HEREDITARY ANGIOEDEMA DUE TO C1-INHIBITOR DEFICIENCY

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• Hospital Universitario La Paz
• GARGNANO, 1\textsuperscript{st} October 2012
Conflict of interests

- Speaker fees from Shire HGT, Inc./Jerini AG and ViroPharma
- Consultancy fees from Shire HGT, Inc./Jerini AG, ViroPharma and CSL Behring
- Funding for travel and meeting attendance from CSL Behring and Shire HGT, Inc.
- Investigator in clinical trials for Dyax, Pharming, CSL Behring and Shire HGT, Inc./Jerini AG
## CONSENSUS TABLE ON ANGIOEDEMA WITHOUT WHEALS

<table>
<thead>
<tr>
<th>Temporary Name of Angioedema</th>
<th>Name of Angioedema</th>
<th>Clinical Diagnosis</th>
<th>Laboratory Diagnosis</th>
<th>Therapeutic approach</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown origin responsive to anti-histamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-inhibitor related</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sporadic with normal C1 inhibitor non-responsive to anti-histamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With sporadic/acquired C1 inhibitor deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary with C1 inhibitor deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary with normal C1 inhibitor</td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>
Grade Working Group.

Systematic literature review.

Strength of recommendations:
• Benefits—harms balance
• Quality of evidence
• Translation of evidence into specific circumstances
• Certainty of baseline risks
• Resource utilization
• Speak same language

• Definitions:
  – Nomenclature:
    • Edema vs angioedema
  – Angioedema (AE)
  – Acute, recurrent, crhonic
  – Sporadic
  – Isolated AE
  – Hereditary
  – Acquired
Grade of evidence

• A  Randomized, double-blind clinical trial of high quality (for example, sample-size calculation, flow chart of patient inclusion, intention-to-treat analysis, sufficient sample size)

• B  Randomized clinical trial of lesser quality (for example, only single-blind, limited sample size: at least 15 patients per study arm)

• C  Comparative trial with severe methodological limitations (for example, not blinded, very small sample size, no randomization) or large retrospective observational studies.

• D  Adapted from existing consensus document or statement based on expert opinion voting during consensus conference
### AE WITHOUT WHEALS. CHARACTERISTICS (I)

<table>
<thead>
<tr>
<th></th>
<th>Histaminergic</th>
<th>Bradykinergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Association to urticaria</td>
<td>YES</td>
<td>NO*</td>
</tr>
<tr>
<td>Erythema</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Pruritus</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Acute treatment: answer to adequate doses of antiH1, corticosteroids, adrenaline</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Maintenance treatment: answer to antiH1, corticosteroids</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

*Be aware marginatum erythema is not urticaria*
<table>
<thead>
<tr>
<th>Acute treatment</th>
<th>HISTAMINER GIC</th>
<th>BRADYKINER GIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Answer to adequate doses of antiH1, corticosteroids, adrenaline</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Answer to C1-INH replacement</td>
<td>NO</td>
<td>Variable</td>
</tr>
<tr>
<td>Answer to bradykinin B2 receptor blocker (icatibant acetate)</td>
<td>NO</td>
<td>Possible</td>
</tr>
<tr>
<td>Answer to kallikrein inhibition other than C1-INH (ecallantide)</td>
<td>YES</td>
<td>Possible</td>
</tr>
</tbody>
</table>
## AE WITHOUT WHEALS. CHARACTERISTICS (III)

<table>
<thead>
<tr>
<th>Maintenance treatment (long term prophylaxis, routine prophylaxis)</th>
<th>HISTAMINER GIC</th>
<th>BRADYKINER GIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Answer to antihistamines, corticosteroids</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Answer to ciclosporine</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Answer to omalizumab</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Answer to tranexamic acid</td>
<td>?</td>
<td>YES</td>
</tr>
</tbody>
</table>
ANGIOEDEMA WITHOUT WHEALS. CLASSIFICATION (some pending issues).

- Classification regarding mediator: Is it enough to classify angioedema into histaminergic and bradykinergic?
- What are the evidences for classifying angioedema into bradykinergic and histaminergic according to the previously described clinical characteristics?
- Response to treatment (definition):
  - Drug
  - Dosis
  - Time to response
# Consensus on Bradykinin Induced Angioedema

## Table

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>HAE-C1-INH</strong></td>
<td>HAE-C1-INH***</td>
<td>BK AE</td>
<td>HAE-C1-INH</td>
<td>HAE-C1-INH</td>
<td>HAE-C1-INH</td>
<td>HAE-C1-INH</td>
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<tr>
<td><strong>HAE type III</strong></td>
<td>AAE-C1-INH***</td>
<td></td>
<td>AAE-C1-INH</td>
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<td>Females</td>
<td>HAE type III</td>
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<td>ACEi AE</td>
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<td><strong>consensus</strong></td>
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</tbody>
</table>

**Notes:**
- HAE-C1-INH: Hypocomplementemic angioedema-C1-inhibitor deficiency
- HAE type III: Hereditary angioedema type III
- BK AE: Bradykinin angioedema
- AAE-C1-INH: Acquired angioedema—C1-inhibitor deficiency
- ACEi AE: ACE inhibitor angioedema
- Females: Only applicable to females

**References:**
- Bowen 2004 / 2008 / 2010
- Gompels 2005
- Geab 2011
- Hawk 2012
- Caballe RO 2012
- Wao (Craig)

**Evidence:**
- Evidence based

**Grade System:**
- Guidelines (WAO Journal)

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**Clarification:**
- The table outlines the consensus reviews and guidelines on Bradykinin Induced Angioedema from various studies and journals, focusing on the genetic and clinical characteristics, treatment options, and evidence-based approach for managing the condition.
DIAGNOSIS
Diagnosis HAE-C1-INH types I, II

- Underdiagnosed
  - Delay in diagnosis:
    - SPAIN (Roche 2005 Ann Allergy Asthma Immunol):
      - Mean 13.1± 15.2 years (Roche 2005 Ann Allergy Asthma Immunol)(range -?65)
    - DENMARK (Bygum 2009 Br J Dermatol):
      - Mean 16.3 years (range 0-63)*
*In nine relatives was established before the onset of clinical symptoms (calculated as a diagnostic latency of 0).
Diagnosis HAE-C1-INH types I, II

Clinical suspicion:
- Recurrent angioedema without urticaria
- Non pruritic, non erythematous
- Recurrent abdominal pain
- Upper airways edema
- Positive family history (more than 25% de novo mutation)
- Unresponsive to antihistamines, corticosteroids and adrenaline
- Attack lasting more than 48 hours
Diagnosis HAE-C1-INH types I, II

- **Laboratory diagnosis:**
  - **C4 ↓**
    - Normal C4 intercrisis (<2%)
  - **Low functional C1 inhibitor (<50%)**
    - Decreased antigenic C1 inhibitor: type I
    - Normal antigenic C1 inhibitor: type II
  - At least two measurements with 1-3 months interval.
Diagnosis HAE-C1-INH types I, II

- Blood C4 ↓ + C1 inhibitor (levels/function) ↓:
  - Specificity 98-100%
  - Negative predictive value 96%

Note: partial C4 deficiency is frequent!!
Diagnosis HAE-C1-INH types I, II

Genetic diagnosis:

- **C1INH gene:**
  - High cost
  - Reserve for doubtful cases
    - De novo mutation
    - Sporadic cases
    - Differential diagnosis with AAE-C1-INH
  - Necessary for:
    - Preimplantational genetic diagnosis
    - Prenatal diagnosis

- Other genes ???
Diagnosis HAE-C1-INH types I, II

- **Family screening:**
  - **C4 (compulsory):**
    - Low cost
    - In all the relatives, even asymptomatic
    - Aims:
      - to increase detection of cases
      - to inform patients of possible risks
  - **Ag C1INH, function C1INH (advisable)**
  - **Genetic tests (doubtful cases)**
Recurrent angioedema without urticaria and/or recurrent colicky abdominal pain and/or recurrent larynx oedema and/or family history of angioedema

C4 N

If clinical symptoms are highly suspicious apply for:
C1INH c, C1INH f, C1q

If all values are normal, repeat during an acute episode

If all values are normal, even in an acute episode

AE episodes related with estrogens + family history

YES

HAE with normal C1INH (also known as HAE type III)

F12 gene mutation

YES

HAE-FXII

NO

NO

Other ethiologies: NSAID, idiopathic,...

Other ethiologies: NSAID, idiopathic,...

ACEi induced AE

ACEi induced AE

HAE-C1INH type I*

HAE-C1INH type II*

Without family history

AEA-C1INH#

✓ Consider concomitant pathology (autoimmune diseases, lymphoproliferative diseases, etc)

✓ Apply for anti-C1INH antibodies

If family history is absent confirm with genetic study

# The possibility of acquired angioedema with C1INH deficiency and normal C1q should be considered

$ Also known as HAE with normal C1INH or HAE type III of unknown origin
RECOMENDATIONS

Suspect hereditary angioedema with C1-INH deficiency when:
• Isolated angioedema without wheals
• Recurrent angioedema
• Non-erythematous angioedema
• Non-pruriginous angioedema
• Laryngeal edema
• Abdominal edema
• Family antecedents
• Onset of symptoms on 1st – 2nd decade
• Prodromal symptoms such as erythema marginatum
• Absence of improvement of acute attacks after treatment with high doses of antihistamines, corticosteroids and adrenaline
• Good response of acute attacks to treatment with human plasma C1 inhibitor concentrate, ecallantide, icatibant acetate, recombinant human C1 inhibitor
• Maintenance treatment: No improvement after chronic treatment with antihistamines (4x dose), short course of corticosteroids (define dose and days)

Quality of evidence (evidence grade): D

Supporting references:
• Consensus documents (Bowen 2004, 2008, 2010; Gompels 2005; Caballero 2011)
• Case series

Cost: low Setting: any Strength of recommendation: High
RECOMENDATIONS

C4 should be used for routine screening of hereditary C1 inhibitor deficiency in patients with recurrent, acute, non-erytematous, non pruriginous angioedema.

Quality of evidence (evidence grade): C

Supporting references:

Cost: low

Technique availability: high

Strength of recomendation: High
RECOMENDATIONS

Serum antigenic C1-INH levels and plasma functional C1-INH should be used for confirmation of hereditary C1 inhibitor deficiency in patients with recurrent acute non-erytematous, non pruriginous angioedema and low serum C4 levels.

Quality of evidence (evidence grade): C

Supporting references: cases series, consensus

Cost: medium

Technique availability: medium

Strength of recomendation: High
RECOMENDATIONS

C1q should be used for differential diagnosis between hereditary and acquired C1 inhibitor deficiency in patients with recurrent acute non-erytematous, non pruriginous angioedema, low serum C4 level and low plasma C1 inhibitor function.

Quality of evidence (evidence grade): C

Supporting references: cases series

Cost: medium

Technique availability: High

Strength of recomendation: High
RECOMENDATIONS

Reconsider acquired or hereditary angioedema with C1-INH deficiency diagnosis in patients with low C1-inhibitor function, normal antigenic C1-INH and normal C4 (moreover if C4 is not in the lower normal range).

Quality of evidence (evidence grade): D

Supporting references: expert experience

Cost: low

Strength of recomendation: High
RECOMENDATIONS

All relatives of patients with AE-C1-INH should be screened at least with anamnesis and C4 levels, independently of having presented or not angioedema

Quality of evidence (evidence grade): D

Supporting references: expert experience, case series

Cost: low

Strength of recommendation: High
TREATMENT
HAE-C1-INH. TREATMENT

- Secondary prevention
- Acute treatment
- Short term prophylaxis
- Long term prophylaxis
SHORT TERM PROPHYLAXIS

SINONIMOUS: PREPROCEDURE PROPHYLAXIS TREATMENT

Are the two terms interchangeable?

Definition: treatment given before a medical or surgical procedure to avoid the development of an angioedema attack

It should include:
- before and during stressful situations (exams, wedding, …)
- trips
- multiple trauma
- other
SHORT TERM PROPHYLAXIS

INDICATIONS

✓ Dental major procedures

✓ Endoscopies, bronchoscopies,…

✓ Surgical intervention which need orotracheal intubation

✓ Any surgical intervention to avoid edema can alter surgical window and can compromise surgical results

✓ Gynecological-obstetric procedures
# SHORT TERM PROPHYLAXIS

## C1-INHIBITOR
- **✓ 1000 U iv, 1-6 hours before procedure**
- **Up to 24 hours before procedure (Cinryze®)**
- **Election treatment**

## ATTENUATED ANDROGENS
- **✓ Estanozolol 4-6mg/day vo 5 days prior and 3 days after the procedure**
  (divided into 2 - 3 dosis)
- **✓ Danazol 400-600mg/día vo 5 days prior and 2 days after the procedure**
  (divided into 2 - 3 dosis)

## Fresh frozen plasma
- **✓ 2U 1 hour before procedure**

## TRANEXAMIC ACID
- **✓ 75 mg/kg/day vo divided into 2-3 dosis 5 days before and 2 days after procedure**

## ISOLATED CASES
- **✓ Icatibant (thyroid biopsy)**
- **✓ Ecallantide**

Cinryze (nfC1INH) unique drug with this indication on label in EU
No comparison studies among the different drugs
# SHORT TERM PROPHYLAXIS

## C1-inhibitor concentrate

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence for efficacy (case series, case reports, open clinical trial)</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Good theoretical rationale for use</td>
<td>Lack of availability in some countries</td>
</tr>
<tr>
<td>Well tolerated</td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td>Unknown dose (fix vs weight based)</td>
</tr>
</tbody>
</table>
## SHORT TERM PROPHYLAXIS

### Attenuated androgens

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Need to start several days prior to procedure</td>
</tr>
<tr>
<td>Low cost</td>
<td>Lower efficacy than C1 inhibitor (expert opinion)</td>
</tr>
<tr>
<td>Availability</td>
<td>Unknown side effect in STP use</td>
</tr>
<tr>
<td></td>
<td>Unavailable in some countries</td>
</tr>
</tbody>
</table>
LONG TERM PROPHYLAXIS

SINONIMOUS: MAINTENANCE TREATMENT, ROUTINE PROPHYLAXIS

Are the three terms interchangeable?

Definition: chronic treatment given to diminish frequency, severity and duration of angioedema attacks

LTP OUTCOME:
• Which is the aim?
  • Nr attacks?
  • Maximum Nr attacks / year?
  • No severe attacks?
  • No incapacity?
  • Increase in HRQoL

Cicardi JACI 1997: 1-2 mild attacks per year
LONG TERM PROPHYLAXIS

**INDICATIONS** (Craig 2009, Bowen 2010, Caballero JIACI 2011b, Cicardi 2012)

- Frequency (more than one attack per month, more than 24 days per year)

- Location: Upper airway attacks, abdominal attacks that alter daily life, cervicofacial attacks

- Special situations:
  - Rapid progression attacks
  - No control with on demand acute treatment
  - High use of health resources (> 3 ER visits/year, > 1 hospitalizations/year, ICU admittance, orotracheal intubation)
LONG TERM PROPHYLAXIS

INDICATIONS (Craig 2009, Bowen 2010, Caballero JIACI 2011b, Cicardi 2012)

✓ Inadequate access to health care resources

✓ High burden of disease:
  ✓ >10 days lost on work or studies
  ✓ High impact in family life or free time
  ✓ Incapacity more than 5 days a month
  ✓ Alteration of HRQoL
LONG TERM PROPHYLAXIS

1. **ATTENUATED ANDROGENS:**
   - stanozolol (*Winstrol®*)
   - danazol (*Danatrol®*)
   - oxandrolone
   - tibolone

2. **ANTIFIBRINOLITYCS:**
   - Tranexamic acid (*Amchafibrin®*)
   - Epsilon amino caproic acid (*Caproamin®*) *(Frank 1972)*

3. **PLASMA DERIVED C1-INHIBITOR** (*Berinert®, Cinryze®*)
   - Cinryze® *(Zuraw NEJM 2010)*
   - Berinert® *(case series)*

4. **NADROPARIN** *(Majluf-Cruz 2011)*
<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Journal</th>
<th>Drug class</th>
<th>Drug</th>
<th>Controls</th>
<th>N° included patients</th>
<th>cross-over design</th>
<th>p &lt;0.05</th>
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<tr>
<td>Frank</td>
<td>1972</td>
<td>NEJM</td>
<td>AFs</td>
<td>aminocaproic</td>
<td>placebo</td>
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<td>AFs</td>
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<td>NEJM</td>
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<tr>
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<td>1977</td>
<td>Ann Int Med</td>
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<td>methyltest</td>
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<td>JACI</td>
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<td>Waites</td>
<td>1996</td>
<td>NEJM</td>
<td>c1 inhibitor</td>
<td>vapo-heated c1 inhibitor</td>
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<td>Zuraw</td>
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<td>NEJM</td>
<td>c1 inhibitor</td>
<td>C1inhibitor</td>
<td>placebo</td>
<td>22</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>
Long term prophylaxis: attenuated androgens

- stanozolol, danazol, oxandrolone.

- ↑ C1-esterase by increasing hepatic synthesis.
  - ↑ mRNA C1-inhibitor in hepatocytes

- Minimal efficacious dose.
Attenuated androgens: side effects

- amenorrhea, menstrual alterations
- hirsutism
- libido decrease
- weight gain
- lipoprotein alterations
- Depression
- Increase in hepatic enzymes
- hepatic adenoma
- hepatic carcinoma
- teratogenicity
Long term prophylaxis: antifibrinolytic agents

- EACA, tranexamic acid
- Inhibit plasmin activation

- Indications:
  - children
  - Pregnancy
Antifibrinolytic agents: side effects

- muscular cramps
- weakness
- fatigue
- sedation
- orthostatic hypotension
- vascular thrombosis
LONG term prophylaxis
C1-INH concentrate

ADVANTAGES
• Effective
• Few adverse events
• Long term availability in market in EU without major events

DISADVANTAGES
• No dosing studies
• No dosis interval studies
• Human plasma product
• Breakthrough attacks occur despite 1000 units twice a week
• Intravenous
• Expensive
OTHER ACTIONS

✓ AVOID ESTROGENS (Case series)

✓ AVOID ACE INHIBITORS (Case series)

✓ Hepatitis B vaccination

✓ Pharmacological treatment of concomitant infections

✓ If recurrent abdominal attacks → discard *Helicobacter pylori* infection (Farkas Lancet 2001)
SPECIAL ISSUES

• Specific groups:
  – Children
  – Female patients (mainly pregnancy)

• Home treatment availability (acute tx)

• Self-treatment:
  – Acute tx
  – Long term prophylaxis:
    • Oral
    • Sc
    • Intravenous
THANKS FOR YOUR ATTENTION