema Society (CHAES)/Société d'Angioédème Héréditaire du Canada (SAHC; www.haecanada.com) held a Canadian International Consensus Conference on HAE in Toronto, Ontario, Canada, in October 2003 and held the follow-up second Canadian Consensus Conference in conjunction with the meeting on Comprehensive Care for Rare Blood Disorders hosted by the Network of Rare Blood Disorder Organizations (NRBDO) in Toronto, Ontario, Canada, on February 3, 2006. Proceedings and the PowerPoint presentations from this conference are available on the Canadian Hemophilia Society Web site[16] (http://www.hemophilia.ca/nrbdo/en/home.php). This meeting was patterned after the European C1-INH Deficiency Workshops organized by the European C1-INH Deficiency Working Group Hungarian HAE Working Group and after the first Canadian Consensus Conference that brought together government agencies; blood product suppliers; comprehensive care treatment team members, including nurses and physicians (family physicians and specialists, including hematologists, dermatologists, allergists, immunologists, pediatricians, and internists); HAE patient group representatives; and industry sponsors.[8,16–21] The consensus was reviewed at the Fifth C1 Inhibitor Deficiency Workshop held in Budapest on May 31 through June 3, 2007.[16]

Papers for discussion at the first Canadian Consensus meeting were published in the December 2003 edition of *Transfusion and Apheresis Science,* a special issue dedicated to HAE.[18,19] The consensus was, therefore, an agreement among patients, patient groups, and treatment team members on how to approach the diagnosis, therapy, and management of HAE. That final first Canadian Consensus was reviewed by the patient groups and treatment teams listed on the authorship and was presented as a living algorithm approach[17] for the management of HAE types 1 and 2 with a comprehensive review of HAE guest edited by Henriette Farkas and published in supplement form in the same journal issue.[8] Since that time, another consensus was published by the UK Primary Immunodeficiency Association.[22] We have not attempted to include approaches to AAE or type 3 HAE but offer our updated algorithm for the diagnosis, therapy, and management of types 1 and 2 HAE. We hope that the algorithm will be validated by treatment teams and await with interest the results on ongoing phase 3 clinical trials in HAE.[16] The program and abstracts from the Fifth C1 Inhibitor Deficiency Workshop are available at www.haenet.hu.[16] We hope that this approach will be openly discussed and modified at upcoming international HAE conferences and by patient groups and treatment teams and encourage changes in the proposed approach as new evidence comes to light. Exciting investigational therapies were discussed at the 2 meetings, but the algorithm is limited to the treatments available in 2007 in most countries. This dynamic algorithm (a revision of the first 2003 Canadian Consensus published in the *Journal of Allergy and Clinical Immunology*[17] and presented herein with the minor revisions based on the February 3, 2006, Toronto Canadian Consensus Conference and the Budapest Fifth C1 Inhibitor Deficiency Workshop on June 2, 2007[16]) recognizes that there are many different and possibly equally valid approaches to management of HAE and is meant to be a recommendation for an approach that needs ongoing validation. We agree that Consensus Conferences are a poor replacement for double-blind, placebo-controlled trials. Until the results of such trials are available, consensus may provide some guidance and stimulate research that will encourage undertaking further clinical trials.[16]

PATIENT GROUP PERSPECTIVE

The HAE patient societies, including the CHAES/SAHC, have proposed establishment of comprehensive care clinics for the diagnosis, therapy, and management of HAE, including the development of home infusion and home care programs.[16,21] Similar to the presentation by Hungarian-sponsored HAE workshops in their publication,[8] we think it appropriate to share the patient perspective of HAE management to help administrators reflect on the development of comprehensive care clinics for HAE. The perspective of one Canadian patient with HAE is presented on the Canadian HAE Network Web site (http://www.haecanada.com, "Patient Perspective" section).

CLINICAL CHARACTERISTICS

HAE may present as recurrent angioedema (swelling) without urticaria (without hiving) and usually nonpruritic (without itch).[23] Sometimes there is a nonpruritic serpentine erythematous rash.[24] Distinguishing features of HAE are reviewed by Zingale et al[5] and Bork et al.[24] Swelling may affect any part of the body, including the extremities, face, trunk, gastrointestinal tract, genitourinary regions, or upper airways. Abdominal symptoms may mimic infantile colic, acute appendicitis, or other forms of acute abdomen, and symptoms may include nausea, vomiting, abdominal pains, and postattack diarrhea.[23–26] In patients with known HAE and a strong indication that the abdominal attack may be HAE related, infusion with C1-INH replacement therapy can be used to differentiate acute abdomen from an HAE attack.[26] Age of onset is variable, and patients may present at younger than 1 year with colic or rarely swelling.[27] Laryngeal attacks are uncommon before the age of 3 years and tend to occur later than other symptoms.[23,27] Attacks frequently worsen around puberty.[23,27,28] Symptoms often worsen with estrogen-containing birth control pills or hormone replacement therapy.[28,29] Untreated attacks tend to be prolonged, typically increasing during the first 24 hours and then slowly and spontaneously subsiding at more than 48 to 72 hours. However, some attacks may last longer than 72 hours as the swelling migrates from site to site. Attack triggers may include stress, minor trauma (such as dental procedures), menstruation, pregnancy, some drugs (eg, oral contraceptives, ACE-Is), or infections.[5,16,23] However, triggers are often unidentified. Attacks tend to be periodic, sometimes coming in clusters, and often followed by several weeks of remission. Attacks may not respond to treatment with epinephrine, antihistamines, or glucocorticoids.[5,16,23,30]

DIAGNOSIS

Indications for testing include clinical suspicion at any age or, if the family history is positive, test at any age. Tests may not be reliable in patients younger than 1 year (false-negative and false-positive testings may occur unless using genetic typing). Testing performed in patients before the age of 1 year should be confirmed after the age of 1 year.[31] A serpiginous rash is sometimes seen with the prodrome of HAE, but clinical urticaria (hives) usually make the diagnosis of HAE unlikely.[24] An algorithm approach to angioedema has been presented by Zingale et al.[5] Figure 1 shows the HAE diagnostic algorithm.

DIAGNOSTIC TESTING

If C1-INH deficiency is clinically suspected, we recommend screening with serum C4 and C1-INH proteins. C4 is normal between swelling events in only 2% of cases, so a normal C4 level should make one question the diagnosis of HAE. If there is a low index of suspicion, it may be more cost effective to screen with C4 alone (it is not necessary to screen with CH_{50} or C3).[32] If serum C4 and C1-INH antigenic protein levels are both low and AAE not suspected, then the diagnosis is compatible with type 1 HAE (we suggest repeating testing once to confirm). If AAE is possible (ie, no family history and later onset of symptoms, such as age older than 40 years), then serum C1q antigenic protein testing is required, and if levels are low, the diagnosis is highly compatible with AAE (C1q antigenic protein is reduced in 75% of AAE but normal in HAE). If the C4 level is normal or low and the C1-INH antigenic protein level normal but clinical suspicion is strong, HAE is NOT ruled out. We recommend obtaining a C1-INH functional assay. If the C1-INH functional activity is low with normal or elevated C1-INH antigenic protein and normal C1q levels, this finding is compatible with type 2 HAE. Testing should be repeated at least once more to confirm the diagnosis. If C4 antigenic protein and C1-INH functional assays are both normal, types 1 and 2 HAE can be ruled out. However, this does not rule out the recently described types of HAE (sometimes called type 3 HAE or estrogen-dependent angioedema), with normal C1-INH protein and function occurring mainly in women, including HAE due to mutations in the coagulation factor XII gene and other defects yet to be identified.[8,11–13,16] The same is true for ACE-I–related angioedema. If C4 and C1-INH protein levels are normal, these tests should be repeated during an acute attack (Fig 1).

Genetic testing is not necessary to confirm the diagnosis of types 1 and 2 HAE, and similar to other autosomal dominant disorders, approximately 25% of patients may represent de novo mutations.[16] However, genetic testing may be necessary to investigate type 3.[16] C1-INH functional assays vary, and we recommend standardizing the functional assays and establishing specialized laboratories capable of accurately measuring C1-INH function and establishing an international set of reference patient samples to facilitate independent quality assurance programs for laboratories claiming to test for HAE. (For example, one of our authors, E. Wagner, surveyed Canadian laboratories testing for HAE, with results of the survey summarized in http://www.haecanada.com - diagnosis section Canadian testing facilities.) Physicians are reminded that patient sample handling for complement testing must be strictly adhered to obtain reliable results (http://www.haecanada.com – diagnosis section – sample handling).

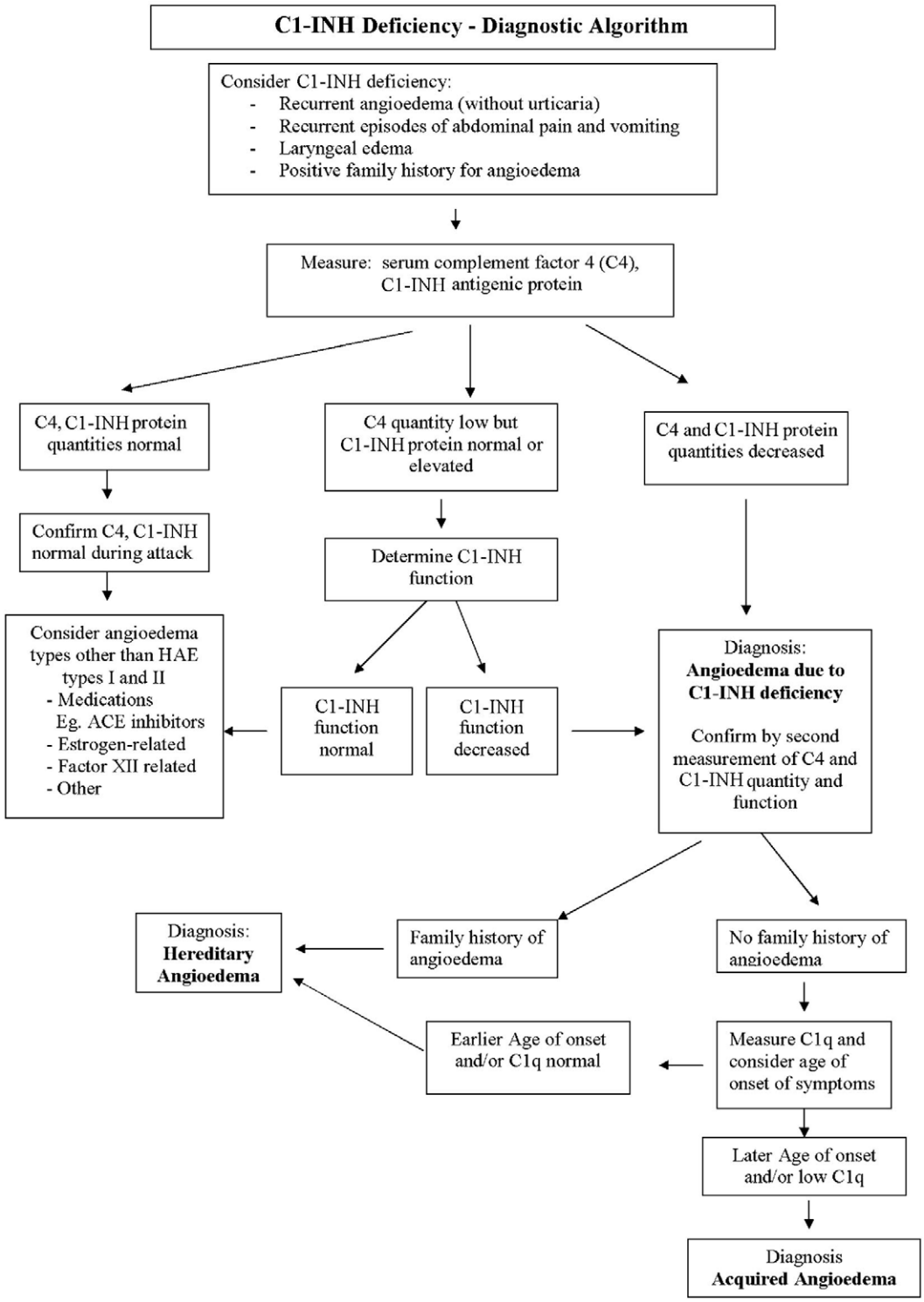

Figure 1. C1 inhibitor (C1-INH) deficiency diagnostic algorithm. This Figure is reprinted with permission from the American Academy of Allergy, Asthma and Immunology from Bowen et al.[17] HAE indicates hereditary angioedema; ACE, angiotensin-converting enzyme.

BASELINE LABORATORY TESTING AT DIAGNOSIS AT ANY AGE

Baseline bloodborne pathogen surveillance (hemovigilance) samples should be collected and stored at baseline and annually through national programs similar to the Canadian hemophilia hemovigilance program (Dr Bruce Ritchie: bruce.ritchie@ualberta.ca; http://www.ahcdc.ca/BBPSP; baseline sample storing for testing for human immunodeficiency virus; human T-cell lymphoma; hepatitis B, C, and G; and future testing for possible emerging pathogens).[16,17,22,33] C1-INH hormone replacement (C1INHRP) therapy may have to be administered at any time on an emergency basis. Therefore, hemovigilance and baseline chemical analysis and urinalysis are best performed at diagnosis. Methods of production for C1-INH replacement therapy may differ, and risk of bloodborne pathogen transmission may differ among products. CSL Behring safety data collected since 1985 on Berinert P (pasteurized C1-INH replacement material) have shown no viral transmission to date (including enveloped and nonenveloped viruses, such as hepatitis B and C and human immunodeficiency virus 1 and 2).[16,17,22,34]

Attenuated androgens and antifibrinolytics may predispose patients to atherogenesis and liver disorders.[16,17,22,35,36] Serum lipid profile should be obtained before androgen administration. Abdominal liver spleen ultrasonography can be considered before continuous androgen administration and performed every 2 years if receiving regular androgen therapy and annually if treated for more than 10 years with androgens. Liver function studies, including alanine aminotransferase, total bilirubin, alkaline phosphatase (prothrombin time, partial thromboplastin time, and albumin could be included), creatine kinase, lactic dehydrogenase, blood urea nitrogen, creatinine, complete blood cell count, and differential, and urinalysis should be performed at diagnosis.

VACCINATION RECOMMENDATIONS

It is recommended that patients who may need to receive blood products receive vaccination to hepatitis B (may be in combination with a hepatitis A vaccine such as Twinrix).

MEDICATIONS TO AVOID IN PATIENTS WITH HAE

Some medications may trigger or worsen angioedema events in patients with HAE and should be avoided, including ACEIs[5,16] and estrogen contraceptives.[8,16,28,29] Plasminogen activators are a theoretical risk, but the benefit may outweigh the risk.[37–39]

SHORT-TERM PROPHYLAXIS: MINOR MANIPULATIONS

If only mild manipulation, such as mild dental work, is required or if C1INHRP therapy is immediately available, then no prophylaxis is required. If C1INHRP therapy is not available, then danazol prophylaxis is required. Injection of local anesthetic may precipitate an attack. Figure 2 shows the HAE prophylaxis algorithm.

If considering more than mild manipulation such as dental work, danazol is recommended (even in children and in women in the last trimester of pregnancy; avoid in the first 2 trimesters of pregnancy[16,17,22,27]). The recommended dosage is 2.5 to 10 mg/kg daily, with a maximum of 600 mg/d, for 5 days before and 2 days after the event. C1INHRP therapy should be immediately available when possible.

Tranexamic acid is much less predictable for acute prevention compared with danazol but more often recommended than ε-aminocaproic acid (EACA).[8,16,17,22,27,35] Because of the safety of danazol given in the short term, we do not recommend use of tranexamic acid or EACA for short-term prophylaxis. C1INHRP therapy should be immediately available when possible.

SHORT-TERM PROPHYLAXIS: INTUBATION OR MAJOR PROCEDURES

C1INHRP therapy 1 hour before surgery (to be used if intubation is used; not available in all countries and currently not available in the United States). The recommended dosage is 500 U up to a weight of 50 kg (110 lb), 1,000 U for weight greater than 50 kg (110 lb) and less than 100 kg (220 lb), and 1,500 U if weight is greater than 100 kg (>220 lb). A second dose of an equal amount should be immediately available at time of surgery.[8,16,17,40] Repeat daily or as needed until there is no further risk of angioedema.

If C1INHRP therapy is not available, then danazol is recommended. Solvent- or detergent-treated fresh frozen plasma is another option 1 or more hours before surgery. If solvent- or detergent-treated fresh frozen plasma is not available, regular fresh frozen plasma is a less safe alternative. The dose has not been studied but is usually 2 U per adult infusion (200 mL per unit). For coagulopathies, 10 mL/kg of solvent- or detergent-treated fresh frozen plasma has been used,[41] which may be appropriate for HAE, but neither the dose nor timing before the procedure have been studied.

C1 INH prophylaxis is the safest prophylactic agent during pregnancy.

LONG-TERM PROPHYLAXIS

If a patient experiences more than 1 severe event per month or is disabled more than 5 days per month or if the patient has a history of previous airway compromise, then consider prophylaxis with tranexamic acid, androgens, or C1INHRP therapy on demand. The number of events per year does not predict severity of the next event or whether the first or next event will be an airway event.

Attenuated androgens danazol and stanozolol (stanozolol is available in the United States through pharmacies that compound the drug) are the usual agents, with methyltestosterone and oxandrolone as alternatives.[16,17,22,36] These agents may be more effective than antifibrinolytic agents.[35] Contraindications usually include pregnancy and lactation, cancer, and childhood (until finished growing). Adverse effects may in-

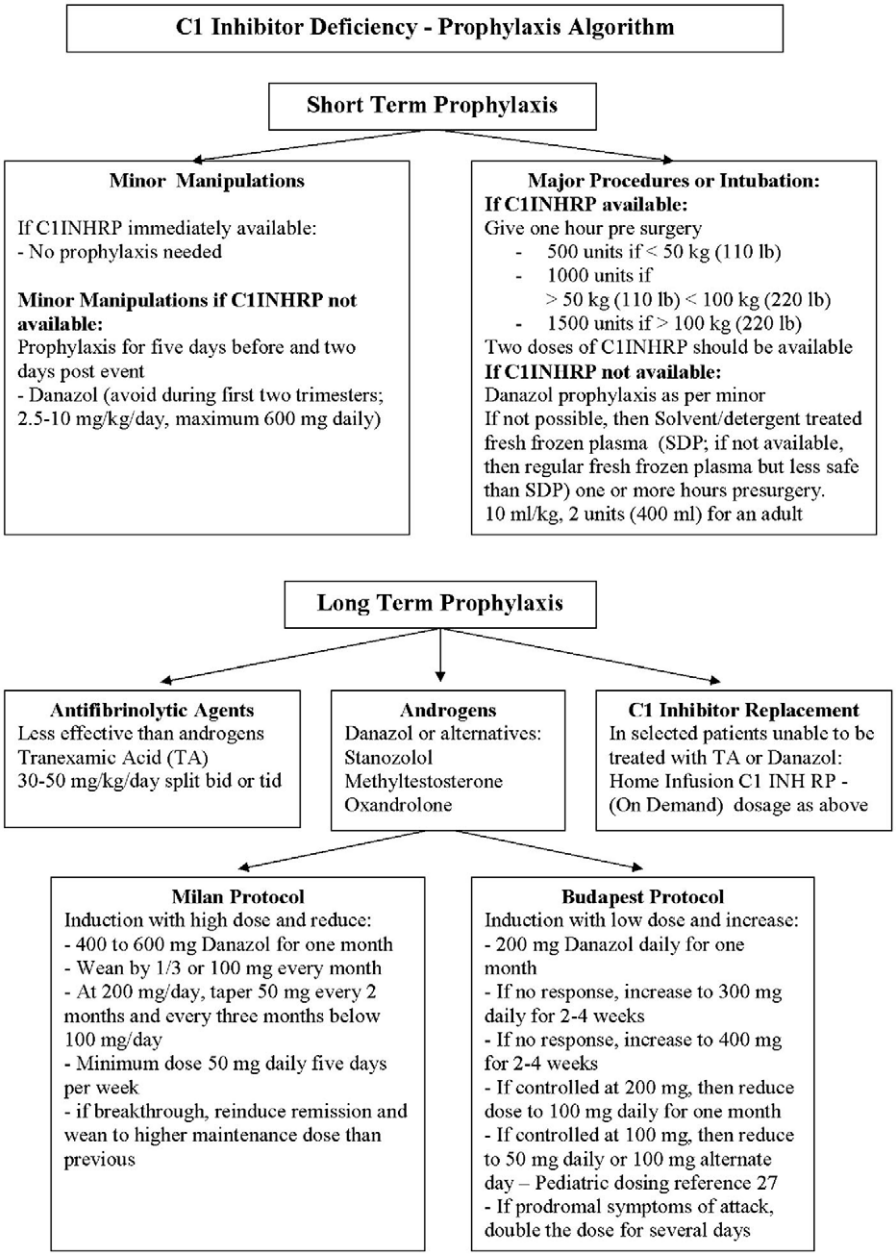

Figure 2. C1 inhibitor deficiency prophylaxis algorithm. This Figure is reprinted with permission from the American Academy of Allergy, Asthma and Immunology from Bowen et al.[17] C1INHRP indicates C1 inhibitor hormone replacement.

clude hair growth, weight gain, acne, voice deepening, vasomotor symptoms, decreased breast size, menstrual irregularities, decreased libido, hepatic necrosis or cholestasis, altered liver enzymes, liver neoplasms (hepatocellular adenomas or carcinomas), hypertension, atherogenesis with altered lipid metabolism, polycythemia, and hemorrhagic cystitis.[16,17,22,36,42–51]

According to the Milan protocol,[52] induction with high-dose danazol of 400 to 600 mg daily for 1 month should be initiated. The patient should be weaned off the drug by one-third or 100 mg every month as long as there is no breakthrough. At 200 mg/d, slow the tapering with reductions of 50 mg every 2 months, and every 3 months, the dose should be less than 100 mg/d. The usual minimum dose is 50 mg/d 5 days per week. If breaking through with more than 6 attacks per year, then increase the dose to reinduce remission and then wean again to a higher dose than previous.

According to the Budapest protocol,[27,53] induction with low-dose danazol of 2.5 mg/kg daily up to 200 mg daily for 1 month should be initiated. If no response, then increase the dose to 300 mg/d for 2 weeks to 1 month (maximum of 200 mg for children[27]). If no response, then increase to 400 mg daily for 2 weeks to 1 month. If controlled at 200 mg, then reduce the dose to 100 mg/d for 1 month. If still controlled, then reduce to 50 mg/d or try 100 mg on alternate days. Androgen therapy is not recommended for children but has been used in the prepubertal setting.[27,53] If the sensation of prodromal attack symptoms or mild clinical manifestations develop or if patients are exposed to a precipitating factor (eg, upper airway infection), the dose should be doubled for several days.

To monitor androgen levels, every 6 months a complete blood cell count, measurement of liver enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), lipid profile, and urinalysis should be performed. For adults with a dose of 200 mg/d or less of androgens, suggest annual liver spleen ultrasonography. In adults with doses higher than 200 mg/d or in prepubertal patients, suggest 6 months of liver spleen ultrasonography for the detection of focal lesions.

Tranexamic acid (not available in the United States) has mostly replaced EACA.[35] Tranexamic acid may not be as effective as androgen therapy in HAE[54] but may be useful in AAE.[14] Tranexamic acid is mostly used when prophylaxis is indicated before Tanner V puberty stage. Adverse effects may include myalgia, elevated serum creatine phosphokinase or aldolase level, rhabdomyolysis, muscle weakness, hypotension, and fatigue.[35,55–63] The tranexamic acid dosage recommended is 30 to 50 mg/kg daily (split 2 to 3 times daily).[8,16,17,22,27,35,53]

Patients should be allowed to keep a supply of C1INHRP for personal use at home or with travel, to be either self-administered or infused by a caregiver or at a medical facility. To facilitate early infusion for acute HAE events and to facilitate prophylaxis therapy where indicated, home C1INHRP self-infusion programs should be offered to patients[8,16,17,22,27,64,65] (created similarly to hemophilia self-infusion programs, which have existed for 35 years[64]). An example of home infusion technique can be viewed at http://www.haecanada.com, home infusion section.

C1INHRP should be administered at 500 U up to a weight of 50 kg (110 lb), 1,000 U for a weight of more than 50 kg (110 lb) to less than 100 kg (220 lb), and 1,500 U if weight is more than 100 kg (>220 lb).

C1INHRP should be reconstituted and warmed to body temperature before infusion. If a severe event, do not wait to warm the product before administration. DO NOT SHAKE because this will denature the protein. Administration should be via a peripheral vein for more than 10 minutes. Epinephrine is not routinely recommended to have on hand for home C1INHRP administration (systemic reactions uncommon[34]).

Patients are encouraged to carry "alert" identification (such as a wallet card, an example of which is available for downloading from http://www.haecanada.com, wallet card section) and an accompanying letter indicating C1-INH deficiency and outlining instructions for administration of the C1INHRP. HAE organization Web sites should provide infusion instructions for downloading by patients and comprehensive care clinics. Home self-infusion protocols should be available on the patient Web sites (example: http://www.haecanada.com, self infusion section).

If significant angioedema attacks are frequent despite androgen or tranexamic acid prophylaxis and C1INHRP on demand is given more than once per 10 days, then C1-INH prophylaxis at the previously mentioned dosage given every 5 to 7 days (sometimes more frequently for short periods) can be considered.[8,16,17,22]

C1-INH prophylaxis is the safest prophylactic agent during pregnancy.

TREATMENT OF ACUTE HAE ATTACKS

The first-line therapy for treatment of any significant angioedema event is C1INHRP (C1INHRP administered at 500 U up to a weight of 50 kg, 1,000 U for a weight of more than 50 kg to less than 100 kg (220 lb), and 1,500 U if weight is more than 100 kg).[8,16,17,22,27,66]

If C1INHRP is not available, other therapies may include increasing (usually doubling) the androgen (danazol or stanozolol) dose, tranexamic acid (Table 1), early use of adrenaline (if other therapy is not available but treating physicians should be prepared that it may have no benefit[30]), pain management, intravenous fluids, and supportive care. Use of fresh frozen plasma (solvent detergent preferred) could theoretically worsen attacks and remains controversial.[67]

BLOOD PRODUCT RISKS

Blood product infusion risks are reviewed annually by the Canadian Pediatric Society, Infectious Diseases and Immunization Committee,[68] and the safety profile for pasteurized C1INHRP has been previously presented.[34] We recommend patients receiving blood products should undergo annual hemosurveillance similar to the Canadian Hemophilia Program (Dr Bruce Ritchie, bruce.ritchie@ualberta.ca).[33] To date, bloodborne pathogen transmission with pasteurized C1INHRP has not been reported.[16,22,34]

COMPREHENSIVE CARE CLINICS

We recommend that a comprehensive care clinic programs be established for the diagnosis, therapy, and management of HAE similar to the model for comprehensive care of hemophilia in Canada.[8,16,17,19,22,21,27,64] A suggested CHAES/SAHC clinic model for HAE is included in http://www.hemophilia.ca/nrbdo/en/home.php, conference proceedings and conference recommendations,[16,18,19,21] and is outlined in Table 2.

DATABASE REGISTRY FOR HAE

We recommend comprehensive care clinics be encouraged to register HAE patients in national and international database registries to facilitate progress in management of this

Table 1. Treatment of Acute Hereditary Angioedema Attacks[a]

Treatment	Cutaneous swellings		Abdominal attack	Laryngeal attack
	Other than face or neck	Face or neck		
Wait and see (spontaneous resolution)	+	−	−	−
Tranexamic acid[b]	+	+	+	−
C1INHRP concentrate[b]	+/−	+	+	+
ICU (intubation,[c] tracheotomy)	−	−	−	+

Abbreviations: C1INHRP, C1 inhibitor hormone replacement; ICU, intensive care unit.
Symbols: minus sign, negative; plus sign, positive.
[a] Table modified and reprinted with permission from the American Academy of Allergy, Asthma and Immunology from Bowen et al.[17]
[b] Tranexamic acid (oral or intravenous), 15 mg/kg every 4 hours, or C1INHRP concentrate (intravenous), 500 U for those who weigh less than 50 kg, 1,000 U for those who weigh 50 to 100 kg, and 1,500 U for those who weigh more than 100 kg.
[c] Consider intubation early in progressive laryngeal edema.

Table 2. Goals of Comprehensive Care Clinics for Hereditary Angioedema[a]

1. Psychosocial support for patients, their families, and clinic staff.
2. Education regarding responsible self/family care (home care model) and provide home and self-infusion instruction and support, including self-infusion training and guidelines to ensure patient safety and emergency services assistance.
3. An environment conducive to research and clinical trials for improved patient care and outcome.
4. Standards of care and treatment protocols and assess outcome measures and monitoring including quality of life assessments, therapy monitoring including infusion log tracking (to record lot numbers and infusion details for C1 inhibitor product used by each patient), treatment side effect monitoring programs, attack trigger monitoring.
5. Patient information systems: interclinic networking to facilitate product recalls (such as the Patient Notification System), collect data on outcome measures of various therapies and to facilitate participation in clinical trials and encourage participation in provincial/territorial, national, and international data base registries.
6. 24-Hour support and information line for patients and physicians in communities across Canada.
7. Informative wallet cards and letters, including care plans to be carried by all patients and encourage carrying alert materials (such as MedicAlert).
8. Clinical audit with respect to outcome measures.
9. Hemovigilance hemosurveillance protocols.
10. Access to specialized diagnostic facilities.
11. Counseling regarding the risk benefit of therapies including the risks of blood products.
12. A team of specialists, including immunologists/allergists, hematologists, gastroenterologists, genetic counseling, endocrinologists, obstetrics/gynecology, pain management specialists, social workers, nurses, occupational and vocational guidance counselors, emergency physicians, internists, and pediatricians.
13. Decentralization of care through outreach.
14. An advisory or oversight board with patient group representation for each clinic.

[a] Modified by permission from www.haecanada.com, comprehensive care clinics section.

disorder. The European HAE network PREHAEAT chaired by Marco Cicardi established a European HAE Register (www.haeregister.org) and invited international collaboration in this and the International Hereditary Angioedema group (http://www.haei.org/) to facilitate advancement in HAE management. Countries are encouraged to fund database registry for HAE and fund participation in international collaborative efforts, including the HAEI database registry and other international collaborative efforts (similar need for the patients with rare blood disorders, including hemophilia, HAE, and hemoglobinopathies, including sickle cell and thalassemia; discussed at the NRBDO conference of February 3 to 5, 2006, in Toronto and at the Fifth C1 Inhibitor Deficiency Workshop).[8,16,19,21] These database registries share common issues of privacy, confidentiality, and ownership of data and therefore benefit by sharing clinics or at least the clinic models. Similar to the Canadian hemophilia program, patients own their own data. Consent to share their anonymous data is encouraged and in the HAEI registry is required. Clinicians who contribute to the registries will have access to their own data as individual or group reports.[8,9,16,21]

EMERGING THERAPIES

Double-blind, placebo-controlled clinical trials are under way, including human blood product C1-INH products, kallikrein inhibitor, bradykinin β_2-receptor inhibitor, and recombinant C1-INH. Results of these trials should be available in the near future and should provide expanded options for therapy (http://www.hemophilia.ca/nrbdo/en/home.php, conference presentations; Fifth C1 Inhibitor Deficiency Workshop).[16]

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