Clinical Pearls and Pitfalls

Modern preoperative and intraoperative management of hereditary angioedema

Anthony M. Szema, M.D., F.C.C.P., F.A.C.A.A.I., F.A.A.A.A.I., F.A.C.P.,*# George Paz, M.D.,*¶ Louis Merriam, M.D.,# Francis Stellaccio, M.D., D.A.B.A.,§ and James Jen, M.D.#

ABSTRACT

Hereditary angioedema (HAE), deficiency of C1 esterase inhibitor, poses a risk of airway compromise during trauma, including surgery, due to activation of the complement cascade. Classical surgical management includes emergent/slash tracheostomy and cricothyrotomy, associated with high complication rates. We provide here an evidence-based review of available medical literature to construct guidelines for managing patients with HAE pre- and intra-operatively. We also describe our experience with a patient for whom we cared using these guidelines. Our objective was to explain new preventive measures to prevent airway compromise in HAE and their level of evidence for averting potential therapeutic misadventure. We analyzed PUBMED literature regarding airway management and etiology of angioedema and its prevention, followed by application of guidelines based on these data in a patient with HAE undergoing inguinal hernia repair. An analysis of contemporary literature yielded key points: (1) using a Cook Exchange catheter to facilitate re-intubation, (2) measuring cuff leak pressure to verify whether airway pressure had increased during surgery, (3) visualizing the airway directly using a fiberoptic laryngoscope connected to a digital flat-screen monitor for real-time assessment, (4) following conventional dictum to double stanozolol dosages 2 weeks before admission, (5) administering fresh frozen plasma pre- and intraoperatively, and (6) preparing recombinant C1 esterase inhibitor for instantaneous intraoperative use; and using FDA-approved human-derived C1-esterase inhibitor prophylactically. Biotechnology in the form of novel but currently available and in-practice medical devices, as well as new therapeutic agents, have expanded the armamentarium for safely managing patients with HAE pre- and intraoperatively.

(Allergy Asthma Proc 30:338–342, 2009; doi: 10.2500/aap.2009.30.3225)

Key words: Airway, angioedema, C1, esterase, hereditary, inhibitor, intraoperative, management, preoperative

Question

How do you manage a patient with hereditary angioedema (HAE), awaiting an inguinal hernia repair, pre- and intraoperatively?

A. No precautions are necessary.
B. Danazol dose should be decreased 24 hours before surgery.
C. (1) Use a Cook exchange catheter (Cook Critical Care, Bloomington, IN) to facilitate reintubation, (2) measure cuff leak pressure to verify whether airway pressure has increased during surgery, (3) visualize the airway directly using a fiberoptic laryngoscope connected to a digital flat-screen monitor for real-time assessment, (4) follow conventional dictum to double stanozolol/danazol dosages 2 weeks before admission, (5) administer fresh frozen plasma (FFP) pre- and intraoperatively, (6) prepare recombinant C1 esterase inhibitor for instantaneous intraoperative use, (7) avoid medications associated with precipitating angioedema—such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, and (8) treat with C1 esterase inhibitor product derived from human plasma (Cinryze, i.v. q 3–4 days; ViroPharma, Inc., New York, NY) approved by the Food and Drug Administration (FDA) October 10, 2008.
D. Slash tracheostomy is the preferred method of airway management preoperatively.
E. Cricothyrotomy is associated with low rates of complications and is sufficient for all HAE patients preoperatively.

*From the Departments of *Medicine, #Surgery, §Anesthesia, and ¶Pediatrics, State University of New York Stony Brook School of Medicine, Stony Brook, New York*
A Szema is conducting an open-label phase II study of the safety and efficacy of recombinant human C1 inhibitor for the treatment of acute attacks in patients with hereditary angioedema, sponsored by Pharming, N.V.
Address correspondence and reprint requests to Anthony M. Szema, M.D., SUNY Stony Brook, T16-041, Stony Brook, NY 11794-8161
E-mail address: anthony.szema@stonybrook
Copyright © 2009, OceanSide Publications, Inc., U.S.A.

Since its initial description by Heinrich Irenaus Quincke in 1882, HAE, deficiency of C1 esterase inhibitor, not only has been associated with spontaneous

DO NOT COPY
Copyright @ Oceanside Publications, Inc. All rights reserved.
For permission to copy, go to www.copyright.com

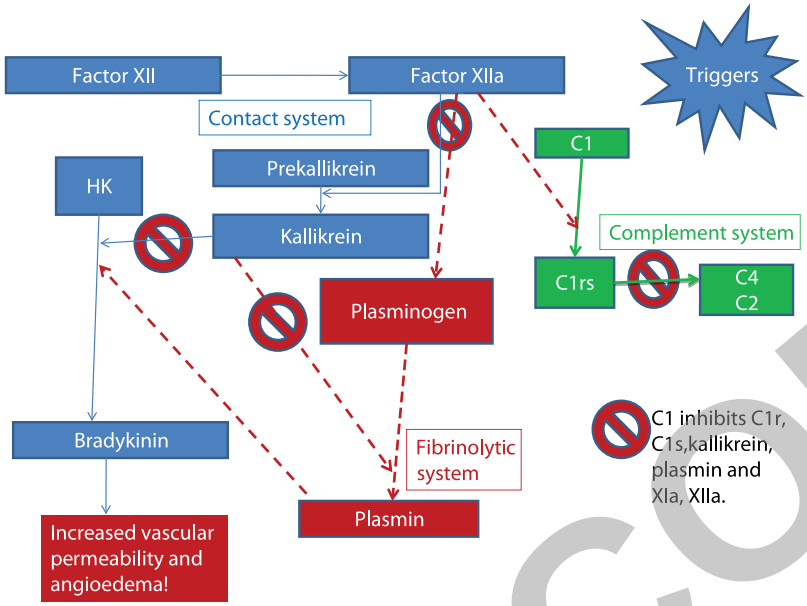

Figure 1. *Depletion of C1 INH leaving three systems unregulated in response to triggers with subsequent bradykinin overproduction.*

attacks of edema, but also has been recognized to pose a risk of airway compromise during trauma, including surgery, because of activation of the complement cascade. Classic surgical management has included emergent/slash tracheostomy and cricothyrotomy, which are associated with high complication rates.

CLINICAL CHARACTERISTICS AND PATHOPHYSIOLOGY

Recurrent attacks of angioedema not responding to antihistamines are the hallmark of C1 inhibitor disorders. Symptoms usually present in childhood and worsen during puberty. Skin and submucosal edema develops gradually over several hours, increasing slowly within 12–36 hours and subsiding within 2–3 days. Frequency of such attacks varies from weekly to one to two times per year.[1] Prodromal erythema (usually in the extremities) may be present but urticaria is not a feature of C1 inhibitor (INH) deficiency and another cause should be sought for the patient's angioedema symptoms. The 15 to 33% mortality rate reported is typically caused by laryngeal edema. Approximately 25% of patients have abdominal pain, nausea, and vomiting as the most prominent symptoms. It is caused by narrowing of the intestinal walls because of the angioedema. The endoscopic appearance is suggestive.[2] Computed tomography imaging may reveal ascites and bowel wall thickening. Drugs (*e.g.*, angiotensin-converting enzyme inhibitors and estrogen), infection, and emotional stress can precipitate attacks of angioedema. Patients with known HAE should consult with their physician about substitute medications. Before surgery, we would recommend discontinuing angiotensin-converting enzyme inhibitor. Dental procedures are the precipitating cause in up to 50% of attacks and can lead to fatal asphyxiation between 4 and 30 hours after procedure.

C1 INH disorders are generally divided into two categories: inherited and acquired. Inherited HAE is an autosomal dominant disease that affects 1 in 10,000 to 1 in 50,000 persons and has been reported in all races with no gender predominance.[3] Approximately 20–30% of patients with HAE do not have a family history and most likely represent new mutations.[4] Two main types exist. Type I accounts for ~85% of HAE cases and is caused by decreased production of C1 INH. Type II accounts for the rest and is identified by normal or elevated quantities of functionally impaired C1 INH. There is another type of familial, nonallergic angioedema that affects women (estrogen-dependent/estrogen-associated angioedema) but is not related to C1 INH levels or function. This is called type III HAE.[5]

Acquired C1 inhibitor disorder is a rare disease caused by catabolism of C1 INH and C1q with a specific autoantibody directed toward the C1 INH molecule. This acquired form has been associated with cancers, myeloproliferative disorders, autoimmune diseases, and infections. A cartoon of the complement cascade and the role of C1 INH is depicted in Fig. 1.

DIAGNOSIS

It is difficult to differentiate between surgical emergencies and C1 INH disorders when abdominal pain is the main symptom. This leads to unnecessary appendectomies or exploratory laparotomies before correct diagnosis of the patient. Endoscopic evaluation has

Copyright @ Oceanside Publications, Inc. All rights reserved.
For permission to copy, go to www.copyright.com
DO NOT COPY

Table 1 **Universal strength of recommendations for hereditary angioedema therapy**

Grade of Recommendation	Clarity of Risk/Benefit	Methodologic Strength of Supporting Evidence	Implications
1A	Clear	Randomized trials without important limitations	Strong recommendation; can apply to most patients in most circumstances without reservation
1B	Clear	Randomized trials with important limitations (inconsistent results, methodologic flaws)	Strong recommendations, likely to apply to most patients
1C+	Clear	No RCTs, but RCT results can be unequivocally extrapolated, or overwhelming evidence from observation studies	Strong recommendation; can apply to most patients in most circumstances
1C	Clear	Observation studies	Intermediate-strength recommendation; may change when stronger evidence available
2A	Unclear	Randomized trials without important limitations	Intermediate-strength recommendation; best action may differ depending on circumstances of patients' or societal values
2B	Unclear	Randomized trials with important limitations (inconsistent results, methodologic flaws)	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances
2C	Unclear	Observation studies	Very weak recommendations; other alternatives may be equally reasonable

Source: Ref. 9.
RCT = randomized clinical trial.

DO NOT COPY

been reported to show diffuse redness and bulging mucosa during an acute HAE attack resembling submucosal tumors.[2] Mucosal changes were segmental and returned to normal within days of attack resolution. Therapeutic challenge with C1 INH may be a more certain way to differentiate between an acute attack of angioedema and a true surgical diagnosis. Such an approach was initiated with our recent case of a patient requiring inguinal hernia repair in the setting of HAE. Pain and abdominal discomfort persisted after a trial of recombinant C1 INH (minimal relief). Recombinant C1 INH during the procedure usually gives relief within 0.5–1.5 hours with complete resolution of symptoms in 24 hours. If symptoms of an acute abdominal attack due to the surgery persist at a high intensity 2 hours after the infusion of C1 INH, additional concentrate may be given along with consideration of alternative diagnosis.[2] In our case, the patient's manifestation of HAE was peripheral extremity swelling attacks (linear red erythema preceded rapid arm, hand, and leg swelling after self-discontinuation of stanozolol).

MANAGEMENT

Universal levels of evidence for our recommendations are shown in Table 1, modified from the CHEST guidelines for levels of evidence for the management of pulmonary embolism. A Cook exchange catheter (Cook Critical Care, Bloomington, IN) is a device that remains in place during intubation and after extubation. This facilitates reintubation (Fig. 2). Measurement of cuff leak pressure intraoperatively (Fig. 3) allows detection of rapid increases in airway pressure. The literature has longstanding recommendations for increasing (doubling) stanozolol doses[6] for 2 weeks before the procedure as well as the administration of fresh frozen plasma (FFP) 24 hours before and intraoperatively.[3,7] On October 10, 2008, the U.S. Food and Drug Administration (FDA) approved C1 esterase in-

Copyright @ Oceanside Publications, Inc. All rights reserved.
For permission to copy, go to www.copyright.com

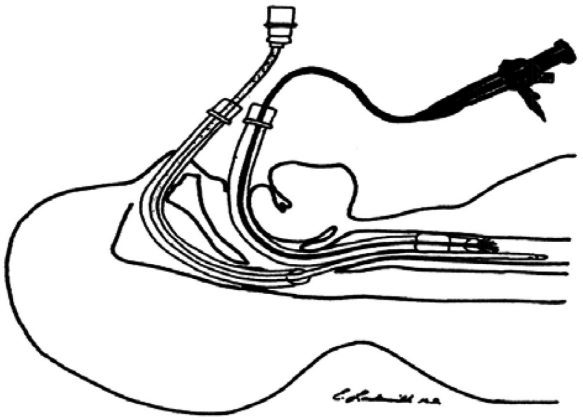

Figure 2. Cook exchange catheter. Airway instrumentation for tracheal extubation in an adult patient with a difficult airway. Nasal and oral endotracheal tubes, no. 11 Cook airway exchange catheter (Cook Critical Care, Bloomington, IN), and fiberoptic bronchoscope in position. After removal of the oral endotracheal tube (ETT), the nasal ETT remains in the posterior pharynx along with the intratracheal Cook airway exchange catheter.

hibitor (human) from U.S. source plasma. C1 esterase inhibitor (human) is indicated for routine prophylaxis against angioedema attacks in patients with HAE. The drug Cinryze C1 Inhibitor (human) is for i.v. use only. A dose of 1000 U of CINRZE can be administered every 3 or 4 days for routine prophylaxis against angioedema attacks in HAE patients. First manufactured by Lev Pharmaceuticals (New York, NY), the company was acquired by ViroPharma on October 21, 2008. C1 esterase (human) is effective in preventing or decreasing the frequency of attacks in most but not all HAE patients. It is not used for acute attacks. In a study of 20 subjects, side effects include viral upper respiratory tract symptoms and rash.

Another product, the recombinant C1 esterase inhibitor product (human gene expressed in rabbit milk or rhucin), from Pharming, N.V. (The Netherlands), is being studied in clinical trials only for the treatment of attacks, rather than preventing attacks. A case report of autoantibodies to endogenous C1 INH has been reported. Normal C4 and C1 INH levels and functional assay in the setting of angioedema should prompt detection of autoantibodies to C1 INH.[8]

Correct answer to question: C

Pearls

The management described previously serves as an update to the presurgical protocol/posttrauma protocol. Key components include using

- Increased stanazol to 4 mg p.o. b.i.d. for 2 weeks before surgery (1C).
- Give FFP, 3 U/day, before procedure with checking of serum C4, C1 esterase inhibitor levels and function after the first and second unit of FFP (1C+).
- FFP, 2 U, intraoperatively, during the procedure (2C).
- Availability of Recombinant C1 esterase inhibitor before procedure (2C).

Figure 3. Cuff leak pressure (arrow) estimated 15 cm of water before extubation.

DO NOT COPY
Copyright @ Oceanside Publications, Inc. All rights reserved.
For permission to copy, go to www.copyright.com

- Administration of Recombinant C1 esterase inhibitor during procedure if any evidence of gastrointestinal tract mucosal edema (2C).
- Measurement of cuff leak pressure of the endotracheal tube of 8–25 cm of water with maintenance of pressures <30 cm of water at the end of surgery (2C).
- If >30 cm of water is measured, use a Cook exchange catheter to allow for ease of reintubation as needed (2C).
- Human plasma-derived C1 esterase inhibitor, as described.

Biotechnology in the form of novel but currently available and in-practice medical devices, as well as new therapeutic agents, have expanded the armamentarium for safely managing patients with HAE pre- and intraoperatively. Other authors have used plasma kallikrein inhibitors, C1 inhibitor concentrate, and tracheal obturators for tracheotomized patients. Gene markers for HAE may prove helpful as technology advances and becomes readily available.[6]

Pitfalls

- The Lev product, although recently FDA approved for prescription use, is not readily available (anticipated in New York State in April, 2009), and the current U.S. supply is *via* research centers that are enrolled in its clinical trial. Do not administer recombinant C1 esterase inhibitor (rhucin) to patients who are allergic to rabbits.

ACKNOWLEDGMENT

We acknowledge the expert assistance of Research Coordinator Jackie Skarre, N.P. Patients with hereditary angioedema may contact her at jackie.skarre@stonybrook.edu.

REFERENCES

1. Banerji A, Oren E, Hesterberg P, et al. Ten-year study of causes of moderate to severe angioedema seen by an inpatient allergy/immunology consult service. Allergy Asthma Proc 29:88–92, 2008.
2. Hara T, Shiotani A, Matsunaka H, et al. Hereditary angioedema with gastrointestinal involvement: Endoscopic appearance. Endoscopy 31:322–324, 1999.
3. Frank MM. Hereditary angioedema. J Allergy Clin Immunol 121:S398–S401, 2008 (quiz S19).
4. Frank MM, and Jiang H. New therapies for hereditary angioedema: Disease outlook changes dramatically. J Allergy Clin Immunol 121:272–280, 2008.
5. Craig TJ. Appraisal of danazol prophylaxis for hereditary angioedema. Allergy Asthma Proc 29:225–231, 2008.
6. Martin L, Raison-Peyron N, Nothen MM, et al. Hereditary angioedema with normal C1 inhibitor gene in a family with affected women and men is associated with the p.Thr328Lys mutation in the F12 gene. J Allergy Clin Immunol 120:975–977, 2007.
7. Pesci SA, Almassi G, Bojrab R, et al. Management of hereditary angioedema during off-pump coronary arterial surgery. Ann Thorac Surg 1079–1818, 2008.
8. Lin JH, Casillas AM, and Sattar S. C1-esterase inhibitor autoantibodies in a patient with acute tongue swelling. Allergy Asthma Proc 28:93–96, 2007.
9. Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: The 7th ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 126(3 Suppl):338S–400S, 2004. □

DO NOT COPY

Copyright @ Oceanside Publications, Inc. All rights reserved.

For permission to copy, go to www.copyright.com

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.