



:: Non histamine-induced angioedema



- This document is a translation of the French recommendations drafted by Dr. Laurence Bouillet, reviewed and published by Orphanet in 2009.
- Some of the procedures mentioned, particularly drug treatments, may not be validated in the country where you practice.

Synonyms:

bradykinine-induced angioedema, angioneurotic edema, non-allergic angioedema, hereditary angioedema, bradykinic angioedema

Definition:

Defined non-pruritic, non-inflammatory, subcutaneous or submucosal edema that recurs more or less frequently and disappears without residual effects. It is not histamine induced: it **does not respond to corticosteroids and prophylactic anti-histamines are ineffective**. Its main mediator is bradykinin. It may be hereditary or acquired. **Involvement is the main cause of death** (25% of death in the absence of suitable treatment). The edema can involve the **digestive tract**; it presents **sub-obstructive symptoms with a risk of hypotension**.

Further information:

[See the Orphanet abstract](#)

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Pre-hospital emergency care recommendations

Call for a patient suffering from non histamine-induced angioedema

Synonyms

- ▶ angioneurotic edema, hereditary angioedema, bradykinic angioedema

Aetiology

- ▶ Types I and II hereditary angioedema: congenital deficit in C1 Inhibitor
- ▶ Type III hereditary angioedema: increased function of Hageman factor
- ▶ Acquired angioedema: acquired C1 Inhibitor deficiency (may or may not be associated with C1Inh or C1q antibodies)

All these angioedemas are sub-cutaneous or sub-mucosal, non-pruritic, recurring, disappear without residual effects and are mediated by bradykinin not histamine



Special risks in an emergency

- ▶ Laryngeal edema (25% mortality rate if untreated)
- ▶ Facial edema
- ▶ Digestive tract edema: pseudo-obstructive syndrome

Frequently used long term treatments

- ▶ Baseline treatment: danazol or tranexamic acid
- ▶ Prophylaxis during dental treatment or surgical interventions: danazol which increases C1Inh

Complications

-  - facial edema can be complicated by laryngeal edema
-  - digestive tract edema simulates a surgical condition (obstructive syndrome) and can lead to pain, ascites or hypovolaemia and sometimes a state of shock

Specific medical care prior to hospitalisation

- ▶ symptomatic treatment of dyspnea, hypovolaemia, pain and vomiting (abdominal forms)
- ▶ anti-histamines and corticosteroids are ineffective
- ▶ two treatment options
 - Concentrated C1Inh (BERINERT®): slow injection IV over at least 5 minutes of 500 U (if <20 kg) or 1,000 U (if >20 kg, to be given in two doses with an interval of at least 5 minutes)
 - Icatibant (FIRAZYR®), bradykinin receptor inhibitor): sub-cutaneous injection of 30 mg AR if needed 6 hours later
- ▶ failing that: tranexamic acid 1 g every 4 - 6 hours in adults and 10 mg/kg every 6 hours in infants
- ▶ admission to intensive care

Recommendations for hospital emergency departments

Emergency issues and recommendations

- ▶ Laryngeal edema
- ▶ Facial edema
- ▶ Severe abdominal crises

1. Laryngeal crisis:

▶ Emergency diagnostic measures:

- Evaluate the severity:
 - Any **laryngeal involvement** (dysphagia, weak or inaudible voice, dyspnea)

▶ Emergency therapeutic measures:

Therapeutic measures based on **concentrated C1Inh** (Bérinert[®], Behring) **or icatibant** (Firazyr[®], Jerini-Shire) should be administered **as soon as possible**.

- **Hospitalise immediately in an intensive care unit and contact a doctor providing specialised management.**
- **Do not use corticosteroids or anti-histamines** which are ineffective in this condition.
- **Check that the airways are clear using assisted ventilation and oxygen therapy**, if needed.
- Where possible, install an **IV catheter**.
- Start treatment **immediately** by **injecting icatibant** (30 mg **sub-cutaneously except in infants and pregnant women**) **or concentrated C1Inh by IV as soon as emergency teams arrive** if the patient has the product at home or if it is carried in the ambulance:

C1Inh:

- Time to act: 30 minutes
- Administration: IV over 5 minutes in the giving set
- Dose if weight > 20 kg: 1,000 U
- Dose if weight < 20 kg: 500 U, whatever the weight
- Repeat after 1 hour if effect insufficient

Icatibant:

- Time to act: 40 - 60 min
- Administration: Sub-cutaneous injection
- Dose rate: 30 mg
- Repeat after 6 hours if effect insufficient

- **Continue to manage in the intensive care unit**, following the advice of the doctor who usually manages the case

2. Facial edema:

Every patient with **facial edema has the potential to develop laryngeal edema**

▶ **Emergency therapeutic measures:**

- **Hospitalisation** for surveillance
- **Administration of tranexamic acid orally or IV in the absence of any contra-indication** to this product at a dose of 1 g every 4 - 6 hours in adults and 10 mg/kg/injection every 6 hours in children
- **If the symptoms worsen**, IV injection of **concentrated C1Inh or sub-cutaneous icatibant**.

3. **Abdominal crisis:**

▶ **Emergency diagnostic measures:**

- Evaluate the severity:
 - All **pseudo-obstructive differential diagnoses** with pain, ascites, hypovolaemia
- Emergency investigations:
 - **Abdominal ultrasound or scan if severe abdominal crisis present** in order to eliminate differential diagnoses

▶ **Emergency therapeutic measures:**

- Implement **pain evaluation using the routine protocols**
- Start **analgesic treatment and symptomatic treatment of vomiting**
- **IV injection of tranexamic acid, in the absence of any contra-indication** to this product (**nursing mother, thrombo-embolic conditions**), at a dose of 1 g every 4 - 6 hours in adults and 10 mg/kg/injection every 6 hours in children
- **In the event of a failure or a case that is painful from the beginning**, start a substitute treatment using IV concentrated C1Inh (slow IV or in the perfusion, 500 U if <20 kg, 1,000 U if >20 kg) or **sub-cutaneous icatibant** (30 mg)
- **If the treatment has not produced its effects within 30 - 90 minutes, consider another diagnosis** (e.g.: possibility of a surgical obstruction)
- Plan for **hospital based surveillance until the signs have improved**

Orientation

- ▶ Where: **any hospital with an intensive care unit, with available icatibant or concentrated C1Inh, if the patient does not have any at home, and doctors capable of performing a tracheotomy.**
- ▶ When: **rapid access** when possible with a **mobile emergency doctor service.**
- ▶ How: transporting the patient in a mobile emergency doctor service allows early administration of the appropriate drug.

Drug interactions

- ▶ No drug interactions with Béринert® or Firazyr®

Anesthesia

Major risk of laryngeal edema if intra-tracheal intubation

- ▶ **If emergency: Concentrated C1Inh (Béринert®) 1,000 U by slow IV, 1 hour in advance;** the administration **may be repeated if necessary** in the hours following the procedure.
NB: It is possible to perform intra-tracheal intubation first then to start a C1Inh perfusion.
- ▶ If not an emergency: pre-medicate patient with danazol 600 mg/day for 10 days in adults (10 mg/kg in children). The C1Inh level should be checked on the 7th day and must have reached at least 50% of the reference target level. **Concentrated C1Inh must be available where the intervention occurs.** After anesthetic, danazol 600 mg/day is continued for 5 days in adults (10 mg/kg in children) then return to the normal individual treatment.
- ▶ **Special case of parturition:** an **epidural** is recommended

- **If the patient has had few crises during pregnancy**, there is no need for any prophylactic treatment but **Bérinert® must be rapidly available in the labour room.**
- If the patient has had many crises during pregnancy, administration of Bérinert® 1,000 U at the start of labour, monitoring in hospital for one week.

Preventive measures

- ▶ Prophylactic measures for dental treatment or any intervention

Additional therapeutic measures and hospitalisation

- ▶ **Nutrition:** in case of a crisis with abdominal pain, nausea or vomiting, nutrition should be light or even reduced to just drinks.
- ▶ **Supporting the family:** information and awareness of the screening tests (for hereditary angioedemas) should be provided to the family along with the address of an expert centre that both patient and family can consult.

Organ donation



- C1Inh is mainly synthesised by the liver; **organ donation is therefore possible except for the liver.**

Phone numbers in case of Emergency

- ▶ Jerini/Shire phone numbers for Firazyr®:
 - to order +800 3472997-0 (international freephone number),
 - for Medical Information +800 7020 7020 (international freephone number), +44 1256 89 49 00 (UK, charged national phonenummer), +44 1429 7770 (IR, charged national phonenummer)

Documentary resources

- ▶ Gompels MM, Lock RJ, Abinun M, Bethune CA, Davies G, Grattan C, et al. C1inhibitor deficiency: consensus document. Clin Exp Immunol 2005; 139:379-94
- ▶ Bowen T, Cicardi M, Farkas H, Bork K, Kreuz W, Zingale L, et al. Canadian 2003 international consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. J Allergy Clin Immunol 2004; 114: 629-37

These guidelines have been prepared in collaboration with Dr. Laurence Bouillet of the Centre national de Référence des Angio-œdèmes à kinines (CREAK) and the Association des Malades Souffrant d'Angioedèmes (AMSAO) and Dr Gilles Bagou - SAMU-69, Lyon

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