

Canadian 2003 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema

Tom Bowen, MD, FRCPC,^a Marco Cicardi, MD (on behalf of PREHAET),^{b*} Henriette Farkas, MD PhD,^c Konrad Bork, MD,^d Wolfhart Kreuz, MD,^e Lorenza Zingale, MD,^b Lilian Varga, PhD,^c Inmaculada Martinez-Saguer, MD,^e Emel Aygören-Pürsün, MD,^e Karen Binkley, MD FRCPC,^f Bruce Zuraw, MD,^g Alvin Davis, III, MD,^h Jacques Hebert, MD, FRCPC,ⁱ Bruce Ritchie, MD, FRCPC,^j Jeanne Burnham,^k Anthony Castaldo,^l Alejandra Menendez,^m Istvan Nagy,ⁿ George Harmat, MD, PhD,^{ee} Christoph Bucher, MD,^o Gina Lacuesta, MD, FRCPC,^p Andrew Issekutz, MD, FRCPC,^q Richard Warrington, MB, PhD, FRCPC,^r William Yang, MD, FRCPC,^s John Dean, MBBS, FRCPC,^t Amin Kanani, MD, FRCPC,^u Donald Stark, MD, FRCPC,^v Christine McCusker, MD, FRCPC,^w Eric Wagner, PhD,^w Georges-Etienne Rivard, MD, FRCPC,^w Eric Leith, MD, FRCPC,^x Ellie Tsai, MD, FRCPC,^y Michael MacSween, MD, FRCPC,^p John Lyanga, MD, FRCPC,^z Bazir Serushago, MD, FRCPC,^{aa} Art Leznoff, MD, FRCPC,^{bb} Susan Wasserman, MD, FRCPC,^{cc} and Jean de Serres, MD^{dd} *Calgary, Edmonton, and Claresholm, Alberta, Canada, Milan, Italy, Budapest, Hungary, Mainz and Frankfurt, Germany, Toronto, Ottawa, Oakville, Kingston, Windsor, and Hamilton, Ontario, Canada, La Jolla, Calif, Boston, Mass, Quebec City and Montreal, Quebec, Canada, Annandale, Va, Buenos Aires, Argentina, Zurich, Switzerland, Halifax, Nova Scotia, Canada, Winnipeg, Manitoba, Canada, and Vancouver, British Columbia, Canada*

From ^athe Departments of Medicine and Paediatrics, University of Calgary, Calgary (Consensus Conference Chairperson); ^bthe Department of Internal Medicine, Università degli Studi di Milano, Ospedale S. Giuseppe, Milan; ^cthe Department of Internal Medicine, Kutvolgyi Clinical Center, Semmelweis University, Budapest; ^dthe Department of Dermatology, University Hospital of the Johannes Gutenberg-University of Mainz; ^ethe Department of Pediatrics, J. W. Goethe University Hospital, Frankfurt; ^fthe Department of Medicine, University of Toronto, Toronto, Canada; ^gthe Department of Experimental and Molecular Medicine, Scripps Research Institute, La Jolla; ^hthe Department of Pediatrics, Harvard Medical School, Boston; ⁱthe Department of Medicine, Laval University, Quebec City; ^jthe Departments of Medicine and Medical Oncology, University of Alberta; ^kthe Canadian Hereditary Angioedema Society/Société d'Angioédème Héritaire du Canada, Claresholm, Alberta (Consensus Conference Co-chair); ^lHereditary Angioedema Association USA, Annandale; ^mGrupo de Pacientes de AEH de Argentina, Buenos Aires, Argentina; ⁿHungarian HAE Patients' Association, Budapest; ^oAllergiestation, Dermatologische Klinik, Universitätsspital, Zurich, Switzerland; ^pthe Department of Medicine, Dalhousie University, Halifax; ^qthe Department of Pediatrics, Dalhousie University, Halifax; ^rthe Department of Medicine, University of Manitoba, Winnipeg; ^sthe Department of Medicine, University of Ottawa, Ottawa; ^tthe Department of Pediatrics, University of British Columbia, Vancouver; ^uthe Department of Medicine, University of British Columbia, Vancouver; ^vthe Department of Pediatrics, Montreal Children's Hospital, McGill University, Montreal; ^wthe Department of Pediatrics, Hôpital Sainte Justine, University of Montreal, Montreal, Quebec, Canada; ^xthe Department of Medicine, University of Toronto, Oakville; ^yprivate practice, Kingston; ^zthe Department of Medicine, University of Western Ontario, Windsor; ^{aa}the Departments of Pediatrics and Medicine, University of Calgary; ^{bb}the

Department of Medicine, University of Toronto, Toronto; ^{cc}the Department of Medicine, McMaster University, Hamilton; ^{dd}ZLB Behring Canada, Ottawa, and the Department of Medicine, McGill University, Montreal; ^{ee}Madarász Sreet Childr'n's Hospital, Budapest.

*On behalf of PREHAET, European Concerted Action "Novel methods for predicting, preventing, and treating attacks in patients with hereditary angioedema." Participants: Marco Cicardi, MD, Milan, Italy; Konrad Bork, MD, Mainz, Germany; Laurence Bouillet, MD, Grenoble, France; Anette Bygum, MD, Odense, Denmark; Henriette Farkas, MD, PhD, Budapest, Hungary; Erik Hack, MD, Amsterdam, The Netherlands; Margarita López-Trascasa, PhD, Madrid, Spain; Erik Waage Nielsen, MD, Bodø, Norway; Christoph Bucher, MD, Zürich, Switzerland; Lennart Truedsson, PhD, Lund, Sweden; and Hilary Longhurst, MD, London, United Kingdom.

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Reprint requests: Tom Bowen, MD, FRCP(C), Clinical Professor of Medicine and Paediatrics, University of Calgary, 705 South Tower, 3031 Hospital Dr NW, Calgary, Alberta, Canada T2N 2T8. E-mail: tbowen@pol.net. 0091-6749/\$30.00

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C1 inhibitor deficiency (hereditary angioedema [HAE]) is a rare disorder for which there is a lack of consensus concerning diagnosis, therapy, and management, particularly in Canada. European initiatives have driven the approach to managing HAE with 3 C1-INH Deficiency Workshops held every 2 years in Hungary starting in 1999, with the third Workshop having recently been held in May 2003. The European Contact Board has established a European HAE Registry that will hopefully advance our knowledge of this disorder. The Canadian Hereditary Angioedema Society/Société d'Angioédème Héritaire du Canada organized a Canadian International Consensus Conference held in Toronto, Ontario, Canada, on October 24 to 26, 2003, to foster consensus between major European and North American HAE treatment centers. Papers were presented by investigators from Europe and North America, and this consensus algorithm approach was discussed. There is a paucity of double-blind placebo-controlled trials in the treatment of HAE, making levels of evidence to support the algorithm less than optimal. Enclosed is the consensus algorithm approach recommended for the diagnosis, therapy, and management of HAE and agreed to by the authors of this article. This document is only a consensus algorithm approach and requires validation. As such, participants agreed to make this a living 2003 algorithm (ie, a work in progress) and agreed to review its content at future international HAE meetings. The consensus, however, has strength in that it was arrived at by the meeting of patient-care providers along with patient group representatives and individual patients reviewing information available to date and reaching agreement on how to approach the diagnosis, therapy, and management of HAE circa 2003. Hopefully evidence to support approaches to the management of HAE will approach the level of meta-analysis of randomized controlled trials in the near future. (*J Allergy Clin Immunol* 2004;114:629–37.)

Key words: Hereditary angioedema, C1 inhibitor deficiency, C1 inhibitor, consensus

C1 inhibitor (C1-INH) deficiency presents in patients with the congenital (hereditary angioedema [HAE]) and acquired (acquired angioedema [AAE]) forms of angioedema. Three variants of HAE have been described: HAE I with low C1-INH protein and function (85% of cases; autosomal dominant)¹⁻⁴; HAE II with normal protein but low C1-INH function (15% of cases, autosomal dominant)^{1-3,5}; and a newly described estrogen-dependent inherited form of angioedema with normal protein and function.⁶⁻⁸ AAE has been seen with some B-cell malignancies (C1q antigen low), and angioedema has been seen with some medication use (eg, angiotensin-converting enzyme inhibitors). Patients with HAE might experience recurrent edema of the subcutaneous tissues (extremities, genitals, face, trunk, or elsewhere; Fig 1), intestinal swelling and abdominal pain, and life-threatening swelling of the airway (a cartoon of some of the possible pathophysiology is included in Fig 1). The incidence of HAE is estimated at 1:10,000 to 1:150,000, with most authors quoting a range of 1:10,000 to 1:50,000 and the gene encoding C1-INH mapping to chromosome 11q12-q13.1.⁹ The risk of dying as a result of airway obstruction is not clear, but deaths from this complication, if left untreated, are not uncommon.^{3,10}

Abbreviations used

AAE:	Acquired angioedema
C1-INH:	C1 inhibitor
C1INHRP:	C1-INH replacement
HAE:	Hereditary angioedema
SDP:	Solvent/detergent-treated fresh frozen plasma
TA:	Tranexamic acid

Approaches to the diagnosis, therapy, and management of this disorder seem to vary between countries, with many countries having access to C1-INH replacement product and some not having such access. With the absence of consensus in approach to the management of this disorder, the Canadian Hereditary Angioedema Society/Société d'Angioédème Héritaire du Canada held a Canadian International Consensus Conference on HAE from October 24th to October 26th, 2003, in Toronto, Ontario, Canada, to investigate whether a consensus algorithm approach to this disorder could be achieved.^{1,2,6,10-21} This conference was patterned after 3 European C1-INH Deficiency Workshops organized by the Hungarian HAE Working Group. The workshops have been held at 2-year intervals from 1999 through 2003.¹⁴ As established by the Hungarian workshops, the Canadian Consensus Conference brought together government agencies; blood product suppliers; comprehensive care team members, including nurses and physicians (family physicians, hematologists, allergists-immunologists, pediatricians, and dermatologists); HAE patient group representatives from around the world; and industry sponsors.^{11,12,14} Papers for discussion at the meeting were submitted in advance for peer review and have been published in the December 2003 edition of *Transfusion and Apheresis Science*, a special issue dedicated to hereditary angioedema.^{1,2,10-18} The consensus was therefore an agreement between patients, patient groups, and treatment team members alike on how to approach the diagnosis, therapy, and management of HAE. The final consensus has been reviewed by the patient groups and treatment teams listed as part of the authorship of this article and is presented as a living algorithm approach for the management of HAE types I and II.

We did not attempt to include approaches to AAE or estrogen-dependent angioedema. It is hoped that the algorithm will be validated by treatment teams with the experience and desire to improve the level of evidence supporting this algorithm. It is further hoped that this approach will be openly discussed and modified at upcoming international HAE conferences to improve the lives of our patients with HAE. Patient groups and treatment teams alike are encouraged to recommend changes in the proposed approach. Changes will obviously be required as more options become available for diagnosis, therapy, and management of HAE. Exciting investigational therapies were discussed at the Canadian meeting, but the algorithm is limited to the treatments available in 2003 in most of the participating countries.

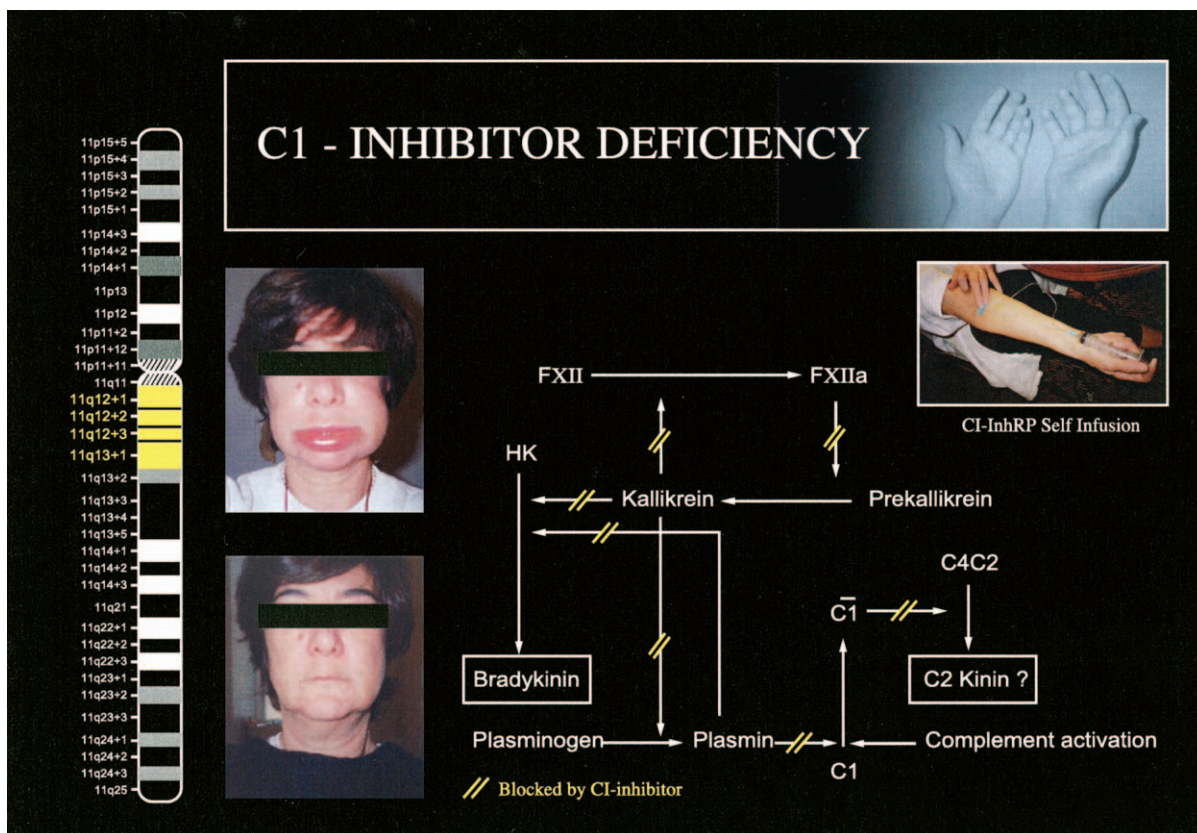


FIG 1. C1-INH deficiency. This figure was developed through the collaboration of Tom Bowen, Scott Andrews, Marco Cicardi, and Al Davis.

This dynamic algorithm recognizes that there are many different and possibly equally valid approaches to the management of HAE and is meant to be a recommendation for an approach yet to be validated. Because countries vary in the treatments available to them, the approaches must obviously differ. European clinical experience has been validated in clinics with patient populations of up to more than 400 patients, large clinics indeed when one remembers the rare nature of this disorder.^{2,10,13,14,19} We agree that consensus conferences are a poor replacement for double-blind placebo-controlled trials. Until the results of such trials are available, consensus might provide some guidance and stimulate research that will encourage undertaking of such clinical trials.

CONSENSUS ALGORITHM

1. Clinical characteristics²

- Recurrent angioedema (swelling) without urticaria (without hiving) that is usually nonpruritic (without itch, although sometimes there is a nonpruritic serpentine erythematous rash).²²
- Swelling can affect the extremities, face, trunk, gastrointestinal tract, genitourinary regions, or upper airways (any area of the body can be involved; Fig 1).
- Abdominal symptoms might mimic infantile colic, acute appendicitis, or acute abdomen, and symp-

toms might include nausea, vomiting, abdominal pains, and postattack diarrhea.²³

- Age of onset is variable, and the patient might present at less than 1 year of age with colic or, rarely, swelling (attacks frequently worsen around puberty). Laryngeal episodes tend to occur later than other symptoms but might have onset in early childhood.¹⁰
- Symptoms often worsen with estrogen-containing birth control pills or hormone replacement therapy.¹³
- Attacks tend to be prolonged, typically increasing over the first 24 hours and then slowly spontaneously subsiding over 48 to 72 hours. Some attacks might last longer than 72 hours as the swelling migrates from site to site.
- Attack triggers might include minor trauma (eg, dental procedures), stress, menstruation, pregnancy, some drugs (eg, oral contraceptives and angiotensin-converting enzyme inhibitors), or infections. However, triggers are often unidentified.
- Attacks tend to be periodic and are often followed by several weeks of remission. Attacks are not usually daily occurrences.
- Attacks might not respond to treatment with epinephrine, antihistamines, or glucocorticoids. However, some experiences suggest epinephrine might be tried, particularly early in an attack if other therapy is not available.²⁴

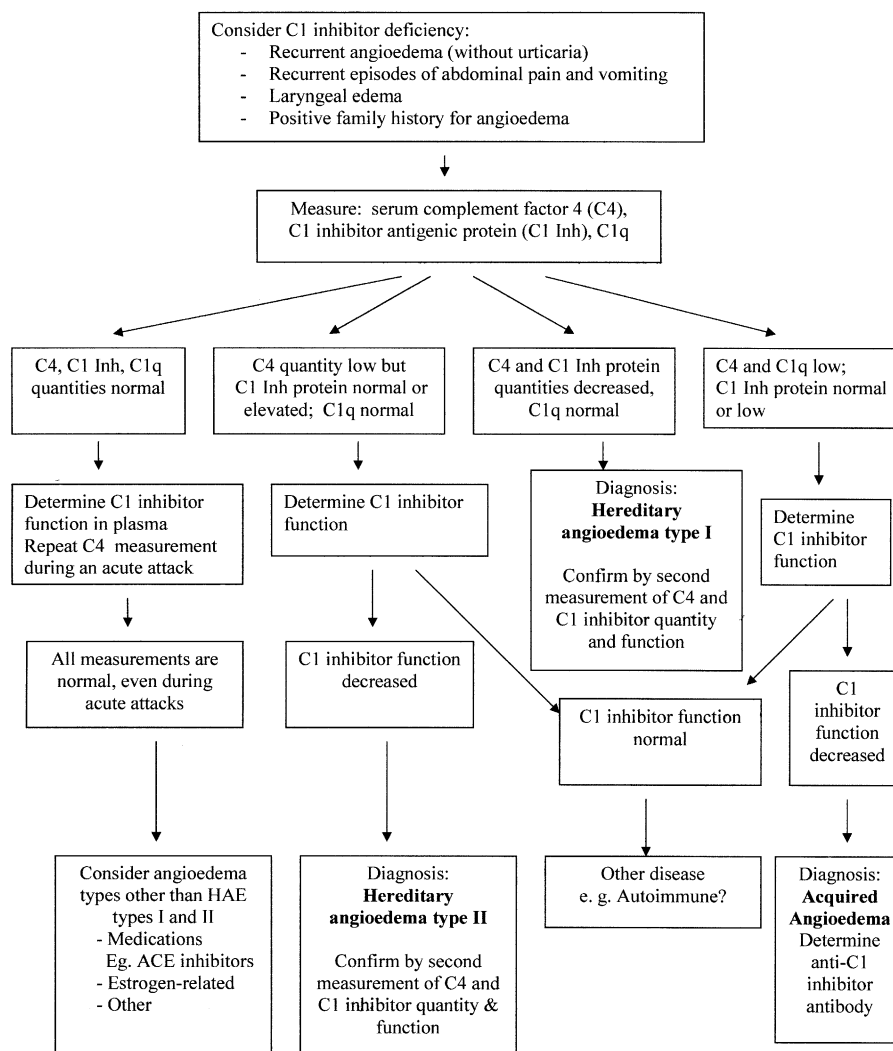


FIG 2. C1-INH deficiency diagnostic algorithm.

2. Diagnosis (see Fig 2 for HAE Diagnostic Algorithm)

a. Indications for testing

- i. Clinical suspicion at any age.
- ii. If a positive family history, test at any age.

- b. Tests might not be reliable at less than 1 year of age (false-negative and false-positive test results might occur). Tests done before 1 year of age should be confirmed after 1 year of age. The diagnosis of HAE cannot be reliably made before 1 year of age (unless using genetic typing).²⁵

3. Testing (see Fig 2 for HAE Diagnostic Algorithm)

- a. If clinical suspicion of C1-INH deficiency, screening with serum C4 and C1-INH proteins is recommended.

- i. If serum C4 and C1-INH antigenic proteins are both low and AAE is not suspected, then the diagnosis is type I HAE (repeat testing once is suggested to confirm diagnosis). If AAE is

possible, then serum C1q antigenic protein testing is required; if low, it is likely AAE.

- ii. If C4 and C1-INH antigenic proteins are both normal but clinical suspicion is strong, HAE is not ruled out. Obtaining a C1-INH functional assay is recommended. Low C1-INH functional activity is suggestive of type II HAE (<1% have normal C4 between attacks^{2,26}). Repeat testing is suggested to confirm.
- iii. If C4 antigenic protein and C1-INH functional assay results are both normal, this rules out type I and type II HAE. This does not rule out estrogen-dependent HAE.
- iv. If C4 antigenic protein and C1-INH functional assay results are both low, then C1-INH antigenic protein assay should be done to clarify type I HAE (low antigenic protein) from type II HAE (normal antigenic but low functional protein).

- v. 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 provide quality assurance of testing laboratories.
 - vi. C1q antigenic protein level might be of value in diagnosing AAE because this is typically reduced in patients with AAE but normal in patients with HAE.
 - vii. Genetic testing. Similar to other autosomal dominant disorders, from one quarter to one third of patients might represent de novo mutations.²⁷ Genetic testing is not necessary to confirm the diagnosis of HAE.
- 4. Baseline laboratory testing at diagnosis at any age**
- a. Baseline bloodborne pathogen surveillance samples should be stored (hemovigilance,¹⁸ serology, and samples for nucleic acid testing). C1-INH replacement therapy might have to be administered at any time on an emergency basis. Therefore hemovigilance and baseline chemistries and urinalysis are best done at diagnosis.
 - b. Baseline serology (IgG antibodies) to HIV, human T-lymphotropic viruses (HTLV 1 and 2), hepatitis B and C, and other hepatitis viruses (eg, hepatitis G virus) are recommended before infusion of blood products.
 - c. An abdominal liver spleen ultrasound should be obtained before androgen administration.
 - d. Liver function studies, including alanine aminotransferase, total bilirubin, alkaline phosphatase, creatine kinase, lactic dehydrogenase, blood urea nitrogen, and creatinine measurement; complete blood count and differential; urinalysis; and thyroid-stimulating hormone and thyroid antibody measurement should be performed at diagnosis.
- 5. Vaccination recommendations**
- a. It is recommended that patients chronically receiving blood products receive vaccination to hepatitis B.
- 6. Medications and drugs to avoid in patients with HAE²⁸**
- a. Angiotensin-converting enzyme inhibitors.²⁹⁻³¹
 - b. Estrogen contraceptives.^{6,13,32-38}
 - c. Plasminogen activators are a theoretic risk, but the benefit might outweigh the risk.³⁹⁻⁴¹
- 7. Short-term prophylaxis: Minor manipulations (eg, dental work; see Fig 3)**
- a. If only mild manipulation, such as mild dental work, no prophylaxis is indicated if C1-INH replacement (C1INH RP) is immediately available (dose; see 8a below). If C1INH RP is not available, then danazol or tranexamic acid (TA) prophylaxis is recommended as below. Injection of local anesthetic might precipitate an attack.
 - b. If considering more than mild manipulation, such as dental work, danazol is recommended (even in

children and in patients in the last trimester of pregnancy; avoid in the first 2 trimesters of pregnancy).^{13,14,42-56} The recommended dosage is 10 mg/kg/day (maximum, 600 mg daily) for 5 days before and 2 days after the event. C1INH RP should be made immediately available (dose; see 8a below) when possible.

- c. TA (currently not available in the United States) is thought not to be as predictable for acute prevention as danazol but is more often recommended than ϵ -aminocaproic acid.^{13,17,54,57-67} The recommended TA dosage is 75 mg/kg/day (split 2 or 3 times per day) for 5 days before and 2 days after the event. C1INH RP is to be made immediately available (dose; see 8a below) when possible.

8. Short-term prophylaxis: Intubation or major procedures (see Fig 3)

- a. C1INH RP 1 hour before surgery (to be used if intubation is used, Berinert PR, ZLB Behring; currently not available in the United States). The recommended dosage is 500 units up to a weight of 50 kg (110 lb), 1000 units for weight of greater than 50 kg (110 lbs) but less than 100 kg (220 lbs), and 1500 units for weight of greater than 100 kg (>220 lbs). A second dose of an equal amount is to be made immediately available at the time of surgery.^{2,10,13-15,29,32,68-74} Repeat daily or as needed until there is no further risk of angioedema.
- b. If C1INH RP is not available, then danazol or TA prophylaxis is recommended as in 7. Solvent/detergent-treated fresh frozen plasma (SDP) is an option 1 or more hours before surgery. If SDP is not available, regular fresh frozen plasma is a less safe alternative. The dose has not been studied but is usually 2 units per adult infusion (200 mL per unit). For coagulopathies, 10 mL/kg SDP has been used,⁷⁵ and this might be appropriate for HAE, but neither the dose nor the timing before the procedure have been studied.

9. Long-term prophylaxis (Fig 3). If the patient experiences more than one severe event per month or is disabled more than 5 days per month, then consider prophylaxis with TA, androgens, or C1INH RP on demand. The number of events per year does not predict the severity of the next event or whether the first or next event will be an airway event.

- a. Androgen.^{13,52,54,76} The attenuated androgens danazol and stanozolol (stanozolol is not available in the United States) are the usual agents, with methyltestosterone and oxandrolone as alternatives. These might be more effective than antifibrinolytic agents.³ Contraindications usually include pregnancy and lactation, cancer, and childhood. Side effects might include 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^{52,76} or carcinomas),

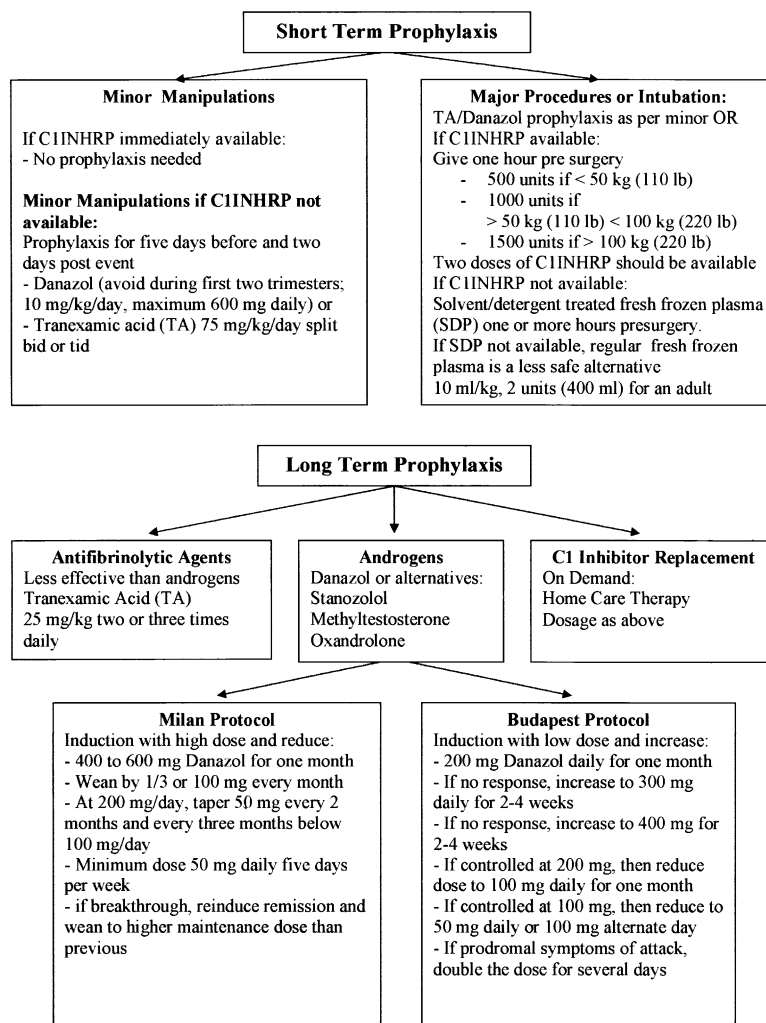


FIG 3. C1-INH deficiency prophylaxis algorithm.

hypertension, atherogenesis with altered lipid metabolism, polycythemia, and hemorrhagic cystitis.

- i. Milan protocol.¹³ Induce at a high dose and reduce: 400 to 600 mg of danazol daily for 1 month. Wean by one third or 100 mg every month, as long as there is no breakthrough. At 200 mg/day, slow the tapering with reductions of 50 mg every 2 months; every 3 months less than 100 mg/day. The usual minimum dose is 50 mg daily 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 previously used.
- ii. Budapest protocol.⁵⁴ Induce at a low dose and increase: 200 mg of danazol daily for 1 month. If no response, then increase the dose to 300 mg daily for 2 weeks to 1 month. 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 daily for 1

month. If still controlled, then reduce to 50 mg daily or try 100 mg on alternate days. Androgen therapy is not recommended for children but has been used in the prepubertal setting.⁵⁴

If the sensation of prodromal attack symptoms or mild clinical manifestations develops or if patients are exposed to a precipitating factor (eg, upper airway infection), it is recommended to double the dose for several days.

- iii. Androgen monitoring. Every 6 months, perform a complete blood cell count, a liver enzyme measurement (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase), a lipid profile determination, and urinalysis. For adults receiving a dose of 200 mg/day or less androgen, annual liver spleen ultrasonography is suggested. In adult patients with higher doses (300-600 mg/day) or in prepubertal patients, 6-month liver spleen ultrasonography for the detection of focal lesions is suggested.

TABLE I. Treatment of acute HAE attack

	Cutaneous swelling			
	Extremities, trunk	Face, neck	Abdominal attack	Laryngeal attack
Wait and see (spontaneous resolution)	+	±	—	—
Tranexamic acid*	+	+	+	+
C1-INH concentrate*	—	±	+	+
ICU (intubation,† tracheotomy)	—	—	—	+

General measures for treatment of acute attacks: (1) treat as early as possible before development of a full-blown attack (prodromal symptoms); (2) some patients receiving danazol can abort attacks by increasing the dose of danazol at the first signs or prodrome of an attack.

ICU, Intensive care unit.

*Dosages: (1) tranexamic acid (oral or intravenous), 25 mg/kg up to 1 g every 3 to 4 hours (maximum, 75 mg/kg/day); (2) C1-INH concentrate (intravenous), 500 units at less than 50 kg, 1000 units at 50 to 100 kg, and 1500 units at greater than 100 kg.

†Intubation: consider early in progressive laryngeal edema.

- b. Antifibrinolytic agents. TA (not available in the United States) has mostly replaced ε-aminocaproic acid.¹⁷ TA might not be as effective as androgen therapy³ but might be useful in AAE.¹⁷ TA is mostly used when prophylaxis is indicated before Tanner V puberty stage. Side effects might include myalgia, increased serum creatine phosphokinase or aldolase levels, rhabdomyolysis, muscle weakness, hypotension, and fatigue. The recommended TA dosage is 50 to 75 mg/kg/day (25 mg/kg 2 to 3 times daily).^{17,54}
- c. C1INH RP on demand.¹⁵ It is recommended that home-care C1INH RP therapy be offered to patients. Patients should be allowed to keep a supply of C1INH RP for personal use at home or with travel to be either self-administered or infused by a caregiver (Figs 1 and 3).
 - i. Dose. C1INH RP: 500 units up to a weight of 50 kg (110 lb), 1000 units for a weight of greater than 50 kg (110 lb) but less than 100 kg (220 lb), and 1500 units for a weight of greater than 100 kg (>220 lb).
 - ii. Administration. C1INH RP 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 through a peripheral vein over 10 minutes. Epinephrine is not routinely recommended to have on hand for home C1INH RP administration.
 - iii. Patient identification and instructions. Patients are encouraged to carry alert identification or an accompanying letter indicating C1-INH deficiency and outlining instructions for administration of the C1INH RP. It is recommended that HAE organization Web sites provide infusion instructions for downloading by patients.

10. Treatment of acute HAE attacks (see Table I)

- a. The first-line therapy for treatment of a severe event is C1INH RP, with dosage and administration as per 9c above.
- b. If C1-INHRP is not available, other therapies might include increasing the danazol dose, TA

(dosage in Fig 3), early use of adrenaline (might not be effective), pain management, intravenous fluids, or supportive care. Use of fresh frozen plasma (solvent detergent or regular) could theoretically worsen attacks and remains controversial.²

11. Blood product risks

- a. Blood product infusion risks are reviewed by the Canadian Paediatric Society Infectious Diseases and Immunization Committee.⁷⁷

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