

# Angioedema: Perioperative management

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## Abstract

**Objective:** To describe the perioperative management of a patient with acquired angioedema (AAE).**Methods:** A 66-year-old Caucasian male presented from an outside hospital with a history of acquired angioedema and gastrointestinal stromal tumor–related intractable urticaria and mastocytosis. He was admitted for urgent laparoscopic partial gastrectomy, secondary to gastric outlet obstruction symptomatology. Previous combined attacks were characterized by a widespread rash, abdominal pain and respiratory distress resulting in hospitalization. Following preoperative consultation with the patient's allergist and a hospital pharmacist, he was treated preoperatively with fresh frozen plasma and his home prednisone dose. CI-inhibitor (Berinert®) was on standby along with epinephrine, given that the underlying etiology (CI-inhibitor deficiency vs histaminergic) was not known.**Results:** There were no intraoperative complications, and the patient was discharged home 3 days after the procedure.**Conclusions:** Optimization of perioperative outcomes in patients, especially during urgent or emergent surgery, with a history of angioedema requires the development of a patient-specific perioperative plan, including prophylaxis, rescue therapies and opioid-sparing strategies.

## Keywords

Perioperative, angioedema, hereditary angioedema, acquired angioedema, anesthesiology, mast cell, laryngeal edema, airway, CI-inhibitor

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## Introduction

Angioedema is a life-threatening condition due to the risk of airway compromise throughout the perioperative period. It affects up to two-thirds of patients with hereditary angioedema (HAE) or acquired angioedema (AAE) during their lifetimes with a 15%–33% mortality rate.<sup>1,2</sup>

It is critical to develop a definitive perioperative plan for prophylaxis, intraoperative management and rescue in consultation with an allergist and a pharmacist. This case describes a patient with gastrointestinal stromal tumor (GIST)-related mastocytosis and intractable urticaria admixed with AAE, and, for the first time, consolidates and presents previously described and variable treatment modalities. It also serves as a reference for medical providers of patients with HAE or AAE who are being optimized prior to surgery.

## Case study

A 66-year-old obese Caucasian male with a history of hypertension, prostate cancer, deep vein thrombosis (on

rivaroxaban) and intractable urticaria (onset 2 years ago; on prednisone 30 mg daily) presented for urgent laparoscopic partial gastrectomy for a GIST, secondary to gastric outlet obstruction. He reported two attacks per year characterized by a widespread rash, abdominal pain and respiratory distress (beyond a reasonable degree caused by gastro-esophageal reflux disease) that resulted in hospitalization. Preoperative evaluation revealed development of non-pruritic, non-erythematous rashes, flushing and abdominal pain with reduced doses of prednisone. Examination revealed clear breath sounds, absent stridor

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and no rash or abdominal pain. Given the urgent nature of the surgery, and unknown etiology of his AAE, it was necessary to prepare for a primary pathophysiology of C1-inhibitor (C1-INH) deficiency and histaminergic AAE.

In preparing for both etiologies of AAE, and balancing pharmacoeconomics as well as the urgency of the surgery, and prophylactic versus emergency intervention, the patient's allergist, a hospital pharmacist, and attending anesthesiologist were consulted. He was treated 1 h preoperatively with two units of fresh frozen plasma (FFP) and his home prednisone dose. C1-INH (Berinert®) was on standby along with an epinephrine bolus (10 mcg/mL) and infusion (16 mcg/mL). Prior to induction of anesthesia, an arterial line was placed to optimize hemodynamic monitoring. For pain control, and to avoid opioid-induced mast cell degranulation, the patient received multimodal pain therapy that included preoperative bilateral transversus abdominis and rectus sheath anesthetic blocks (60 mL 0.5% ropivacaine, 8 mg dexamethasone) and intravenous (IV) infusions of lidocaine (2 mg/min) and ketamine (5 mcg/kg/min; 50 mg bolus on anesthetic induction). Diphenhydramine (12.5 mg IV) and hydrocortisone (50 mg IV) were also administered. An easy, atraumatic intubation was performed using a video laryngoscope with the observation of moderate laryngeal edema. The laryngeal edema was likely due to the patient's body habitus and mild chronic gastroesophageal reflux disease. IV fluids were minimized to avoid further airway edema (1700 mL Plasma-Lyte).

There were no intraoperative complications, thus the decision to extubate was based on a repeated direct laryngoscopy, revealing stable edema consistent with intubation. He was discharged on post-operative Day 3.

## Discussion

### *Perioperative pathophysiology*

The most commonly identified perioperative agents of mast cell-mediated angioedema are antibiotics, neuromuscular blockers (succinylcholine, atracurium and mivacurium), opioids (meperidine and morphine), latex and radiocontrast agents. Edema occurs in variable locations in both mast cell and kinin etiologies; however, the extremities and face are most consistently involved, placing the airway at risk. Urticaria, pruritus and flushing are characteristic of a mast cell process.

Kinin-related etiologies include those mediated by hereditary and acquired causes, as well as angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers. The most common precipitators of HAE and AAE attack are minor trauma and emotional upset. Regardless of HAE and AAE subtypes, all result in deficient or dysfunctional C1-INH, a protease inhibitor that inhibits kallikrein. Kallikrein activates bradykinin, which causes vasodilation and vascular permeability. AAE onset is in the fourth decade of life or later, and without genetic history.

### *Perioperative therapy*

C1-INH replacement is generally accepted as the first-line rescue treatment for HAE and AAE (refer Table 1 for complete summary). Three C1-INH products are commercially available in the United States: Ruconest®, Berinert® and Cinryze®. Ruconest® is indicated for the treatment of acute HAE attacks in adults and adolescents; use is not established for prophylaxis or for the treatment of laryngeal attacks.<sup>3</sup> Berinert® is indicated for the treatment of laryngeal HAE attacks in adult and pediatric patients, but prophylactic use is not widely established.<sup>4</sup> In contrast, Cinryze® is approved for prophylaxis in adolescent and adult patients with HAE.<sup>5</sup> All the three products carry the risk of hypersensitivity reactions and venous thromboembolic events.

All surgical or anesthetic interventions with mechanical impact to the upper aerodigestive tract should receive C1-INH prophylaxis 1–6 h prior to the procedure.<sup>2,9–12</sup> Dosing depends on the manufacturer. The dose may be repeated in more complex surgeries, those of extended duration and those with significant blood loss.<sup>12</sup> At least one dose of C1-INH (Berinert®) should be available for rescue.

Androgens and FFP may be utilized as prophylaxis independently, or in conjunction with C1-INH. Androgens promote hepatic C1-INH synthesis. Published recommended therapeutic durations vary from 4–7 days preoperatively through 3–5 days post-operatively. Dosing ranges from 4 mg of danazol every 6 h<sup>2</sup> to 200 mg every 8 h<sup>9</sup> with or without the addition of prophylactic C1-INH administration.<sup>8,11</sup> FFP is described most consistently as a rescue agent and as third-line prophylactic agent after androgens. A volume of 10 mL/kg or 2–4 units should be administered 1–6 h preoperatively.<sup>1,9,10</sup> Though FFP replenishes C1-INH, it can theoretically worsen an attack by replacing depleted complement factors. Cardiac function should be assessed as FFP administration contributes to intravascular volume.

Icatibant, a bradykinin B2 receptor antagonist and ecallantide, a plasma kallikrein inhibitor, provide effective rescue treatment for angioedema (30 mg subcutaneously 30 min preoperatively).<sup>6,7,9,10,12,13</sup> The use of icatibant for prophylaxis is based on limited evidence.<sup>12</sup> Icatibant and ecallantide may not be widely available in the acute care setting, so other modalities should be relied upon.

## Conclusion

This case presents a concise suggestion of the treatment modalities available in the perioperative management of HAE and AAE. Prophylaxis and rescue depend on availability of therapies, presence of preoperative angioedema, procedural risk and degree of airway manipulation. Preoperatively and emergently, a patient should receive C1-INH. Danazol and FFP are alternative options. In the absence of C1-INH, FFP should be immediately available for emergent events. In our case, due to C1-INH cost, and the patient's good preoperative control of edema, he

**Table 1.** Therapeutic options for HAE and AAE.

Product	Mechanism	Indication	Dose	Special instructions
Ruconest® (C1 esterase inhibitor (recombinant)) <sup>3</sup>	Increases C1-INH activity	Treatment of acute HAE and AAE attacks (without laryngeal edema) in adults and adolescents (not approved in pediatrics)	<84 kg: 50 units/kg slow IV injection over 5 min ≥84 kg: 4200 units slow IV injection over 5 min	If symptoms persist, a second dose can be administered within a 24-h period Risk of VTE and hypersensitivity reactions
Berinert® (C1 esterase inhibitor (human)) <sup>4</sup>	Increases C1-INH activity	Prophylaxis and treatment of HAE and AAE attacks in adult and pediatric patients	20 IU/kg IV at 4 mL/min	Reconstituted product is 50 IU/mL Must be given in a dedicated line Use silicone-free syringe Risk of VTE and hypersensitivity reactions
Cinryze® (C1 esterase inhibitor (human)) <sup>5</sup>	Increases C1-INH activity	Short and long term prophylaxis against HAE and AAE attacks in adults and adolescents	Short term 10–20 units/kg IV or 1000 units IV Long term: 1000 units IV over 10 min every 3–4 days	Use silicone-free syringe Risk of VTE and hypersensitivity reactions
Kalbitor® (ecallantide) <sup>6</sup>	Kallikrein inhibitor	Treatment of acute HAE and AAE attacks in patients 12 years and older	30 mg SQ in three separate 10-mg injections	An additional dose of 30 mg may be administered within a 24 hour period
Firazyr® (icatibant) <sup>7</sup>	Bradykinin receptor antagonist	Treatment of acute HAE attacks in adults 18 years and older	30 mg SQ	Additional injections of 30 mg may be given every 6 h up to three doses in 24 h
Danazol <sup>8</sup>	Androgen analog; promotes synthesis of C1-INH	Short or long term prophylaxis against HAE or AAE attacks	Dosing strategies differ; 4 mg orally four times daily 5–7 days before procedure and 200 mg orally three times daily for 5 days before through 3 days after procedure Maintenance dose for HAE is 100–200 mg orally 2–4 times daily	Contraindicated in pregnancy (female virilization) Chronic use: risk of hepatic adenocarcinoma (>10 years of 100 mg daily)
FFP <sup>1,9,10</sup>	Blood product; replenishes C1-INH	Short term prophylaxis against HAE or AAE attacks	2–4 units (adult dose) IV 1–6 h preoperatively	Theoretically can worsen an acute attack by replacing depleted complement factors Infused volumes may not be tolerated

HAE: hereditary angioedema; AAE: acquired angioedema; FFP: fresh frozen plasma; C1-INH: C1-inhibitor; IV: intravenous; VTE: venous thromboembolism.

received two units of FFP prior to the surgical procedure. C1-INH was made available for rescue, and given the patient's history of mastocytosis, he was treated with pre-operative steroids and diphenhydramine. The presumptive diagnosis of mastocytosis was made, given the nature of the GIST, without time for formal tests including, but not limited to, elevated tryptase, bone-marrow biopsy or c-kit mutation.<sup>14</sup> To avoid opioids, a multimodal pain management strategy that relied on regional anesthesia was utilized. Despite avoiding opioids for presumptive mastocytosis, an opioid-limiting strategy improves enhanced recovery after surgery (ERAS) and decreases opioid-induced hyperalgesia (OIH).<sup>15</sup> Thorough planning with a multidisciplinary team of anesthesia providers,

pharmacists and allergists will allow optimal outcomes in the perioperative period.

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### Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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## Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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