REVIEW

Current management of hereditary angio-oedema (C'1 esterase inhibitor deficiency)

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Hereditary angio-oedema is characterised by recurrent swellings in any part of the body and also by recurrent attacks of severe abdominal pain. The disease is inherited in an autosomal dominant manner but up to 25% of cases can occur as a spontaneous mutation. Attacks of swelling can be precipitated by trauma, certain drugs, and emotional stress. Treatment usually involves a combination of prophylaxis, using androgens or antifibrolytic drugs, and replacement with C'1 esterase inhibitor concentrate for acute attacks and before surgery or other traumatic procedures.

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Hereditary angio-oedema (HAE) is characterised by recurrence of cutaneous and mucous membrane swellings in any part of the body. Symptoms usually appear early in life and are normally accompanied by a family history because the disease is inherited in an autosomal dominant manner. The spontaneous mutation rate is about 25% and more than 100 different C'1 inhibitor gene mutations have been described.[1] The prevalence of the disease has been estimated at 1/50 000, with no reported bias in different ethnic groups.

In HAE type I (up to 85% of all patients), there is a deficiency in the amount of C'1 inhibitor protein present in the plasma as a result of only one gene functioning. However, plasma values are usually 5–30% of normal rather than the 50% value that might be expected.[2] Interestingly, it has been shown that fibroblasts from some patients with type I HAE synthesise approximately 20% of normal amounts of C'1 inhibitor in vitro and also that the fractional catabolic rate of C'1 inhibitor is enhanced in asymptomatic patients with HAE from 0.025 to 0.035 of the plasma pool each hour,[2] which might help to explain this discrepancy. There is also some evidence that certain amino acid substitutions found in type I HAE affect the intracellular transport of C'1 inhibitor and result in a strong reduction or the total impairment of protein secretion.[1] In HAE type II, the circulating C'1 inhibitor concentration is normal but not all functional. Functional C'1 inhibitor synthesised by fibroblasts from patients with type II HAE is nearly 50% of normal, in contrast to the findings in patients with type I disease.[2] High plasma concentrations of dysfunctional C'1 inhibitor are found because the mutant protein is secreted normally and its inability to form complexes with proteases increases its half life in the circulation. Dysfunctional proteins often result from substitutions at the reactive site residue Arg 444, but may also result from changes at several positions outside the reactive site loop. HAE type III has been described, where the C'1 inhibitor has a structural abnormality that binds to albumin, forming an inactive complex, and the plasma concentrations of C'1 inhibitor are normal or high.[3]

C'1 inhibitor is the main regulator of the activation steps of the classical complement pathway. This protein is mainly produced in the liver, but also by activated monocytes and other cell types.[4] C'1 inhibitor also regulates the activation of kallikrein, plasmin in the fibrinolytic pathway, the activation of factor IX in the coagulation cascade, and activated Hageman factor. In the presence of C'1 inhibitor deficiency the classical complement pathway can be inappropriately or prematurely activated. Immune complexes trigger the activation of the first component C'1 to C'1 esterase. C'1 esterase then acts with its natural substrates C'4 and C'2 to form the complex C'2,4 (C'3). This new complex leads to the activation of anaphylactoid-like substances and vasoactive peptides. C'1 inhibitor protein blocks both the spontaneous activation of C'1 and the formation of activated C'1, therefore not allowing the C'2,4 complex to be created. In the kinin releasing system, C'1 inhibitor deficiency allows for an increase in bradykinin. In the fibrinolytic system, C'1 inhibitor deficiency leads to an increase in fibrin split products. The coagulation pathway is affected by premature activation of factor IX. The end result is increased vascular permeability and massive uncontrolled oedema, but the precise chemical responsible for the oedema is still unknown.[5]

CLINICAL CHARACTERISTICS

A diagnosis of HAE is suspected by a history of recurrent attacks of peripheral angio-oedema and of abdominal pain. Symptoms include recurrent circumscribed, non-pruritic, non-pitting oedema. It can affect virtually any part of the body, but is more common in the extremities.[6] Episodes of swelling may also involve the upper respiratory tract, including the tongue, pharynx, and larynx. This contributed to the 15–33% mortality from the disease previously reported in the literature.[7] Abdominal pain, nausea, and vomiting are the dominant symptoms in approximately 25% of all

Abbreviations: FFP, fesh frozen plasma; HAE, hereditary angio-oedema; HCV, hepatitis C virus; HGV, hepatitis G virus

patients, and are caused by constriction produced by intestinal wall and mesenteric oedema.[8]

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Classically, the oedema and swelling gradually develop over several hours, slowly increasing for 12–36 hours, and then subside after one to three days. Although it is rare to find the disease without symptoms there is an extreme variability in their frequency and severity.[5] There seems to be little, if any, correlation between symptoms and type of genetic defect—even patients from the same family sharing the same mutation show wide differences in phenotype.[5] Attacks of severe swelling can occur in some patients on a weekly basis and in others only happen once or twice a year.

Attacks are seen during childhood in most patients.[9 10] Although the diagnosis is usually made in the 2nd or 3rd decade of life,[9 11–13] it is well documented that between 50% and 75% of patients had their first attack by the age of 12 years. Data from the largest patient group studied (over 340 patients from 120 different kindreds) and followed over a period of more than 20 years[5 11 14–17] confirms that almost 40% had onset of their symptoms before the age of 5 years, and 75% before the age 15. Data from smaller studies on children only provide more striking evidence that most experienced their first symptoms in early childhood, before the age of 6 years.[18 19] Occasional patients will have their first symptoms even earlier, before the age of 1.[15 20–22] Attacks in children are usually not as frequent and/or severe as in adults, except the recurrent colicky abdominal pain seen in 40–80% of children.[10 18 23]

There is usually a family history of similar complaints.[6]

Angio-oedema can be precipitated by minor trauma to the tissue, such as dental work,[9] said to be a cause in up to 50% of all cases,[24] by certain drugs such as oestrogen and angiotensin converting enzyme inhibitors, by emotional stress (even in children), or by infection.[25]

Acute attacks of abdominal pain can mimic surgical emergencies and before diagnosis is established, patients with HAE frequently undergo unnecessary appendectomy or exploratory laparotomies. Equally, after diagnosis, there is always the worry that true abdominal emergencies will not have surgery performed in good time.[5] Barium studies, carried out during an acute attack, have been reported to show signs of massive submucosal oedema, spiculation, and fold thickening or effacement.[26] The gastrointestinal involvement appears to be segmental and transient with reversion to normal by several days after an attack. In a report of an endoscopy carried out during an acute attack of HAE the gastric mucosa was described as diffusely reddish and oedematous and the mucosal surface in involved areas bulged remarkably, mimicking a submucosal tumour.[27] Histological examination of the bulging area merely showed moderate inflammatory cell infiltration of the lamina propria.[27] These findings are relatively non-specific and response to treatment with C'1 inhibitor concentrate may be the only way to differentiate a surgical condition from an acute attack of HAE.[5]

The diagnosis is classically confirmed by the low C'4 concentration in the serum and in most cases by low amounts of C'1 inhibitor protein, as assessed by immunohistochemistry. If C'1 inhibitor values appears normal or raised and C'4 is low, a test of C'1 inhibitor function should be carried out.[9 28] All such tests should be carried out on a fresh serum sample—one less than four hours old.

MANAGEMENT

Management of patients with HAE should cover their long term, short term, and acute needs. It is important in the general management of these patients to search for potentially treatable triggers of attacks and deal with them. Infected teeth should be looked for and treated, oral contraceptives and hormone replacement therapy should make minimal use of oestrogen, with progesterone only pills such as levonorgestrel being used, and alcohol should only be taken in very moderate amounts. Attacks are likely to become more frequent at times of lifestyle stress, so it may be sufficient to use prophylactic drugs during such periods only, thus minimising adverse effects. Nevertheless, there will be a group of patients who will require continuous, long term prophylaxis and careful thought should be given to the choice of drugs.

Long term prophylaxis

Long term prophylaxis should be considered in each individual, but it is necessary to devise a regimen for each affected individual guided by the severity of their disease. Frequent attacks of peripheral angio-oedema (extremities, trunk), although unpleasant and annoying, are not dangerous and do not require long term prophylaxis. However, prophylactic administration of antifibrinolytic agents (ε-aminocaproic acid[29] and tranexamic acid[30]), androgens (methyltestosterone,[31] fluoxymesterone, and oxymetholone[32 33]), or synthetic, attenuated androgens (danazol[34–36] or stanazolol[36–39] has proved useful in reducing the frequency or severity of attacks.

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Antifibrinolytic agents seem to inhibit C'1 and plasmin activation with consequent "sparing" of C'1 inhibitor usage. They decrease the number and the severity of attacks,[24] but are not as effective in this as the synthetic anabolic steroids.[29] Their side effects include nausea, vertigo, diarrhoea, menorrhagia, postural hypotension, tachyphylaxis, fatigue, and muscle cramps with an increase in muscle enzymes concentrations,[14 29 30 40–42] and concerns about thrombus formation and thrombotic episodes.[9] However, recent reports have suggested that these side effects are less common than previously thought, particularly the thrombus formation.[42] The finding of tumours of the retina and liver in experimental animals after long term use of tranexamic acid[9] has limited its use in the USA,[8] but not in Europe.[17 23] Although a teratogenic effect of ε-aminocaproic acid has been postulated in the period of embryonic growth and development,[9 43] it is being used in the USA,[44] it has been used in children,[18] and, surprisingly, has been recommended during pregnancy.[45] A starting dose of 0.5–1 g of tranexamic acid up to four times a day should be used depending on disease severity, reducing to 0.5 g once or twice a day as the attacks remit.

Anabolic steroids increase the hepatic production of C'1 inhibitor protein.[9] Their side effects, which are dose dependent, include weight gain, virilisation, muscle pains and cramps, headaches, depression, fatigue, nausea, constipation, menstrual irregularities, and liver function derangement.[39 46 47] Decreased growth rate in children[48–50] is the main contraindication for their use in this age group. Androgens can cause masculinisation of the female fetus[51 52] and thus are not recommended during pregnancy. The most worrying effects of all the 17α-alkylated androgens, including danazol and stanazolol, are those on liver metabolism, in particular cholestatic jaundice,[53] peliosis hepatis,[54] and hepatocellular carcinoma.[55–58] The recently observed first cases of hepatocellular adenomas developing in patients with HAE on long term prophylaxis with danazol have caused particular concern.[59] A dose of 200 mg once or twice a day will usually suffice in adults, but because of the wide variations between individuals with this condition up to 400 mg twice a day may be required.

Long term prophylaxis of attacks in children

This is a relatively unexplored issue,[18 19] and most references state that the use of antifibrinolytics and androgens is not recommended because of the serious side effects of these drugs.[28 60] Because severe or life threatening attacks of HAE are less common during childhood, it is rarely necessary to start long term prophylaxis in children.[8 23] Long term prophylaxis is justified only in severely affected children, defined by frequent attacks of laryngeal oedema (one or more attacks each month) and/or frequent, recurrent attacks of colicky abdominal pain causing distress and disability. In this situation, antifibrinolytics are preferred to androgens.[17–19] The individual minimal effective dose, irrespective of serum concentrations of C4 and/or C1 esterase inhibitor, for both antifibrinolytics and/or androgens used for long term prophylaxis has to be established and careful clinical and laboratory follow up of hepatic and renal functions and blood coagulation is mandatory.[8 14 17 18 23 30 35 36 39 41 42 47 61–65] However, benefit of long term administration of high dose ϵ-aminocaproic acid (12–24 g/day) in children was associated with side effects in all, but with the dose adjusted for each child's need (6 g/day and 12 g/day for < 11 year olds and > 11 year olds, respectively), the control of symptoms was still satisfactory without unpleasant side effects.[18] Tranexamic acid at a dose of 50 mg/kg/day[17] or 1.5 g/day[23 41] has been used long term with similar benefit and no side effects. The use of danazol in children[66 67] is a cause for concern, even when used with caution.[68 69] The finding of an increased incidence of arterial hypertension in patients with HAE treated with danazol long term[64 65] further highlights the theoretical possibility of an increased risk of arteriosclerosis because the long term use of androgens has been reported to decrease the concentration of high density lipoproteins.[8 70–72] However, it has been proposed that the long term use of antifibrinolytics, by plasmin inhibition, could also predispose to arteriosclerosis.[18 73] This is of particular interest if long term prophylaxis is to be started during childhood because several decades of treatment may be needed.

C'1 inhibitor concentrate has been used successfully for long term replacement in selected adult patients,[74] and more recently it has been shown to be superior to a placebo in a double blind controlled study.[60] Based on the clinical benefit seen in these patients, a role for C'1 inhibitor concentrate in long term prophylaxis for children has been suggested,[60] supporting the few earlier proposals.[8 75] The psychological benefit to both the children and their parents by the possibility of home availability of the concentrate, or even of treatment at the earliest sign of an attack involving the upper airway is an important advantage of replacement treatment with C1 inhibitor concentrate,[60 75 76] although the disadvantages and major obstacles to this approach to the management are expense[69] and the possibility of viral transmission, even with the use of heat treated preparations of C'1 inhibitor concentrate.[77]

Treatment of acute attacks

This depends on their severity. Episodes of peripheral swelling only usually do not require treatment, but stanozolol (up to 6 mg/day) can be given during an attack.[78] Involvement of the upper airway usually begins slowly; voice alteration and dysphagia will precede total airway obstruction. If there is any suspicion of airway involvement C'1 inhibitor concentrate should be given promptly at a dose of 1000 to 1500 IU (vide infra). This both shortens the duration of attacks by about a third and also halves the time to the beginning of the relief of symptoms.[28] For acute attacks of abdominal oedema, pain relief should be given at an appropriate level and C'1 inhibitor concentrate should be infused at the same dose as above (vide infra). The patient should be closely observed because the median time, on average, to the beginning of the relief of symptoms after concentrate infusion is about six hours, with resolution after 24 hours.[28] If symptoms persist at a high intensity after this, an alternative diagnosis should be considered.

Treatment of choice for acute attacks manifesting as airway obstruction and life threatening asphyxia and/or severe colicky abdominal pain is replacement with C'1 inhibitor concentrate.[12 75 79–88] C'1 inhibitor concentrate is available throughout Europe, it has been used in Australia[89] and Canada,[90] but although it has been available since the early 1980s,[91] and shown to be effective in a controlled trial,[60] the USA authorities have still not approved its use (FS Rosen, personal communication, October 1998). In an uncontrolled trial during long term follow up of 14 children with HAE,[23] acute attacks in six children were treated with a single dose of 500 IU of C'1 inhibitor concentrate (Immuno AG, Vienna, Austria) on 30 separate administrations. Progression of facial and laryngeal oedema was aborted 30–60 minutes after the infusion and gradually disappeared over the next 24–36 hours. The dose had to be repeated after 60 minutes on only two separate occasions because laryngeal oedema continued to progress. Concentrations of C1 inhibitor and C4, when measured 12 and 24 hours after the infusion in two patients, showed an expected increase. None of the children required endotracheal intubation or tracheotomy, and no side effects were observed.

If concentrate is not available then fresh frozen plasma (FFP) may be given, although this may worsen symptoms during the acute phase[8 9 43] because it contains a high concentration of complement components.

Short term prophylaxis

Short term prophylaxis for surgical procedures is the third arm of treatment in these patients. If surgery or dental work is to be carried out on a planned basis, an infusion of C'1 inhibitor concentrate should be given (or if this is not available, FFP) six to 12 hours before the procedure.[23 60] It is impossible to predict the requirements of an individual patient in such a situation—in general, one infusion of 1500 IU of concentrate should be sufficient for dental work and most planned surgery for an adult patient, but a top up may be required, particularly if there is postoperative infection.

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Administration of antifibrinolytics or attenuated androgens, starting five days before the procedure and the following two days thereafter,[17] is an alternative. Tranexamic acid has been used at a daily dose of 4 g (1 g four times daily) for adults[92 93] or 2 g (500 mg four times daily) for children,[23] given 48 hours before and after surgery. However, it seems that most authors prefer attenuated androgens even in children[8 17] at a dose of 100–600 mg/day for danazol or 2–6 mg/day for stanazolol, given 48 hours before and after surgery.[8 14 17 39]

Last but not least, thorough explanation of the nature of the disease to both children and their parents is essential for successful management of HAE.

TREATMENT DURING PREGNANCY

Treatment of the disease during pregnancy has special problems. Of published reports, some anecdotes report worsening of the disease,[79] but few attribute stillbirths to the disease.[94] In a series of 25 pregnancies in affected patients, only two had an increase in frequency of attacks, and none of these was related to the delivery itself.[9] Ideally, all prophylactic drugs should be stopped during pregnancy and, if possible, before conception. If prophylaxis is required, tranexamic acid

Take home messages

- Hereditary angio-oedema (HAE) is caused by mutation of the C' inhibitor gene, and is inherited in an autosomal dominant manner
- Defective C' inhibitor protein causes inappropriate activation of the classical complement pathway and also has effects on the coagulation cascade, all of which result in massive, uncontrolled oedema
- Patients suffer from peripheral angio-oedema, abdominal pain, and nausea, and swelling of the upper respiratory tract contributes to the mortality associated with the disease
- Treatment usually involves a combination of prophylaxis and replacement, depending on the individual patient's needs at any particular time
- Longterm prophylactic drugs include antifibrinolytics and androgens, although antifibrinolytics are preferred to androgens in children
- Treatment of acute attacks is usually by replacement with C'1 inhibitor concentrate, which is also used for short term prophylaxis for surgical procedures, although antifibrinolytics or attenuated androgens are sometimes used
- However, the viral safety of C'1 inhibitor concentrate is of concern and it should only be given for short term prophylaxis or severe attacks of swelling

at standard doses should be used. Severe attacks during pregnancy should be treated with concentrate as in the non-pregnant patient. Vaginal delivery does not require special precautions; there may be local swelling of the vulva and infusion sites but this will usually settle without intervention. If an operative delivery is required, concentrate should be given if endotracheal intubation is to be carried out but, if possible, regional analgesia should be used.[25]

C'1 INHIBITOR CONCENTRATE: SAFETY CONCERNS

The viral safety of C'1 inhibitor concentrate, as with any blood product, is always a matter of concern. There are reports of transmission of hepatitis C virus (HCV) by non-virus inactivated C'1 inhibitor concentrates used before 1985.[15 95 96] Several studies confirmed the safety of a heat treatment step in the production of a C'1 inhibitor concentrate,[28 60 96 97] and no transmission of the human immunodeficiency virus, HCV, or hepatitis G virus (HGV) was observed in these studies. Nonetheless, because it has recently been shown that HGV could be transmitted in both unmodified and virus inactivated concentrates,[77] surveillance of patients treated with concentrate is essential.[98]

C'1 inhibitor concentrate should only be given for severe attacks of swelling where there is a risk of airway involvement and for severe attacks of abdominal pain. Liver function and viral status of these patients should be monitored regularly and careful records kept of all infusions given. Patients should be fully informed of the potential risks and involved in treatment decisions.

Recombinant preparations of C'1 inhibitor concentrate are being developed with phase I/II trials to be undertaken (PL Yap, personal communication, 2001) and if successful would overcome many of these difficulties.

It is perhaps surprising that FFP, known to be effective in the treatment of acute attacks[99 100] and in short term prophylaxis,[101–103] but carrying significant risks of viral transmission, anaphylactoid reactions, alloimmunisation, and excessive intravascular volume[8 28] is preferred as replacement treatment in the USA.[13 104–106]

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REFERENCES

1 **Tosi M**. Molecular genetics of C'1-inhibitor. *Immunobiology* 1998;**199**:358–65.
2 **Prada AE**, Zahedi K, Davis AE. Regulation of C'1-inhibitor synthesis. *Immunobiology* 1998;**199**:377–88.
3 **Cullmen W**, Opferkuck W. Deficiencies in regulator proteins I. C'-1 inhibitor. *Progress in Allergy* 1986;**39**:311–34.
4 **Johnson AM**, Alper CA, Rosen FS, *et al*. C'-1 inhibitor: evidence for decreased hepatic synthesis in hereditary angioedema. *Science* 1971;**173**:553–4.
5 **Cicardi M**, Bergamaschini L, Cugno M, *et al*. Pathogenic and clinical aspects of C'-1 inhibitor deficiency. *Immunobiology* 1998;**199**:366–76.
6 **Carrer FMJ**. The C'-1 inhibitor deficiency. *Eur J Clin Chem Clin Biochem* 1992;**30**:793–804.
7 **Moore GP**, Hurley WT, Pace SA. Hereditary angioedema. *Ann Emerg Med* 1988;**17**:1082–6.
8 **Sim T**, Grant JA. Hereditary angioedema: its diagnostic and management perspectives. *JAMA* 1990;**88**:656–64.
9 **Frank MM**, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. *Ann Intern Med* 1976;**84**:580–93.
10 **Donaldson VH**, Rosen FS. Hereditary angioneurotic edema: a clinical survey. *Pediatrics* 1966;**37**:1017–27.
11 **Agostoni A**, Marasini B, Martignoni GC, *et al*. Hereditary angioneurotic oedema. *Klin Wochenschr* 1975;**53**:679–84.
12 **Bork K**, Witzke G. Hereditary angioneurotic oedema: clinical experience and new approaches to diagnosis and therapy. *Dtsch Med Wochenschr* 1979;**104**:40–59.
13 **Brickman CM**, Hosea SW. Hereditary angioedema. *Int J Dermatol* 1983;**22**:14–17.
14 **Cicardi M**, Bergamaschini L, Marasini B, *et al*. Hereditary angioedema: an appraisal of 104 cases. *Am J Med Sci* 1982;**284**:2–9.
15 **Agostoni A**. Inherited C1 inhibitor deficiency. *Complement Inflamm* 1989;**6**:112–18.
16 **Agostoni A**, Cicardi M. Hereditary and acquired C1 inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine* 1992;**71**:206–15.
17 **Agostoni A**, Cicardi M, Cugno M, *et al*. Clinical problems in the C1 inhibitor deficient patients. *Behring Inst Mitt* 1993;**93**:306–12
18 **Gwynn CM**. Therapy in hereditary angioneurotic oedema. *Arch Dis Child* 1974;**49**:636–40.
19 **Abinun M**, Mikuska M, Milosavljevic J. Problems of longterm prophylaxis in children with hereditary angioedema. *Periodicum Biologorum* 1986;**88**(suppl 1):221–2.
20 **Bedford S**. Hereditary angiooedema. *Proc R Soc Med* 1971;**64**:1049–50.
21 **Ohela K**. Hereditary angioneurotic oedema in Finland: clinical, immunological and genealogical studies. *Acta Med Scand* 1977;**201**:415–27.
22 **Nielsen EW**, Thidemann H, Holt J, *et al*. C1 inhibitor and diagnosis of hereditary angioedema in newborns. *Pediatr Res* 1994;**35**:184–7.
23 **Abinun M**. Diagnosis and treatment of hereditary angioedema, a genetically determined deficiency of C1 inhibitor. MSc Thesis, Medical School, University of Belgrade, 1988.
24 **Karlis V**, Glickman RS, Stern R, *et al*. Hereditary angioedema. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997;**83**:462–4.
25 **Chappatte O**, De Swiet M. Hereditary angioneurotic oedema and pregnancy. Case reports and review of the literature. *Br J Obstet Gynaecol* 1988;**95**:938–42.
26 **Pearson KD**, Buchignani JS, Shimkin PT, *et al*. Hereditary angioneurotic edema of the gastrointestinal tract. *Am J Roentgenol Radium Ther Nucl Med* 1972;**116**:256–61.
27 **Hara T**, Shiotani A, Matsunaka H, *et al*. Hereditary angioedema with gastrointestinal involvement: endoscopic appearance. *Endoscopy* 1999;**31**:322–34.
28 **Kunschak M**, Engl W, Maritsch F, *et al*. A randomized, controlled trial to study the efficacy and safety of C'-1 inhibitor concentrate in treating hereditary angioedema. *Transfusion* 1998;**38**:540–49.
29 **Frank MM**, Sergent JS, Kane MA, *et al*. Epsilon aminocaproic acid therapy of hereditary angioneurotic edema: a double blind study. *N Engl J Med* 1972;**286**:808–12.
30 **Sheffer AL**, Austen KF, Rosen FS. Tranexamic acid therapy in hereditary angioneurotic edema. *N Engl J Med* 1972;**287**:452–4.
31 **Spaulding WB**. Methyltestosterone therapy for hereditary episodic edema (hereditary angioneurotic edema). *Ann Intern Med* 1960;**53**:739–45.
32 **Davis PJ**, Davis FB, Charache P. Longterm therapy of hereditary angioedema (HAE). Preventive management with fluoxymesterone and oxymetholone in severely affected males and females. *Hopkins Medical Journal* 1974;**135**:391–8.
33 **Sheffer AL**, Fearon DT, Austen KF. Clinical and biochemical effects of impeded androgen (oxymetholone) therapy of hereditary angioedema. *J Allergy Clin Immunol* 1979;**64**:275–80.
34 **Gelfand JA**, Sherins RJ, Alling DW, *et al* Treatment of hereditary angioedema with danazol: reversal of clinical and biochemical abnormalities. *N Engl J Med* 1976;**295**:1444–8.
35 **Rothbach C**, Green RL, Levine ML, *et al*. Prophylaxis of attacks of hereditary angioedema. *Am J Med* 1979;**66**:681–3.
36 **Agostoni A**, Cicardi M, Martignoni GC, *et al*. Danazol and stanozolol in longterm prophylactic treatment of hereditary angioedema. *J Allergy Clin Immunol* 1980;**65**:75–9.
37 **Gould DJ**, Cunliffe WJ, Smiddy FG. Anabolic steroids in hereditary angiooedema. *Lancet* 1978;i:770–1.

38 **Sheffer AL**, Fearon DT, Austen KF. Clinical and biochemical effects of stanozolol therapy for hereditary angioedema. *J Allergy Clin Immunol* 1981;**68**:181–7.
39 **Sheffer AL**, Fearon DT, Austen KF. Hereditary angioedema: a decade of management with stanozolol. *J Allergy Clin Immunol* 1987;**80**:855–60.
40 **Nilsson IM**, Anderson L, Björkman SE. Epsilonaminocaproic acid (EACA) as a therapeutic agent. Based on 5 year's clinical experience. *Acta Med Scand* 1966;**448**(suppl):21.
41 **Agostoni A**, Marasini B, Cicardi M, *et al*. Hepatic function and fibrinolysis in patients with hereditary angioedema undergoing longterm treatment with tranexamic acid. *Allergy* 1978;**33**:216–21.
42 **Rybo G**. Tranexamic acid therapy is effective treatment in heavy menstrual bleeding. *Clinical Update on Safety Therapeutic Advances* 1991;**4**:1–8.
43 **Donaldson VH**. Therapy of "the neurotic edema". *N Engl J Med* 1972;**286**:835–6.
44 **Van Dellen RG**. Long term treatment of C1 inhibitor deficiency with epsilonaminocaproic acid in two patients. *Mayo Clin Proc* 1996;**71**:1175–8.
45 **Naish P**, Barratt J. Hereditary angioedema. *Lancet* 1979;i:611.
46 **Hosea SW**, Santaella ML, Brown EJ, *et al*. Longterm therapy of hereditary angioedema with danazol. *Ann Intern Med* 1980;**93**:809–12.
47 **Cicardi M**, Bergamaschini L, Tucci A, *et al*. Morphologic evaluation of the liver in hereditary angioedema patients on longterm treatment with androgen derivates. *J Allergy Clin Immunol* 1983;**72**:294–8.
48 **Keele DK**, Worley JW. Study of an anabolic steroid: certain effects of oxymetholone on small children. *Am J Dis Child* 1967;**113**:422–30.
49 **Spooner JB**. Classification of side effects to danazol therapy. *J Int Med Res* 1977;**5**(suppl 3):15–17.
50 **Smith CS**, Harris F. Preliminary experience with danazol in children with precocious puberty. *J Int Med Res* 1977;**5**(suppl 3):109–13.
51 **CastroMagnana M**, Cheruvanky T, Collipp PJ, *et al*. Transient adrenogenital syndrome due to exposure to danazol in utero. *Am J Dis Child* 1981;**135**:1032–4.
52 **Schwartz RP**. Ambiguous genitalia in a term female infant due to exposure to danazol in utero. *Am J Dis Child* 1982;**136**:474.
53 **Wynn V**. Metabolic effects of danazol. *J Int Med Res* 1977;**5**(suppl 3):25–35.
54 **Westaby D**, Paradinas FJ, Ogle SJ, *et al*. Liver damage from longterm methyltestosterone. *Lancet* 1977;ii:261–3.
55 **Johnson FL**, Lerner KG, Siegel M, *et al*. Association of androgenicanabolic steroid therapy with development of hepatocellular carcinoma. *Lancet* 1972;ii:1273–6.
56 **Ziegenfuss J**, Carabasi R. Androgen and hepatocellular carcinoma. *Lancet* 1973;i:262.
57 **Cattan D**, Vesin P, Wautier J, *et al*. Liver tumours and steroid hormones. *Lancet* 1974;i:878.
58 **Fermand JP**, Levy Y, Bouscary D, *et al*. Danazolinduced hepatocellular adenoma. *Am J Med* 1990;**88**:529–30.
59 **Bork K**, Pitton M, Harten P, *et al*. Hepatocellular adenomas in patients taking danazol for hereditary angioedema. *Lancet* 1999;**353**:1066–7.
60 **Waytes TA**, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vaporheated C1 inhibitor concentrate. *N Engl J Med* 1996;**334**:1630–4.
61 **Agostoni A**, Marasini B, Cicardi M, *et al*. Intermittent therapy with danazol in hereditary angioedema. *Lancet* 1978;i:453.
62 **Sweet LC**, Jackson CE, Yanari SS, *et al*. Danazol therapy in hereditary angioedema. *Henry Ford Hospital Medical Journal* 1980;**28**:31–5.
63 **Macfarlane JT**, Davies D. Management of hereditary angiooedema with low dose danazol. *BMJ* 1981;**282**:1275.
64 **Zurlo JJ**, Frank MM. The longterm safety of danazol in women with hereditary angioedema. *Fertil Steril* 1990;**54**:64–72.
65 **Cicardi M**, Castelli R, Zingale LC, *et al*. Side effects of longterm prophylaxis with attenuated androgens in hereditary angioedema: comparison of treated and untreated patients. *J Allergy Clin Immunol* 1997;**99**:194–6.
66 **Tappeiner G**, Hintner H, Glatzl J, *et al*. Hereditary angiooedema: treatment with danazol. *Br J Dermatol* 1979;**100**:207–12.
67 **Rajagopal C**, Harper JR. Successful use of danazol for hereditary angiooedema. *Arch Dis Child* 1981;**56**:229–30.
68 **Barakat AJ**, Castaldo AJ. Herediatry angioedema: danazol therapy in a 5 year old child. *Am J Dis Child* 1993;**147**:931–2.
69 **Farkas H**, Harmat G, Gyeney L, *et al*. Danazol therapy for hereditary angioedema in children. *Lancet* 1999;**354**:1031–2.
70 **Fraser IS**, Allen JJ. Danazol and cholesterol metabolism. *Lancet* 1979;i:931.
71 **Allen JK**, Fraser IS. Cholesterol, high density lipoprotein and danazol. *J Clin Endocrinol Metab* 1981;**53**:149–52.
72 **Oliver MF**. Hypercholesterolaemia and coronary heart disease: an answer. *BMJ* 1984;**288**:423–4.
73 **Champion RH**, Lachmann PJ. Hereditary angiooedema treated with ϵ-aminocaproic acid. *Br J Dermatol* 1969;**81**:763–5.
74 **Bork K**, Witzke G. Longterm prophylaxis with C1 inhibitor (C1 INH) concentrate in patients with recurrent angioedema caused by hereditary and acquired C1inhibitor deficiency. *J Allergy Clin Immunol* 1989;**83**:677–82.
75 **Abinun M**, Mikuska M. Hereditary angioedema in children: treatment with C1 inhibitor concentrate. *Abstracts. 7th International Congress of Immunology, Berlin*. Berlin: Gustav Fischer Verlag, 1989:144A.
76 **Abinun M**. Hereditary angioedema in childhood. *Lancet* 1999;**353**:2242.
77 **De Filippi F**, Castelli R, Cicardi M, *et al*. Transmission of hepatitis G virus in patients with angioedema treated with steam heated plasma concentrates of C1 inhibitor. *Transfusion* 1998;**38**:307–11.
78 **Glovsky MM**. C'-1 esterase inhibitor transfusions in patients with hereditary angioedema. *Ann Allergy Asthma Immunol* 1998;**80**:439–40.
79 **Logan RA**, Greaves MW. Hereditary angio-edema: treatment with C'-1 esterase inhibitor concentrate. *J R Soc Med* 1984;77:1046–48.
80 **Brackertz D**, Kueppers F. Possible therapy in hereditary angioneurotic edema (HAE). *Klin Wochenschr* 1973;**51**:620–2.
81 **Vogelaar EF**, Brummelhuis HGJ, Krijnen HW. Contribution to the optimal use of human blood. III. Large scale preparation of human C1 esterase inhibitor concentrate for clinical use. *Vox Sang* 1974;**26**:118–27.
82 **Marasini B**, Cicardi M, Martignoni GC, *et al*. Treatment of hereditary angioedema. *Klin Wochenschr* 1978;**56**:819–23.
83 **Agostoni A**, Bergamaschini L, Martignoni G, *et al*. Treatment of acute attacks of hereditary angioedema with C1inhibitor concentrate. *Ann Allergy* 1980;**44**:299–301.
84 **Bergamaschini L**, Cicardi M, Tucci A, *et al*. C1 INH concentrate in the therapy of hereditary angioedema. *Allergy* 1983;**38**:81–4.
85 **Bork K**, Kreuz W, Witzke G. Hereditary angioneurotic edema: clinical features, diagnosis, management and drug therapy. *Dtsch Med Wochenschr* 1984;**109**:1331–5.
86 **Laxenaire MC**, Audibert G, Janot C. Use of purified C1 esterase inhibitor in patients with hereditary angioedema. *Anesthesiology* 1990;**72**:954–5.
87 **Gonzalez JN**, Losada AJP, Burriel JIG, *et al*. Angioedema hereditario. Diagnostico y tratamento durante la infancia. *An Esp Pediatr* 1993;**38**:452–4.
88 **Spickett G**. *Oxford handbook of clinical immunology*. Oxford: Oxford University Press, 1999.
89 **Langton D**, Weiner J, Fary W. C1 esterase inhibitor concentrate prevents upper airway obstruction in hereditary angioedema. *Med J Aust* 1994;**160**:383–4.
90 **Visentin DE**, Yang WH, Karsh J. C1 esterase inhibitor transfusions in patients with hereditary angioedema. *Ann Allergy Asthma Immunol* 1998;**80**:457–61.
91 **Gadek JE**, Hosea SW, Gelfand JA, *et al*. Replacement therapy in hereditary angioedema: successful treatment of acute episodes of angioedema with partly purified C1 inhibitor. *N Engl J Med* 1980;**302**:542–6.
92 **Sheffer AL**, Fearon DT, Austen KF, *et al*. Tranexamic acid: preoperative prophylactic therapy for patients with hereditary angioneurotic edema. *J Allergy Clin Immunol* 1977;**60**:38–40.
93 **Ward Booth P**. Hereditary angioedema. *Lancet* 1979;i:611.
94 **Osler W**. Hereditary angioneurotic oedema. *Am J Med Sci* 1888;**95**:362–7.
95 **Agostoni A**, Cicardi M. Replacement therapy in hereditary and acquired angioedema. *Pharmacol Res* 1992;**6**(suppl 2):148–9.
96 **Cicardi M**, Mannucci PM, Castelli R, *et al*. Reduction in transmission of hepatitis C after the introduction of heat treatment step in the production of C1 inhibitor concentrate. *Transfusion* 1995;**35**:209–12.
97 **Klarmann D**, Kreuz WE, Joseph-Steiner J, *et al*. Hepatitis C and pasteurized C1 inhibitor concentrate. *Transfusion* 1996;**36**:84–5.
98 **Cicardi M**, Agostoni A. Hereditary angioedema. *N Engl J Med* 1996;**334**:1666–7.
99 **Pickering RJ**, Kelly JR, Good RA, *et al*. Replacement therapy in hereditary angioedema: successful treatment of two patients with fresh frozen plasma. *Lancet* 1969;i:326–30.
100 **Beck P**, Wills D, Davies GT, *et al*. A family study of hereditary angioneurotic oedema. *Q J Med* 1973;**42**:317–39.
101 **Jaffe CJ**, Atkinson JP, Gelfand JA, *et al*. Hereditary angioedema: the use of fresh frozen plasma for prophylaxis in patients undergoing oral surgery. *J Allergy Clin Immunol* 1975;**55**:386–93.
102 **Gibbs PS**, LoSasso AM, Moorthy SS, *et al*. The anesthetic and perioperative management of a patient with documented hereditary angioneurotic edema. *Anesth Analg* 1977;**56**:571–3.
103 **Hopkinson RB**, Sutcliffe AJ. Hereditary angioneurotic oedema. *Anaesthesia* 1979;**34**:183–6.
104 **Wall RT**, Frank MM. Use of purified C1 esterase inhibitor in patients with hereditary angioedema. *Anesthesiology* 1990;**72**:957.
105 **Lieberman A**. The use of fresh frozen plasma in hereditary angioedema. *JAMA* 1994;**272**:518.
106 **Galan HL**, Reedy MB, Starr J, *et al*. Fresh frozen plasma prophylaxis for hereditary angioedema during pregnancy. A case report. *J Reprod Med* 1996;**41**:541–4. **[AQ:7]**