Practical Management of C1 Inhibitor Deficiency

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Servicio de Dermatología, Hospital Universitario de La Princesa, Madrid, Spain

Abstract. C1 inhibitor deficiency is a rare syndrome clinically characterized by recurrent episodes of swelling of subcutaneous tissue or angioedema. It can involve the skin, upper respiratory airways and abdomen. There are two main types: hereditary and acquired. Angioedema can involve practically any part of the cutaneous surface, it can cause lethal laryngeal edema and can present as gastrointestinal obstruction. The attacks can be triggered, in general, by trauma, drugs or infections. Diagnosis is confirmed by decreased serum levels of C4 and absence or marked decrease of the level or function of C1 inhibitor. Commonly employed drugs for prophylaxis and treatment of these patients include anabolic steroids, antifibrinolytic agents, and infusion of C1 inhibitor concentrate. Fresh frozen plasma is an option to be considered for short term prophylaxis or treatment of the acute attack. It is convenient to know this syndrome as it is a potentially life-threatening disease. Diagnosis of this rare syndrome is based on clinical features and characteristic alterations of laboratory tests. The acute attack should be treated as quickly as possible. Prophylactic therapy is indicated in certain circumstances (dental procedures, oral surgery).

Key words: angioedema, C1 inhibitor deficiency, androgens, antifibrinolytics.

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occurring only in women, and related to pregnancy or hormone therapy in the majority of cases. This variant is possibly linked to the X chromosome as it has only been observed in women. C1 inhibitor is an enzyme characterized by being the principal regulator of the early activation steps of the classical complement pathway, and of the activation of kallikrein, of plasmin in the fibrinolytic system, of factor XI in the coagulation cascade, and of factor XIIa. In the absence of C1 inhibitor, the classical complement pathway may be activated inappropriately or excessively. The result is an increase in vascular permeability with uncontrolled massive local edema, which causes the specific symptoms of this syndrome. The evidence levels used throughout this article are shown in Table 2.

### Diagnosis

The approach to the 2 main types of angioedema (hereditary and acquired) is similar. An algorithm for the diagnosis of C1 inhibitor deficiency is presented in Figure 1.

<table>
<thead>
<tr>
<th>Variant</th>
<th>Subtype</th>
<th>Frequency (%)</th>
<th>Enzyme Abnormality</th>
<th>Age at Onset</th>
<th>Family History (%)</th>
<th>Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary</td>
<td>Type I</td>
<td>85</td>
<td>Low C1-inh levels in plasma (5-30% of normal values)</td>
<td>Childhood (second decade of life)</td>
<td>+ (50%)</td>
<td>–</td>
</tr>
<tr>
<td>Type II</td>
<td>15</td>
<td>Functional C1-inh deficiency with normal plasma levels</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Estrogen-dependent hereditary angioedema*</td>
<td>Exceptional</td>
<td>Normal C1-inh levels/ function</td>
<td>Normal C4</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Acquired</td>
<td>Type I</td>
<td>5</td>
<td>Increased C1-inh consumption</td>
<td>Adults (fifth decade of life)</td>
<td>–</td>
<td>Lymphoproliferative diseases of B cell origin (monoclonal gammopathy of uncertain significance, chronic lymphocytic leukemia), carcinomas, infections (HIV), autoimmune diseases (arthritis, thyroiditis, glomerulonephritis, inflammatory bowel disease), cold urticaria, lupus erythematosus.</td>
</tr>
<tr>
<td>Type II</td>
<td>5</td>
<td>Anti C1-inh Ab</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

*Entity recently described by Bork et al.4 Abbreviations: HIV, human immunodeficiency virus; C1-inh, C1 inhibitor; Ab, antibody.

### Clinical Aspects

1. Recurrent angioedema (swelling) without urticaria and that is not usually pruriginous. Prodromal erythema (erythema marginatum) has been reported in 25% of cases, and may be confused with urticaria.5,6 Angioedema is not usually painful unless it affects pressure areas or regions in which the subcutaneous cellular tissue is constricted.

2. The swelling usually affects the limbs, face, trunk, gastrointestinal tract, genitourinary region, or upper respiratory tract; however, it can affect any part of the body.

3. The abdominal symptoms can mimic infantile colic, acute appendicitis, or acute abdomen, and include nausea,
vomiting, abdominal pain, and diarrhea after the acute episode.

4. Respiratory symptoms include dysphagia and alterations of the voice as the disorder can affect both the tongue and the pharynx and larynx.

5. On rare occasions, it can cause cerebral edema or pleural effusion or symptoms suggestive of bladder involvement.

6. The age at onset is variable, and patients can present the initial symptoms before 1 year of age; the main symptoms at this age are colic and, rarely, swelling. The attacks increase in severity with puberty. Episodes affecting the larynx usually begin later than other symptoms, though they can occur in childhood.

7. The acute attack of angioedema has been related to multiple triggering factors, but these are not usually identified (Table 3).

8. Acute attacks tend to be prolonged, usually increasing in intensity over the first 24 hours and then resolving over the following 48 to 72 hours. Some attacks can last more than 72 hours as the swelling migrates from one site to another.

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### Table 3. Triggering Factors for Acute Angioedema

<table>
<thead>
<tr>
<th>Triggering Factor</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic</td>
<td>Pollen, dust, food, insect stings</td>
</tr>
<tr>
<td>Drug-related</td>
<td>ACE inhibitors, nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Viral infection</td>
<td>Influenza, rhinovirus</td>
</tr>
<tr>
<td>Trauma</td>
<td>Physical, emotional</td>
</tr>
<tr>
<td>Infections</td>
<td>Bacterial, fungal, viral</td>
</tr>
</tbody>
</table>

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**Figure 1.** Diagnostic algorithm for C1 inhibitor deficiency. Modified from Bowen T, et al. C1-inh indicates C1 inhibitor; ACE, angiotensin converting enzyme.
9. Attacks are usually periodic and normally recur after several weeks of remission. They do not usually occur daily.

Laboratory Tests

1. Laboratory tests should be performed in an accredited laboratory with operating procedures that ensure adequate quality. Determinations should be performed when no treatment is being given, ideally less than 7 days after the previous attack.
2. The measurement of protein C4 in serum is a good screening method for C1 inhibitor deficiency, as it is found to be low in untreated patients (C4 <30% of the normal mean values). If the C4 level is normal, it is not usually necessary to go on to measure C1 inhibitor levels as even if these values are low the diagnosis would be doubtful (evidence level 4). It has been observed that the combination of a low C4 and a decrease in C1 inhibitor function has a specificity of 98% and a negative predictive value of 96% for C1 inhibitor deficiency.
3. The low prevalence of this disease indicates that false positives are common. Measurements obtained before 1 year of age may not be reliable as there is a high prevalence of false positives and negatives. In this case, the measurements should be repeated after 1 year of age.
4. Once the diagnosis is established, determination of C4 levels and C1 inhibitor levels and function is useful for monitoring the response to treatment.
5. The measurement of C1q antigen may be of use in the diagnosis of hereditary angioedema as it is usually low in these cases whereas it is normal in the case of acquired angioedema. The various measurements of complement values for the different types of angioedema are shown in Table 4.
6. As in other disorders with autosomal dominant inheritance, genetic studies reveal de novo mutations in 25%-33% of patients. Genetic study is not necessary to confirm the diagnosis.
7. Study of family members is advisable in cases of hereditary angioedema as it is important to detect asymptomatic children.

The diagnostic criteria for C1 inhibitor deficiency were established in 2004 during the Third C1 Esterase Inhibitor Deficiency Workshop (Table 5).

Table 3. Principal Triggering Factors of an Acute Attack of Angioedema

<table>
<thead>
<tr>
<th>Minor trauma</th>
<th>Dental procedure (&gt; 50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs (evidence level 3)</td>
<td>Estrogens (contraceptives, hormone replacement therapy)</td>
</tr>
<tr>
<td></td>
<td>Angiotensin converting enzyme inhibitors</td>
</tr>
<tr>
<td></td>
<td>Angiotensin II receptor antagonists</td>
</tr>
<tr>
<td></td>
<td>Plasminogen activators</td>
</tr>
<tr>
<td></td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Emotional stress</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>Dental</td>
</tr>
<tr>
<td>Other foci of infection</td>
<td></td>
</tr>
<tr>
<td>Helicobacter pylori (evidence level 3)</td>
<td></td>
</tr>
</tbody>
</table>

Hormonal changes

| Menstruation |
| Pregnancy (evidence level 3) |

Table 4. Measurement of the Complement Fractions in C1 Inhibitor Deficiency.

<table>
<thead>
<tr>
<th>Type of Angioedema</th>
<th>C1q Concentration</th>
<th>C1-inh Concentration</th>
<th>C1-inh Function</th>
<th>C4 Concentration</th>
<th>C3 Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Type I</td>
<td>N</td>
<td>↓</td>
<td>↓</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Type II</td>
<td>N</td>
<td>N/↑</td>
<td>↓</td>
<td>↓</td>
<td>N</td>
</tr>
<tr>
<td>Estrogen-dependent</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Acquired Type I</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>N/↓</td>
<td>N</td>
</tr>
<tr>
<td>Type II</td>
<td>↓</td>
<td>N/↓</td>
<td>↓</td>
<td>↓</td>
<td>N/↓</td>
</tr>
<tr>
<td>Others Related to hormonal changes</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>ACE-inhibitor induced</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Induced by other drugs</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

↓: low value; ↑: raised value. Abbreviations: N, normal; ACE, angiotensin converting enzyme; C1-inh, C1 inhibitor. Modified from Werter et al.
First, primary prevention consists of avoiding the triggering factors of an acute attack of angioedema in so far as is possible. In general, the management of patients with C1 inhibitor deficiency will include long- and short-term prophylaxis and treatment of the acute attack (Table 6). This is a condition that must be kept in mind as, without treatment, mortality can reach 30%-40%, and is due to airway obstruction in the majority of cases.

The adverse effects of the different treatments are shown in Table 7.

**Management**

First, primary prevention consists of avoiding the triggering factors of an acute attack of angioedema in so far as is possible. In general, the management of patients with C1 inhibitor deficiency will include long- and short-term prophylaxis and treatment of the acute attack (Table 6). This is a condition that must be kept in mind as, without treatment, mortality can reach 30%-40%, and is due to airway obstruction in the majority of cases. The adverse effects of the different treatments are shown in Table 7.

### Long-Term Prophylaxis

**Indications:**

1. More than 1 severe episode per month or more than 5 days per month unable to perform usual activities
2. More than 1 episode of severe abdominal pain in a year
3. Occasional episodes of angioedema affecting the head or neck
4. Frequent episodes of peripheral or genital angioedema
5. Need for more than one C1 inhibitor concentrate per year

Attenuated androgens are considered to be the treatment of first choice as, in general, they are more effective than other treatments. If they are ineffective or cause adverse effects, antifibrinolytic agents should be used or, as a last resort, C1 inhibitor concentrates. The antifibrinolytic agents have been shown to be more effective in acquired angioedema than the other treatments available (evidence level 2). Antifibrinolytic agents are contraindicated in active thromboembolic disease.

In childhood patients, the antifibrinolytic agents should be considered to be first choice due to the lower number and severity of adverse effects; if they are not effective, the second choice is C1 inhibitor concentrate. If neither of these works, antiandrogens can be used; these agents are particularly indicated if there is more than 1 abdominal attack per month, though they should be used with caution due to their potential effects on growth.

Combinations of different treatments can be used (for example, fibrinolytic agents with synthetic attenuated androgens), and use of the minimum effective dose is recommended.

The efficacy of attenuated androgens in the treatment of type II acquired angioedema is not clear. Likewise the efficacy of the antifibrinolytic drugs and attenuated androgens in estrogen-dependent hereditary angioedema has not been fully confirmed, although at least 1 patient with such disease has responded to danazol.

There are 2 internationally accepted regimens for the long-term use of danazol for prophylaxis (Table 8).

Hepatitis B virus vaccination is recommended in all patients who frequently receive blood derivatives (C1 inhibitor concentrates or fresh frozen plasma).

### Short-Term Prophylaxis

**Indications for short-term prophylaxis:**

1. Dental procedures
2. Oral surgery
3. Intubation
4. Other procedures, principally those involving areas in which angioedema is clinically manifest

In this situation, C1 inhibitor concentrate is considered to be the first choice treatment and, if this is not available, attenuated androgens or antifibrinolytic agents can be used.
In the case of minor procedures (for example, dental manipulations), a possible course of action if C1 inhibitor concentrate is available is not to give any prophylaxis and to use the treatment only if an acute attack occurs. If C1 inhibitor concentrate is not available, prior prophylaxis with attenuated androgens or antifibrinolytic agents should be given. The use of fresh frozen plasma is accepted, though the possibility of the transmission of viral diseases must always be taken into account. Caution should be observed in the case of dental procedures as attacks can occur up to 36 hours later.

In the case of major procedures or intubation, prophylaxis should be given from the outset, using

### Table 6. Summary of the Therapeutic Management of Patients With C1 Inhibitor Deficiency

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Treatment</th>
<th>Dose (adult)</th>
<th>Dose (child)</th>
<th>Monitoring Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-Term Prophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic attenuated androgens (evidence level 2/3)</td>
<td>Oral danazol (see Table 8)</td>
<td>Oral danazol 100-200 mg/ 24-72 h (only if specifically indicated)</td>
<td>Biannual: blood test with liver function&lt;sup&gt;a&lt;/sup&gt; Annual: lipid profile, PSA, rectal examination Biannual: Liver ultrasound (annual after 10 y of treatment). Evidence level 4&lt;sup&gt;b1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Antifibrinolytic agents (evidence level 2&lt;sup&gt;b2&lt;/sup&gt;)</td>
<td>Oral tranexamic acid In general: 25-75 mg/kg/d. Divide daily dose into 2-3 doses Initial: 1-1.5 g/8-12 h Maintenance: 0.5 g/12-24 h</td>
<td>Oral tranexamic acid In general: 50 mg/kg/ 24-72 h Regimen: 1-2 g/24 h</td>
<td>Biannual: liver function tests (evidence level 4) Annual: eye check</td>
<td></td>
</tr>
<tr>
<td>ε-Aminocaproic acid 8-10 g orally, divided into 2-4 doses/d</td>
<td>ε-Aminocaproic acid. Not more than 6 g/d if &lt; 11 years old and not more than 12 g/d if &gt; 11 years old</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1-inh concentrate</td>
<td>500-1000 U IV 2 times/wk</td>
<td></td>
<td>Biannual: liver function tests, viral serology (HIV, HTLV 1 and 2, HBV, HCV)</td>
<td></td>
</tr>
<tr>
<td>C1-inh concentrate</td>
<td>500, 1000, or 1500 U IV in the previous 24 hours (preferably 1 h before), respectively according to weight &lt; 50, 50-100, or &gt; 100 kg. Have 2 more doses available</td>
<td>&lt; 10 years old: 500 U IV &gt; 10 years old: 1000 U IV in the previous 24 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Short-Term Prophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic attenuated androgens</td>
<td>Danazol 100-600 mg/24 h orally for 5 days before and 2 days after In general 10 mg/kg/d</td>
<td>Danazol 300 mg/24 h orally for 5 days before and 2 days after</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stanozolol 2-6 mg/24 h orally for 5 days before and 2 days after</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antifibrinolytic agents</td>
<td>Tranexamic acid 1 g/6 h orally/IV for 48 hours before and after In general 75 mg/kg/d</td>
<td>Tranexamic acid 500 mg/6 h orally/IV for 48 hours before and after</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ε-Aminocaproic acid 10 mg/d orally, divided into 2-3 doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>2 units (400 mL) IV 1-24 h before surgery</td>
<td>10 mL/kg IV 1-24 hours before surgery</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
### Table 6. Summary of the Therapeutic Management of Patients With C1 Inhibitor Deficiency. (Continued)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (adult)</th>
<th>Dose (child)</th>
<th>Monitoring Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-inh concentrate (evidence level 2)23</td>
<td>500-1500 U IV (according to weight. See above). Reinfusion/re-evaluation if symptoms persist for more than 2 hours</td>
<td>&lt; 10 years old: 500 U IV &gt; 10 years old: 1000 U intravenous</td>
<td>Baseline: liver function tests Hepatitis viruses</td>
</tr>
<tr>
<td>Synthetic attenuated androgens</td>
<td>Danazol maximum 1 g/24 h orally</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antifibrinolytic agents</td>
<td>Tranexamic acid 1 g/6 h orally/IV for 48 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ε-Aminocaproic acid IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fresh frozen plasma (evidence level 3)</td>
<td>2 units IV</td>
<td></td>
<td>Baseline: liver function tests</td>
</tr>
<tr>
<td>Synthetic attenuated androgens</td>
<td>Contraindicated (may be considered in third trimester)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antifibrinolytic agents</td>
<td>Can be used with caution (class B)24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1-inh concentrate</td>
<td>Treatment of attack acute (see above) Severe cases: use is common</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic attenuated androgens</td>
<td>Contraindicated (may be considered in third trimester)</td>
<td></td>
<td></td>
</tr>
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<td>Antifibrinolytic agents</td>
<td>Can be used with caution (class B)24</td>
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<tr>
<td>C1-inh concentrate</td>
<td>Treatment of attack acute (see above) Severe cases: use is common</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+Liver function tests include measurement of aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, total bilirubin, alkaline phosphatase, creatine phosphokinas, urea, creatinine, lactate dehydrogenase.

At diagnosis include complete blood count, urinalysis, thyroid hormones, and antithyroid antibodies.

Abbreviations: IV, intravenous; HIV, human immunodeficiency virus; HTLV, human T-lymphotrophic virus; HBV, hepatitis B virus; HCV, hepatitis C virus; PSA, prostate specific antigen; C1-inh, C1 inhibitor.

Modified from Gompels MM, et al.2

### Table 7. Adverse Effects of the Drugs Used in the Management of Patients With C1 Inhibitor Deficiency

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic attenuated androgens</td>
<td>Weight gain, virilization (acne, alopecia, and hirsutism), reduced libido, muscle pain and cramp, hypertension, headache, depression, fatigue, nausea, constipation, menstrual cycle disturbances, abnormal liver function, masculinization of a female fetus, hepatocellular adenoma, peliosis hepatitis, liver necrosis, cholestasis, adenocarcinoma of the prostate (evidence level 3)20,21 Androgenization, precocious puberty, premature epiphyseal fusion with growth limitation, liver disturbances, atherogenesis, behavioral changes</td>
</tr>
<tr>
<td>Antifibrinolytic agents</td>
<td>Nausea, vertigo, diarrhea, orthostatic hypotension, fatigue, thromboses, muscle cramps with a rise in muscle enzymes, elevated CPK, rhabdomyolysis, possible teratogenicity, tumors of the retina or liver in experimental animals (evidence level 2/3)22 Arteriosclerosis</td>
</tr>
</tbody>
</table>

Abbreviation: CPK, creatine phosphokinase.
either attenuated androgens or antifibrinolytic agents 
(if there is sufficient time) or C1 inhibitor concentrate 
(if this is available). If neither of these options is 
available, prophylaxis should be given with fresh frozen 
plasma.

**Treatment of the Acute Attack**

Treatment of the acute attack is not always necessary. 
Sometimes, if the episode is not generalized, the best option 
is to wait for spontaneous resolution of the angioedema or 
only to give fluid replacement.

All patients should be offered the opportunity to keep 
C1 inhibitor at home in sufficient quantity to treat a laryngeal 
emergency, as these attacks are life-threatening in 50%-75% 
of cases. The product must be reconstituted at room 
temperature before its administration. It must not be shaken 
and it must be administered into a peripheral vein over 
approximately 10 minutes.

Fresh frozen plasma can aggravate the symptoms during 
the acute phase. The possible transmission of diseases such 
as hepatitis B and C must be taken into account, but is ever 
less frequent.

There is no evidence for the effectiveness of epinephrine, 
though its efficacy compares relatively favorably with other 
treatments (corticosteroids or antihistamines).

In the event of an acute attack, suitable analgesics should 
be added to the usual treatment in order to relieve pain if 
it is present (nonsteroidal anti-inflammatory drugs for 
abdominal pain).

If the patient has been on treatment with danazol and 
has an acute episode, the dose may be doubled for several 
days.

Maintenance of the airway is important. Tracheotomy may be necessary if severe laryngeal edema develops.

**Commercial Names of the Different Drugs Employed**

Danazol: Danatrol, 50, 100, and 200 mg capsules (Sanofi-Winthrop Pharmaceuticals, New York, USA).

Stanozolol: Winstrol, 2 mg and depot 1 mL 50 mg (Zambon, Vicenza, Italy).

Oxandrolone: Oxandrin (Savient Pharmaceuticals, New 
Jersey, USA).

Methyltestosterone: Longivol oral, 1, 5, 10, and 25 mg 
tablets (Medical S.A., Spain).

Tranexamic acid: Amchafibrin, 500 mg tablets and 500 
mg ampoules (Fides Rottapharm, Valencia, Spain).

ε-Aminocaproic acid: Caproamin Fides, 2.5 g sachets 
and 4 g ampoules (Fides Rottapharm, Valencia, Spain).

C1-inhibitor concentrate: Berinert, 500 U vials (Immuno 
AG, Vienna, Austria). Not marketed in Spain (request as 
a foreign medicine).

**New Treatments**

Plasma kallikrein inhibitor, DX88 (Dyax Corp., Cambridge, 
Massachusetts, USA).

Bradykinin B2 receptor antagonist, Icatibant (Jerini AG, 
Berlin, Germany).

Serum protease inhibitor. This is not specific as it inhibits 
antithrombin III, β2-microglobulin, α1-antitrypsin, and 
α2-antiplasmin, among others.

Recombinant C1-inhibitor (Pharming Group NV, 
Leiden, The Netherlands).

**Conclusions**

Although C1 inhibitor deficiency is a rare syndrome, it is 
worth being aware of its existence due to its potential
involvement of the upper airways, which can cause death of the patient. The most common type of angioedema due to C1 inhibitor deficiency is the congenital type, which usually becomes evident during the second decade of life with abdominal symptoms. The acquired type is less common and may be triggered by various drugs or hormonal changes. Diagnosis of the disease begins with clinical suspicion (skin swelling with occasional involvement of the upper airways or abdomen). Clinical suspicion must be confirmed by measurement of C4 and quantification of C1 inhibitor in plasma; if necessary, C1 inhibitor function may also be measured. The diagnosis is not always easy as false positives are common and there is a wide variability between laboratories. With regard to treatment, a number of drugs are commonly used in the management of an acute attack, and there are other new drugs still not on the market. There are clear indications for prophylaxis and these should be followed.

Conflicts of Interest
The authors declare no conflicts of interest

References


