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C1 inhibitor deficiency: consensus document

M. M. Gompels,* R. J. Lock,* M. Abinun,† C. A. Bethune,‡ G. Davies,§ C. Grattan,¶ A. C. Fay,** H. J. Longhurst,†† L. Morrison,* A. Price,‡‡ M. Price§§ and D. Watters‡‡

*Department of Immunology and Immunogenetics, North Bristol NHS Trust, Southmead Hospital, Bristol, UK, †Department of Paediatrics, Newcastle General Hospital, Newcastle upon Tyne, UK, ‡Department of Immunology, Derriford Hospital, Plymouth, UK, §Department of Paediatrics, Great Ormond Street Hospital, London, UK, ¶Department of Dermatology, Norfolk and Norwich University Hospital, UK, **Department of Immunology, Newcastle General Hospital, Newcastle-upon-Tyne, UK, ††Department of Immunology, St Bartholomew's Hospital, London, UK, §§Primary Immunodeficiency Association, Alliance House, Caxton Street, London, UK, and §§Department of Dermatology, Brighton and Sussex University Hospitals Trust, UK

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Correspondence: Dr M. M. Gompels, Immunology and Immunogenetics, North Bristol NHS Trust, Southmead Hospital, Bristol BS10 5NB, UK.
E-mail: mark.gompels@nbt.nhs.uk

Summary

We present a consensus document on the diagnosis and management of C1 inhibitor deficiency, a syndrome characterized clinically by recurrent episodes of angio-oedema. In hereditary angio-oedema, a rare autosomal dominant condition, C1 inhibitor function is reduced due to impaired transcription or production of non-functional protein. The diagnosis is confirmed by the presence of a low serum C4 and absent or greatly reduced C1 inhibitor level or function. The condition can cause fatal laryngeal oedema and features indistinguishable from gastrointestinal tract obstruction. Attacks can be precipitated by trauma, infection and other stimulants. Treatment is graded according to response and the clinical site of swelling. Acute treatment for severe attack is by infusion of C1 inhibitor concentrate and for minor attack attenuated androgens and/or tranexamic acid. Prophylactic treatment is by attenuated androgens and/or tranexamic acid. There are a number of new products in trial, including genetically engineered C1 esterase inhibitor, kallikrein inhibitor and bradykinin B2 receptor antagonist. Individual sections provide special advice with respect to diagnosis, management (prophylaxis and emergency care), special situations (childhood, pregnancy, contraception, travel and dental care) and service specification.

Keywords: C1 inhibitor deficiency, hereditary angio-oedema, consensus, treatment, management

Introduction

This document was commissioned by the Primary Immunodeficiency Association (PIA). It represents a consensus from patients, experts and the literature on the diagnosis, therapy and management of C1 inhibitor (C1 INH) deficiency.

For the purpose of this document C1 INH deficiency will include both genetic [types I and II hereditary angio-oedema (HAE)] and acquired [acquired C1 inhibitor deficiency (formerly acquired angio-oedema, AAE)] forms of the disease. It should be noted that this is a rare disorder and much of the literature is based on case studies or small series. The syndrome of type III HAE is referred to where appropriate, but is not part of the spectrum of C1 INH deficiency and as such is not covered in depth in this document. The levels of evidence used are listed in Table 1.

Background

C1 esterase inhibitor deficiency [hereditary or acquired (HAE/AAE)] is characterized by the occurrence of subcutaneous and submucosal swellings in any part of the skin and the respiratory and gastrointestinal tracts. In the hereditary form, symptoms usually appear early in life and are normally accompanied by a family history. Although scattered reports of this disease can be traced back to the last century, hereditary angio-oedema reached its own identity in 1963 (for reviews see Cicardi *et al.* [1] and Fay and Abinun [2]).

Table 1. Levels of evidence; where appropriate we have indicated the level of evidence available to support the views expressed in this document as follows

Level 1	Randomized controlled trial
Level 2	Non-randomized trial or case series
Level 3	Case reports
Level 4	Expert opinion
Level 5	None

Genetics and prevalence

The disease is inherited in an autosomal dominant manner. The spontaneous mutation rate is about 25% and more than 100 different C1 inhibitor gene mutations have been described [3]. The prevalence of the disease has been estimated at 1/50 000, with no reported bias in different ethnic groups.

While it is unusual to find the disease without symptoms, there is an extreme variability in their frequency and severity [4]. There seems to be little, if any, correlation between symptoms and type of genetic defect with patients from the same family, and therefore sharing the same mutation, showing wide differences in phenotype [4].

In HAE type I (up to 85% of all patients), there is a deficiency in the amount of C1 INH protein present in the plasma. This is the result of only one gene functioning. However, plasma values are usually 5–30% of normal rather than the 50% value that might be expected [5]. Increased catabolism of C1 INH, even in asymptomatic patients, and possibly decreased production, are likely factors [3,5]. There is also some evidence that certain amino acid substitutions found in type I HAE affect the intracellular transport of C1 INH and result in a marked reduction or the total impairment of protein secretion [3].

In HAE type II, the circulating C1 INH concentration is normal or high but not fully functional. *In vitro* studies show that C1 INH production in type II HAE is normal in contrast to the findings in patients with type I disease [5]. High plasma concentrations of dysfunctional C1 INH are found because the mutant protein is secreted normally and it is unable to form complexes with proteases, which increases its half-life in the circulation. Dysfunctional proteins often result from substitutions at the reactive site residue Arg444, but may also result from changes at several positions outside the reactive site loop.

HAE type III has been described by Bork *et al.* [6]. In this paper, cases with typical clinical features of C1 INH deficiency were described with normal C1 INH level and function and a normal C4. These cases were all female and appeared to have a dominant mode of inheritance.

AAE is said to affect a tenth as many patients as HAE, although this may be an underestimate. AAE presents in older patients, has no family history and is associated with lymphoproliferative disease or, less commonly, autoimmunity [7,8].

Immunology

C1 INH is the main regulator of the early activation steps of the classical complement pathway. This protein is produced mainly in the liver, but also by activated monocytes and other cell types [9]. C1 INH also regulates the activation of kallikrein, plasmin in the fibrinolytic pathway, the activation of factor XI in the coagulation cascade and activated factor XIIa. In the presence of C1 INH deficiency the classical complement pathway can be inappropriately or excessively activated. Immune complexes trigger the activation of the first component C1 to C1 esterase. C1 esterase then acts with its natural substrates C4 and C2 to form the complex C4b2a. Formation of this new complex (and associated C3 activation) leads to the production of anaphylactic, chemotactic and vasoactive peptides (C2b, C3a, C5a). C1 INH protein blocks both the spontaneous activation of C1 and the formation of activated C1, therefore not allowing the C2,4 complex to be created.

In the kinin releasing system, C1 INH regulates conversion of prekallikrein to kallikrein. C1 INH deficiency results in an increase in kallikrein, which in turn increases bradykinin production. Inhibitory effects of C1 INH on factor XIIa, factor XIa and plasmin have also been described. The end result is increased vascular permeability and massive local uncontrolled oedema. While there is some debate as to the exact component that contributes to the angio-oedema, there is accumulating evidence to support the involvement of bradykinin [4,10–12].

Diagnosis

Clinical

A diagnosis of C1 INH inhibitor deficiency is suggested by a history of recurrent attacks of angio-oedema and of abdominal pain (see Table 2). Symptoms include recurrent circumscribed, non-pruritic, non-pitting oedema. Peripheral pain is not usually a feature, unless swelling occurs on pressure bearing areas or where subcutaneous tissue is limited. Oedema can affect virtually any part of the integument, but is more common in the extremities [13]. 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 reported previously in the literature [14]. Abdominal pain, nausea and vomiting are the dominant symptoms in approximately 25% of all patients, and are the result of constriction by intestinal wall and mesenteric oedema [15]. Urticaria is not a feature of C1 INH deficiency. However, prodromal erythema has been reported in up to 25% of patients which may be mistaken for urticaria [16,17].

Classically, the oedema and swelling develop gradually over several hours, increasing slowly for 12–36 h, and then subside after 2–5 days. However, patients may experience

Table 2. Diagnostic features which should prompt investigations for C1 inhibitor deficiency

Angio-oedema
Recurrent
>24 h
Non-pruritic
Non-responsive to antihistamines
Serpiginous rash
No urticaria
Unexplained abdominal pain
Recurrent
'Colicky'
Family history
Low C4

abdominal attacks with a very sudden and severe onset of pain and no visible oedema. Attacks of severe swelling can occur in some patients on a weekly basis and in others happen only once or twice a year.

Angio-oedema can be precipitated by minor trauma to the tissue, such as dental work (said to be a cause in up to 50% of all cases) [18,19], by certain drugs such as oestrogen [20]or angiotensin converting enzyme inhibitors, by emotional stress or by infection [21].

Acute attacks of abdominal pain can mimic surgical emergencies and, before a diagnosis of HAE is established, patients frequently undergo unnecessary appendicectomy or exploratory laparotomy. Equally, after diagnosis, there is always the concern that true abdominal emergencies will not have surgery performed in good time [4]. Barium studies, carried out during an acute attack, show massive submucosal oedema, spiculation and fold thickening or effacement [22]. 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 C1 INH deficiency the gastric mucosa was described as diffusely reddish and oedematous and the mucosal surface in involved areas bulged remarkably, mimicking a submucosal tumour [23]. Histological examination of the bulging area merely showed moderate inflammatory cell infiltration of the lamina propria [23]. These findings are relatively non-specific and response to treatment with C1 INH concentrate may be the only way to differentiate a surgical condition from an acute attack of C1 INH deficiency [4].

Laboratory

Laboratory tests should be performed in an accredited laboratory registered with a suitable quality assurance scheme (e.g. UK National External Quality Assessment Scheme). Serum C4 level is a good screening test for C1 INH deficiency as serum C4 is invariably low in untreated HAE (C4 < 30% of mean normal level) [24]. It has been shown that for untreated C1 INH deficiency low C4 has 100% sensitivity, 100% negative predictive value and is thus an effective screening test [24]. All patients who are suspected of having C1 INH deficiency should have a C4 level measured. If C4 is normal it is not usually necessary to proceed to C1 INH analysis [24]. If the C4 level is low then C1 INH level and function should be assessed.

The diagnosis of type I HAE (85% of cases) is by demonstrating low amounts of C1 inhibitor protein, as assessed by immunochemistry. If C1 inhibitor value appears normal or raised (and C4 is low), a test of C1 inhibitor function should be carried out [18,25]. An absence of function suggests a type II defect. All such tests should be carried out on a fresh (or freshly frozen) serum sample, i.e. one less than 4 h old.

If C1 INH function or/and level are low and C4 is low then a repeat sample should be obtained to confirm the findings. The low prevalence of the condition means that false positives are common [24]. All testing should be undertaken off treatment, including the administration of C1 INH concentrate or fresh frozen plasma, to allow reversion to untreated levels. Ideally this should be for more than a week but longer if borderline levels are obtained.

Interpretation in very young children is difficult, owing to a paucity of data regarding reference ranges in children. C4 is not a reliable indicator in the very young as, again, the reference range is extended downward with respect to the adult reference range [26]. Data suggest that C1 INH is reduced by 30–50% in normal neonates (cord blood analysis), both antigenically and functionally [27]. In children under 1 year of age a low C1 INH (less than 30% mean adult level) confirms the diagnosis of HAE. However, the diagnosis cannot be excluded in a child under 1 year of age, even if the C1 INH level and function are normal. In this case, investigations should be repeated when the child is over 1 year.

There is evidence that pitfalls in the diagnosis are common, with 11 of 42 cases reviewed recently found to have a questionable diagnosis [28]. Established or transferring cases should be reviewed for validity of the diagnosis. In the presence of a low C1 INH level or function but a normal C4 the diagnosis of HAE must be questioned. We would advise that, in these circumstances, C1 INH be rechecked by a different method (evidence level 4). Currently, genetic tests are not indicated routinely; however, under certain circumstances a genetic test may be of use, if available. In cases where the diagnosis is established, C4 and levels of C1 INH and function may be useful to monitor treatment effect.

Management

Primary prevention

Management of patients with C1 INH inhibitor deficiency 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 and other foci of infection, which may activate complement, should be sought and treated [29,30]. Eradication of *Helicobacter pylori* may be beneficial [31,32] (evidence level 3). Patients and their general practitioners (GPs) should be advised that infections should be treated promptly.

Advice on use of contraceptives and hormone replacement therapy should emphasize avoidance of oestrogen (see below, 'Special situation-contraception'). Angiotensin-converting enzyme (ACE) inhibitors need to be avoided because of their effects on the kallikrein–bradykinin pathway [33]. Both HAE and AAE may be manifest for the first time after treatment with ACE inhibitors or oestrogens [34,35] (evidence level 3). Angiotensin-II receptor antagonists may also induce angio-oedema in normal patients [36,37], although the majority of patients with ACE-inhibitor-induced angio-oedema tolerate angiotensin-II receptor antagonists [38]. Angiotensin-II receptor antagonists may be used with caution in patients with C1 INH deficiency. Beta-blockers or diuretics should be considered first-line treatment for hypertension in patients with C1 INH deficiency. There is no evidence for or against the use of methyldopa to control hypertension in this group of patients.

Attacks are likely to become more frequent at times of physiological or psychological stress, so it may be sufficient to use prophylactic drugs during such periods only, thus minimizing adverse effects. Nevertheless, there will be a group of patients who will require intermittent or continuous, long-term prophylaxis.

The threshold for treatment should be a joint decision between clinician and patient. It should include an assessment of the severity, frequency and life-threatening nature of the attacks. This, in combination with the patient's circumstances, should allow the development of an appropriate treatment plan.

Long-term prophylaxis

The regimen for each affected individual should be guided by the severity of the disease. Frequent attacks of peripheral angio-oedema (extremities, trunk), although unpleasant and annoying, are not dangerous and may not require (contingent upon the patient's judgement) long-term prophylaxis. However, prophylactic administration of antifibrinolytic agents (tranexamic acid [39] or epsilon-aminocaproic acid (EACA; not licensed in the UK) [40]) and/or synthetic attenuated androgens (danazol [41–43] or stanozolol [43–46]), has proved useful in reducing the frequency or severity of attacks (evidence level 2/3). Other androgens (methyltestosterone [47], fluoxymesterone [48] and oxymetholone [48,49]), can be used in adult males (evidence level 3). Non-17 alpha alkylated derivatives, such as nandrolone, appear to be ineffective and should not be used [43].

A graded approach to the level of treatment can be tailored to the individual with minor peripheral episodes. Consideration could be given to a course of tranexamic acid before attenuated androgens. Maintenance treatment should be considered in any patient who has had more than one episode of severe abdominal pain in one year or any head or neck swellings, frequent peripheral or genital swellings or a requirement for concentrate more than once a year. Fatal episodes have occurred in patients who previously have had only mild or benign attacks [50] (evidence level 2).

Antifibrinolytic agents

Antifibrinolytic agents inhibit plasminogen activation with consequent 'sparing' of C1 INH usage. They decrease the number and the severity of attacks [19], but are not as effective in this as the attenuated androgens [40] (evidence level 2). Their side effects include nausea, vertigo, diarrhoea, postural hypotension, fatigue and muscle cramps with an increase in muscle enzymes concentrations [1,39,40,51–53] (evidence level 2/3), and theoretical concerns about thrombus formation and thrombotic episodes [18]. However, recent reports have suggested that these side effects are less common than thought previously; long-term use in menorrhagia has shown no evidence for increased thrombus formation [53]. The finding of tumours of the retina and liver in experimental animals after long-term use of tranexamic acid [18] has limited its use in the United States [15], but not in Europe [54,55]. Although a teratogenic effect of EACA has been postulated in the period of embryonic growth and development [18,56] it is being used in the United States [57], it has been used in children [58] and, surprisingly, has been recommended during pregnancy [59].

A starting dose of 1–1·5 g of tranexamic acid up to two to three times a day [60] should be used depending on disease severity, reducing to 0·5 g once or twice a day as the attacks remit. In children, the dosage will need to be adjusted (see Table 3). Diarrhoea may be a limiting side effect. Patients should be warned of this possibility and, if necessary, the dose titrated against side effects (evidence level 4).

Although there is no evidence of teratogenicity from animal studies, we recommend avoiding the use of tranexamic acid in pregnancy, if possible. The *British National Formulary* (*BNF*) indicates that regular eye examinations and liver function tests (LFT) should be performed, while recognizing that the evidence base for this is minimal. We suggest that fundoscopy should be performed annually, with referral if symptoms occur, and LFT performed every 6 months.

Attenuated androgens

Attenuated androgens increase the biosynthesis of many proteins, including the hepatic production of C1 inhibitor protein [18]. Danazol, stanozolol and oxandrolone are most commonly used. Their side effects, which are dose-dependent, include weight gain, virilization, muscle pains and cramps, headaches, depression, fatigue, nausea, consti-

Table 3. Treatment summary. The regimen for each affected individual should be guided by the severity of their disease and thus titred to individual need. The following is a guide to the dosage and summarizes the advice given in the text

Intervention	Therapy	Dosage (adult)	Dosage (children)	Monitoring tests
Long-term prophylaxis	Attenuated androgens	Danazol 200 mg once or twice per day; up to 400 mg/day in <20% of cases Stanozolol up to 5 mg once or twice per day Oxandrolone 2·5–20 mg divided dose 2–4 times per day (use lowest effective maintenance dose, consider alternate-day or 2× weekly regimen)	[Only if indicated (very rare), see text] Danazol 100–200 mg/day (use lowest effective maintenance dose, consider alternate-day or 2× weekly regimen)	Six-monthly: liver function tests Annual: lipid profile Biennial: hepatic ultrasound (annual after 10 years' treatment)
	Tranexamic acid	Starting dose 1–1·5 g 2–3 times per day, reducing to 0·5 g once or twice per day	1–2 g per day; dosage depends on age and size; general guide is 50 mg/ kg/day (use lowest effective maintenance dose, consider alternate-day or 2× weekly regimen)	Six-monthly: liver function tests
Short-term prophylaxis (e.g. for dental work)	C1 inhibitor concentrate	500–1500 U up to 24 h prior to procedure	<10 years old 500 U, >10 years old 1000 U up to 24 h prior to procedure	
	Attenuated androgens	Danazol 100–600 mg/day for 48 h before and after procedure Stanozolol 2–6 mg/day for 48 h before and after procedure	Danazol 300 mg/day for 48 h before and after procedure	
	Tranexamic acid	1 g given four times daily for 48 h before and after procedure	500 mg given four times daily for 48 h before and after procedure	
Emergency care for acute attacks	C1 inhibitor concentrate	500–1500 U; additional infusion and reassessment if symptoms persist for >2 h	<10 years old 500 U, >10 years old 1000 U	Baseline: liver function tests, hepatitis virology
	Attenuated androgens	Danazol up to 1 g/day Stanozolol up to 16 mg/day		
	Tranexamic acid	1 g given four times daily for 48 h		
	Fresh frozen plasma	2 units (only for use where C1 INH concentrate not available)		Baseline: liver function tests, hepatitis virology
	Pain relief	As appropriate		
Pregnancy	Attenuated androgens	Contraindicated		
	Tranexamic acid	May be used with caution		
	C1 inhibitor concentrate	Emergency care as above. Severe cases may require regular replacement		

pation, menstrual irregularities and liver function derangement [46,61,62] (evidence level 3). Decreased growth rate in children [63–65] is the main contraindication for their use in this age group. Androgens can cause masculinization of the female fetus [66,67] and thus are contraindicated during pregnancy. Androgens, particularly the 17-alpha alkylated androgens, may have hepatic side effects, including cholestatic jaundice [68], peliosis hepatis [69] and hepatocellular adenoma [70–73]. The observed cases of hepatocellular adenomas developing in patients with C1 INH deficiency on long-term prophylaxis with danazol have caused particular concern [74] (evidence level 3). A dose of danazol 200 mg once or twice a day will usually suffice in adults, preventing attacks in 80% of cases [7] (evidence level 2). Because of the wide variations between individuals with this condition the dosage must be titrated to individual need and up to 400 mg twice a day may be required. Conversely, once symptom control is established, many patients remain well on doses as low as 100 mg thrice weekly. Stanozolol at a dose of up to 5 mg once or twice daily can be used where available [46]. To facilitate more accurate titration of dosage a 2 mg tablet has been introduced. Stanozolol is available in the United Kingdom

only by importation and on a 'named patient' basis. The recommended adult dose for oxandralone is 2·5 mg to 20 mg given in two to four divided doses [75]. Again, the doses of these should be titrated according to individual need. In some cases combined therapy, e.g. attenuated androgens plus tranexamic acid, may be beneficial.

Some male and many female patients experience troubling or unacceptable side effects on their prescribed dose of attenuated androgens. It is important to explain the advantages and disadvantages of the treatment regimen, to discuss fully possible side effects with the patient and to monitor regularly the acceptability of such side effects.

Long-term C1 INH prophylaxis

Long-term prophylaxis with C1 INH may be necessary in patients where tranexamic acid or steroids are not effective, not tolerated or contraindicated. This may include those with underlying thromboembolic disease or during pregnancy. Prior to recommending regular therapy, access to C1 inhibitor for acute attacks should be optimized, by home therapy training if necessary. In exceptional cases where this approach does not provide sufficient symptom control, regular C1 inhibitor infusions of 500–1000 U twice weekly may be required.

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 C1 inhibitor concentrate can be given up to 24 h before the procedure [25], or just prior depending on the individual circumstances [55,76]. It is impossible to predict the requirements of an individual patient in such a situation; body mass and previous requirements will be helpful indicators. In general, an infusion of 1000 U of concentrate should be sufficient for most dental work and most planned surgery for an adult patient but requirements may vary from 500 to 1500 U. A further dose may be required, particularly if there is postoperative infection.

Administration of antifibrinolytics or attenuated androgens, starting 5 days before the procedure and the following 2 days thereafter [54], is an alternative. There are no data on the relative efficacy of concentrate to attenuated androgens in this setting. Tranexamic acid has been used at a daily dose of 4 g (1 g four times daily) for adults [77,78] or 2 g (500 mg four times daily) for children [55], given 48 h before and after surgery. However, it seems that most authors prefer attenuated androgens, where concentrate is not used, even in children [18,54] at a dose of 100–600 mg/day for danazol or 2–6 mg/day for stanazolol, given 48 h before and after surgery [1,18,46,54]. See below, 'Dental care', for further information on dental care.

Patient possession of C1 INH concentrate

All C1 INH deficiency patients should be offered the opportunity for home possession of C1 INH, of a sufficient therapeutic dose to treat a laryngeal emergency, as 50–75% have a life-threatening attack at some time [1,79].

A UK audit has shown that home possession could reduce the number of avoidable adverse effects [80] (evidence level 2). In order to be effective good local links to accident and emergency and a care management plan are also essential.

Home possession – patient-directed administration

The management of patient-administered C1 INH concentrate is in need of standardization. Therefore, the attached recommendations (adapted from the TRIC Guidelines for Home Therapy and Home therapy for C1 INH deficiency, St Bartholomew's Hospital) are put forward as example assessment guidelines to be instituted prior to home therapy being initiated (see Table 4).

Home therapy requires the issuing of concentrate and the training of participants of all eligible patients with C1 INH deficiency (see Table 5). It provides a quick, convenient and

Table 4. Home therapy programme recommendations, adapted from TRIC Guidelines for Home Therapy and Home therapy for C1 INH deficiency, St Bartholomew's Hospital. The consultant immunologist/designated specialist and the immunology nurse specialist (or suitably accredited home therapy team) will assess the suitability of an individual for entry into the programme based on the following

Criteria for entry onto the programme
• Proven C1 inhibitor deficiency
• The patient's use of and compliance with prophylactic therapy should be optimal
• In order to maintain required infusion skills, the patient should normally require infusion of C1 INH at least every 3 months
• The patient must be motivated to comply with the home therapy programme and all its implications and willing to be responsible for giving their home therapy. Written consent confirming this must be obtained before the programme is commenced
• The patient must be counselled regarding the risk of transmissible infections from a blood product. The patient should demonstrate an understanding of this and provide written informed consent to receive therapy
• The patient must have a partner willing to attend the home therapy programme who will be present when therapy is required
• Written confirmation of support for home therapy must be agreed with the patient's general practitioner, including emergency support or an agreed pathway of emergency care
• The patient must have access to a telephone when administering therapy
• The patient must have good venous access
• The patient must agree to call for an ambulance if self-cannulation is unsuccessful when concentrate is required
• In most circumstances home therapy is not employed in children (see section 'C1 inhibitor concentrate in children')

Table 5. The home therapy training programme

Should include the following key areas:
• Appropriate use of concentrate
• Hand washing
• Asepsis
• Supply and storage of concentrate and equipment
• Preparation of equipment for administration of concentrate
• Product checking procedure, i.e. dosage; expiry date
• Demonstration of the correct technique for reconstitution of solution
• Cannulation with butterfly
• Blood sampling preinjection/infusion
• Administration of injection/management of infusion
• Management of adverse reactions
• Automatically injectable adrenaline/epinephrine training (for treatment of anaphylaxis of infusion)
• Disposal of equipment
• Documentation, e.g. accurate recording of batch number
• Documentary evidence of the individual's training and competence
• Receiving and monitoring infusion logs and other relevant documentation for any indication of difficulties
• Investigating any adverse reactions/events and taking appropriate action
• Keeping the specialist nurse/consultant immunologist informed of any relevant issues regarding care and treatment
• Compliance with clinic visits
• Performing an annual review of the individual's competence to administer injection/infusion
• Liaising with the individual, their G.P, consultant immunologist, pharmacist and other relevant care providers

probably safe method of dealing with acute attacks of angio-oedema [80]. This is particularly valuable where access to emergency care is likely to be difficult through reasons of resource or geography.

However, there are also a number of important safety considerations. There has to be provision of refrigeration facilities for the storage of the product. Reassuringly, experience has shown that the product retains efficacy for many months under less than optimal storage conditions (e.g. 6 months at 25°C) (evidence level 4). Very recently a new formulation has undergone a series of room temperature storage tests and has shown good long-term stability [81]. Experience with C1 INH indicates that adverse reactions are very rare. Home therapy programmes with intravenous immunoglobulin have demonstrated that it is possible to train patients, with an 'infusion partner', to manage infusions and adverse events safely at home. Because C1 INH is likely to be required when the patient is unwell, 24-h emergency treatment at the local hospital must remain an option. Patients and carers should be encouraged to use this option where appropriate. There is also a requirement to maintain competence in the administration of home infusions. This can be undertaken by infusion practice, using normal saline, and training update at regular intervals.

No home therapy should occur without a well-compiled protocol (Tables 4 and 5). Where provided, home therapy programmes should automatically include systematic audit to acquire evidence on the safety and efficacy of such a programme.

Home possession – healthcare-directed administration

A number of patients may not wish to, be able to or fail to achieve the self-directed administration of C1 INH. An alternative in these cases is to have a supply of concentrate held by the patient for their use under the supervision of the healthcare system. This may involve their general practitioner, local emergency department or a department where they are visiting. There is evidence that self-possession reduces the time patients spend awaiting infusions [80] (evidence level 2).

Any such programme should be accompanied by appropriate information to be carried with the patient and advice as to strategies for resupply of concentrate.

Monitoring side effects of treatment

Tranexamic acid

The *BNF* recommends that patients who receive long-term tranexamic acid have a regular eye examination, but notes that this is based on unsatisfactory evidence [60]. The *BNF* further recommends regular checks of liver function (evidence level 4).

Use of tranexamic acid is contraindicated in active thromboembolic disease. Hence, if there is a personal or family history of thromboembolic disease, we suggest a thrombophilia screen should be performed before commencing treatment (evidence level 4).

Attenuated androgens

Liver function tests should be performed every 6 months; both tranexamic acid and attenuated androgens can cause abnormalities. Danazol and other attenuated androgens may affect lipid metabolism and thus confer an added risk of cardiovascular disease. Therefore, lipids should also be checked at presentation. Fasting lipids need testing only where initial screening is abnormal. Thereafter we recommend checking at 6 months and 1 year. When patients have no increase in their attenuated androgen dose, no weight or dietary change, if lipids are stable after 12 months, further checking annually is sufficient (level of evidence 4).

Hepatic ultrasound

The report of hepatocellular adenomas developing in patients with C1 INH deficiency on long-term prophylaxis with danazol [74] (evidence level 3) has indicated that ultrasound screening may be useful. As yet there are no data to indicate the extent of the problem or the frequency of screening required.

Danazol and other 17-alpha-alkylated steroids are associated with increased risk of peliosis hepatis and hepatic adenoma [82]. We recommend that all patients taking regular or frequent courses of attenuated androgens should have a baseline ultrasound, which should be repeated every 2 years, or annually in patients who have been treated for more than 10 years. This recommendation is based on expert opinion (level 4) [74,83–85].

Emergency care

Treatment of acute attacks depends on their severity. Episodes of peripheral swelling only usually do not require treatment, but stanozolol (up to 16 mg/day [86]) or danazol (up to 1 g/day) given early during an attack may shorten its duration. Involvement of the upper airway usually begins slowly but cases of progression within 20 min have been reported [50]; voice alteration and dysphagia indicate high risk of total airway obstruction. If there is any suspicion of airway involvement C1 INH concentrate should be given promptly. The dose requirement will vary between individuals, dependent on body mass and the seriousness of the condition. In a life-threatening situation we recommend 1000–1500 U. In other situations 500–1000 U is often sufficient. Administering C1 INH concentrate shortens the duration of attacks by about a third and also halves the time to the beginning of the relief of symptoms [25].

For acute attacks of abdominal oedema, pain relief should be given at an appropriate level. Non-steroidal anti-inflammatory drugs are useful in the treatment of abdominal pain. If the attack is severe, C1 INH concentrate should be infused at the same dose as above. Early intervention prevents avoidable pain and reduces disruption to the patient's life. The patient should be observed closely until symptoms start to improve. The median time to the beginning of the relief of symptoms after concentrate infusion is 0·5–1·5 h, with complete resolution of symptoms after 24 h [25]. If symptoms persist at a high intensity 2 h after infusion, additional C1 INH concentrate should be given and alternative diagnoses should be considered.

C1 INH concentrate is available throughout Europe. It has been available since the early 1980s [87], and shown to be effective in case series and a controlled trial [76,88,89] (evidence level 2). If concentrate is not available then fresh frozen plasma (FFP) or solvent detergent-treated plasma may be given (evidence level 3), although this may worsen symptoms during the acute phase [15,18,56] because it contains high concentrations of complement components. A solvent/detergent-treated plasma (Octaplas, Octapharma AG, Vienna, Austria) has been evaluated for use in HAE, but there are few data regarding efficacy [90].

There are no randomized trials comparing plasma with C1 INH concentrate or with placebo. The risk of pathogen transmission may be increased if plasma is used [91,92]. Therefore, plasma is not an acceptable alternative where emergency treatment is foreseeable.

Adrenaline is used to treat angio-oedema and hypovolaemia associated with type 1 hypersensitivity. In the context of HAE there is little evidence that, relative to other treatments, it is efficacious.

Potential new therapies

New inhibitors of the fibrinolytic system, such as the kallikrein inhibitor DX88 (Dyax Corp., Cambridge, Massachusetts, USA) and the bradykinin B2 receptor inhibitor Icatibant (Jerini AG, Berlin, Germany), hold promise for use in the treatment of C1 INH deficiency [93] and trials are commencing. Recombinant C1 inhibitor (Pharming Group NV, Leiden, Netherlands) has been developed and trials should be available in the near future [94].

Special situations

In pregnancy and delivery

Treatment of the disease during pregnancy has special problems. Of published reports, some anecdotes report worsening of the disease [95] (evidence level 3), but few attribute premature labour or stillbirths to the disease [96,97]. 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 [18] (evidence level 2). Ideally, all prophylactic drugs should be stopped during pregnancy and, if possible, before conception. Of particular note, attenuated androgens are contraindicated during pregnancy [98]. If prophylaxis is required, tranexamic acid may be used with caution. Although tranexamic acid crosses the placenta, there are no data to suggest that tranexamic acid is teratogenic. Further, there does not appear to be an increase of thromboembolic events [99] (evidence level 2). Severe attacks during pregnancy should be treated with concentrate as in the non-pregnant patient. Severe cases may require regular C1 INH replacement therapy.

There is little evidence that complications from C1 INH deficiency are common in vaginal delivery. The consequences of an attack during delivery are potentially serious. Individual patients should be discussed with the obstetrician. Consideration should be given to the obstetric risk (e.g. primigravida), C1 INH deficiency history and the patient's own views. The safest obstetric approach would appear to be to administer a predelivery infusion of 500–1000 U C1 INH concentrate [100]. In a low-risk pregnancy without pretreatment with C1 INH concentrate we recommend that C1 INH should be available in the delivery suite. There may be local swelling of the vulva and infusion sites, but this would not be treated unless urethral obstruction was a problem [21]. If an operative delivery is undertaken, regional analgesia is to be preferred to endotracheal intubation in order to avoid laryn-

geal trauma [101] (level of evidence 3). In all situations the clinician should consider the postpartum period one of higher risk of acute attacks.

Contraception

Oestrogens should be avoided where possible. The use of combined oral contraceptives exacerbate symptoms in HAE patients [102,103] (evidence level 3). A recent study reported that over 60% of HAE types I and III patients have more frequent attacks on oestrogens [20] (evidence level 2). In general, progesterone-only pills such as levonorgestrel are preferred. Progesterone may have a mildly protective effect. No published data exists regarding the use and safety of intrauterine devices.

Dental care

Trauma can precipitate acute oedema in patients with C1 INH deficiency. For this reason dental work carries a risk of triggering an attack. Fatal laryngeal attacks have been reported following tooth extraction [88]. However, attacks are unpredictable. Extensive dental work may be carried out without complication and conversely minor work may sometimes precipitate an attack [104].

All patients should be warned of the increased risk of an attack in the 36 h following dental procedures and should have rapid access to C1 INH replacement in the event of an attack [105], irrespective of whether they have received prophylaxis. Recommendation for prophylaxis should take account of the proposed dental procedure and of previous reactions experienced by the patient.

Danazol, C1 INH concentrate and FFP have all been recommended for prophylaxis [88,104,106]. We believe that correction with C1 INH is to be preferred for more invasive dental procedures (e.g. extractions). It is more physiological than treatment with attenuated androgens and is more likely to reliably achieve normal levels of C1 INH. Furthermore, use of C1 INH overcomes any potential doubt regarding adherence with anabolic steroids (evidence level 4).

Travel

The following advice is taken from the Primary Immunodeficiency Association (PIA) advice for HAE patients when travelling in the United Kingdom and abroad. Further advice can be obtained via the PIA website [http://www.pia.org.uk]. The advice falls into two broad categories: general administrative advice and that related to emergency treatment.

General advice

Wear a Medic Alert bracelet. Obtain form E111 from your local post office if travelling in Europe. Arrange travel insurance that will cover HAE. Discuss the situation well in advance with your consultant for advice on medication and emergency treatment. A doctor's letter will be required in order to take C1 INH through airport controls. Medications should be declared at the baggage checks and carried as hand luggage in a coolbag.

Emergency advice

Carry a consultant's letter giving instructions about emergency treatment and a 24-h emergency advice telephone number (translated if travelling abroad). All HAE patients should have an emergency dose of C1 INH to keep with them when travelling away from their home base, as well as standard treatment.

Children

Attacks are seen during childhood in most patients [18,107]. Although the diagnosis is usually made in the second or third decade of life [18,108,109], 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 [1,4,7,54,110] 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 [58,111]. Occasional patients will have their first symptoms even earlier, before the age of 1 year [27,110,112,113]. 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 [55,58,107].

It is important to note that attacks of laryngeal oedema can occur at any age and may be life-threatening [79]. For this reason, particularly where there is a family history, children should be tested at an early age. There are few data confirming the reference range for C1 INH in the very young. We would advocate testing both C4 and C1 INH to confirm the diagnosis in these circumstances.

Long-term prophylaxis of attacks in children

This is a relatively unexplored issue [58,111], and most references state that the use of antifibrinolytics and androgens are not recommended because of the serious side effects of these drugs [25,76].

Severe or life-threatening attacks of C1 INH deficiency are less common during childhood but they do occur. Although earlier reviews suggest prophylaxis is rarely required in children [15,55], this view is changing with increasing experience with tranexamic acid. Long-term prophylaxis is

Table 6. Major considerations regarding potential long-term prophylaxis for C1 INH deficiency in children

Four attacks per year requiring possible admission and intravenous fluids should not be taken lightly
The use of attenuated androgens is hardly ever indicated as long-term prophylaxis prepuberty

justified not only in severely affected children, defined by attacks of laryngeal oedema and/or frequent (more than one every 3 months), recurrent attacks of abdominal pain causing distress and disability. In this situation, antifibrinolytics are preferred to androgens [54,58,111]. The individual minimal effective dose, irrespective of serum concentrations of C4 and/or C1 INH, for both antifibrinolytics and/or androgens used for long-term prophylaxis, has to be established and adjusted with growth. The use of prophylactic attenuated androgens in children is hardly ever indicated and if tranexamic acid is ineffective then regular infusions of C1 INH concentrate should be considered (Table 6).

Attenuated androgens

Attenuated androgens are associated with increased risk of androgenization, premature puberty, accelerated bone fusion with limited growth, liver disorders, atherogenesis and behavioural problems. The use of danazol in children [114,115], particularly its potential effect on development, is a cause for concern, even when used with caution [116,117]. Maintaining the lowest effective dose and an intermittent regimen is very important [118]. Attenuated androgens may be helpful in children with frequent abdominal attacks (>1/month). In this case attenuated androgens should be used for the shortest period and with the smallest effective dose possible. Early withdrawal is advocated and it is recommended that the patient be under joint care with a paediatrician.

Patients with HAE treated with danazol long-term have a theoretical possibility of an increased risk of arteriosclerosis. There is an increased incidence of arterial hypertension [83,119] and the long-term use of androgens has been reported to decrease the concentration of high-density lipoproteins [15,120–122].

Antifibrinolytics in children

Tranexamic acid at a dose of 50 mg/kg/day [54] or 1·5 g/day [52,55] has been used long-term with similar benefit and no side effects. Long-term administration of high dose EACA (12–24 g/day) in children was associated with side effects in all, but when the dose was 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 [58].

It has been proposed that the long-term use of antifibrinolytics, by plasmin inhibition, could also predispose to arteriosclerosis [58,123]. This is of particular importance if long-term prophylaxis is to be started during childhood because several decades of treatment may be needed.

C1 inhibitor concentrate in children

C1 inhibitor concentrate has been used successfully for long-term replacement in selected adult patients [124], and more recently it has been shown to be superior to a placebo in a double-blind controlled study [76]. In an uncontrolled trial during long-term follow-up of 14 children with C1 INH deficiency, acute attacks in six children were treated with a single dose of 500 U of C1 INH concentrate (Immuno AG, Vienna, Austria) on 30 separate administrations. Progression of facial and laryngeal oedema was aborted 30–60 min after the infusion and disappeared gradually over the next 24–36 h. The dose had to be repeated after 60 min on only two occasions because laryngeal oedema continued to progress. Concentrations of C1 INH and C4, when measured 12 and 24 h 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.

Based on the clinical benefit seen in these patients, a role for C1 inhibitor concentrate in long-term prophylaxis for children has been suggested [76], supporting the few earlier proposals [15,125]. In children home therapy is difficult because of technical problems with intravenous access. However, home availability of concentrate has been shown to reduce access time in adults [80] and home possession of concentrate should have similar benefits in children [76,125,126]. Advice should be given that at the earliest sign of an attack involving the upper airway, treatment and medical assistance should be sought. The disadvantages to this approach to the management are expense [117] and the possibility of viral transmission. Despite the lack of evidence of viral transmission with current pasteurized products caution is required when recommending any blood product, particularly in respect of emerging infections.

Abdominal oedema in children may be the major presenting symptom of an acute attack. The many other causes of abdominal pain in childhood need to be considered. The cardinal feature of abdominal oedema in these cases is severe abdominal pain, usually with vomiting, which lasts several hours and may mimic acute appendicitis. Early treatment of symptoms is effective and may reduce the requirement for further treatment. It may also lead to avoidance of inappropriate surgery. Therefore, home possession of C1 INH concentrate may be beneficial. It is important that a management care plan is in place for the patient, ensuring sufficient supply for use and for immediate replacement after use to ensure an adequate supply in case of further attacks. See 'Patient possession of C1 INH concentrate' for further details on home possession of C1 INH.

The appropriate therapeutic dose to be held will depend on the size of the child and should be agreed with the specialist.

Table 7. Advice on use of C1 INH concentrate

C1 INH concentrate should only be given for severe attacks of swelling where there is a risk of airway involvement, for severe attacks of abdominal pain or uncontrolled disease
Liver function and viral status of these patients should be monitored regularly and records kept of all infusions given
Patients should be fully informed of the potential risks and involved in treatment decisions
Consideration should be given to vaccinate patients who are not immune to hepatitis A or B

The viral safety of C1 inhibitor concentrate

As with any blood product, viral safety is always a matter of concern. There are reports of transmission of hepatitis C virus (HCV) by non-virus inactivated C1 INH concentrates used before 1985 [110,127,128]. Several studies confirmed the safety of a heat treatment step in the production of a C1 inhibitor concentrate [25,76,128,129] and no transmission of the human immunodeficiency virus, HCV or hepatitis G virus (HGV) was observed in these studies. None the less, surveillance of patients treated with concentrate is essential [130] (see Table 7).

The patient should be informed of the potential dangers of viral infection, given a clear explanation of the safety record of the product, the comparative risk with using other therapies and the risk of failing to treat laryngeal angio-oedema. We recommend monitoring schedules consisting of pretreatment screening for hepatitis B, hepatitis C, alanine aminotransferase (ALT) and storage of serum and DNA. Six-monthly liver function tests are recommended if concentrate has been infused. Recombinant preparations of C1 INH, if successful, would overcome many of these difficulties.

By analogy with the recommendations in haemophiliac patients [131], consideration should be given to vaccinate patients who are not immune to hepatitis A or B and who currently receive, or may require, blood products. Note that the hepatitis A vaccine is not licensed for use in children under the age of 1 year.

FFP is effective in the treatment of acute attacks [132,133] and in short-term prophylaxis [101,134,135], but carries significant risks of pathogen transmission, anaphylactoid reactions, alloimmunization and excessive intravascular volume [15,25]. FFP is used when C1 INH is unavailable but is not acceptable where emergency treatment is foreseeable or as prophylactic treatment [109,136,137].

Service specification

Diagnosis

The laboratory diagnosis should be made only by a CPA-approved laboratory with the input of a clinical immunologist.

Treatment, local versus regional

Ensure that each region has nominated centres with an immunologist and specialist nurse input. The centre(s) must have a sufficient number of patients and expertise to competently diagnose patients and competently develop individual management plans, written protocols and advice sheets for patients. This should include advice on where and how to seek assistance in the emergency situation, the appropriate testing of relatives and general management of the condition. Appropriate home therapy training should be available. Remote patients will be monitored locally by the dermatologist or other designated physician following protocols with reference back to the regional centre within the protocols.

Information

Patients should have written information on their condition, its treatment, the side effects of treatment and a plan on how to obtain emergency treatment.

Training infusion

- Immunology or equivalent specialist to manage home therapy training programme.
- Immunology or equivalent specialist to liaise with accident and emergency (A&E) departments and GPs regarding treatment of acute attacks of C1 INH deficiency.
- Immunology or equivalent specialist to have a key role in the ongoing education and support of the patient with regard to all aspects of their HAE management programme.
- Emergency care: A&E, primary care and home therapy.

A&E departments

A treatment plan or protocol for the management of patients with C1 INH deficiency should be accessible in the department. Long waiting-time in A&E is a major factor in disruption to work or education and quality of life, and deters patients from seeking appropriate treatment. Protocols should include mechanisms for prioritizing these patients, for example nurse-led protocol-driven treatment with medical review if necessary.

The immunology nurse/nurse specialist should liaise with senior A&E medical and nursing staff to ensure staff have a basic knowledge of C1 INH deficiency and are aware of locally known patients with this diagnosis.

Senior medical and nursing staff should know how to obtain and administer C1 INH concentrate – this should be covered in the protocol.

A&E staff should be aware of how to access specialist (immunology) team if advice is required – this should also be covered in the protocol.

GPs

A treatment plan or protocol for the management of C1 INH deficiency should be sent to GP practices. GPs should be made aware of any C1 INH-deficient patient registered with their practice. If the patient intends to infuse concentrate at home, the patient's GP should be informed. Appropriate emergency cover for any complications must be provided.

The immunology nurse/nurse specialist should liaise with the GP regarding concerns or problems with home therapy, or other relevant issues relating to management of C1 INH deficiency patients.

Outcome measures

In the context of clinical governance, the following are considered as suitable (i.e. measurable) topics for clinical audit.

- Number of acute attacks per patient per year.
- Quality of life scores.
- Attack/pain to needle time.
- Frequency of visits to A&E.
- Death.
- Side effects of treatment, such as abnormal liver function tests or liver ultrasound.
- Compliance of centres with guidelines.

Register of patients

In order to improve further the understanding of HAE and to improve service to patients it is recommended that regional units submit patients' details to the European register. A form for this is provided on the internet at http://www.haeregister.org.

Patients' perspective

The key aims of C1 esterase inhibitor-deficient patients

- For each C1 INH-deficient patient to be able to manage his/her symptoms proactively in such a way that they maintain personal safety and minimal disruption in living a healthy and productive life.
- The universal availability of effective C1 INH deficiency management for all patients.
- To avoid misdiagnosis, inappropriate treatment and unnecessary surgical procedures.

Achievement of key aims

This can be achieved by:

- the referral of all patients to a specialist who has experience of C1 INH deficiency treatment.
- Recognizing the provision and key role of the specialist nurse in educating and supporting C1 INH deficiency patients.
- Effective communication between the team involved in the individual patient's care.
- Disseminating information to both health professionals and patients.
- Networking and information sharing between all the specialities treating C1 INH deficiency patients so that there is an agreed approach to the key issues of C1 INH deficiency management.

Outcomes

- The patient has an enhanced quality of life. He/she is more likely to maintain employment and contribute fully to the life of the community. This reduces the requirement for support.
- It has been well demonstrated in other chronic conditions that the informed patient who takes responsibility for their condition will make fewer demands on healthcare systems.
- The effectiveness of this approach would be shown in fewer visits to GPs, consultants, A&E departments, less use of ambulance services and less need for hospital in-patient treatment.

Acquired angio-oedema

The recent paper by Cicardi *et al.* [8] has shown importantly that in long-term follow-up (up to 24 years, median 8 years), the majority of cases was associated with lymphoproliferative disorders, predominantly monoclonal gammopathies of uncertain significance (MGUS). This is important because approximately 1% of MGUS per year progress to myeloma or a related disorder [138]. A minority of cases is associated with non-haematological malignancy, infection or autoimmune disorders. Where possible, treatment of the underlying pathology may lead to resolution of the disorder [30,32] (evidence level 3). Otherwise, the treatment is similar to HAE. Antifibrinolytics are more effective than attenuated androgens in this group [8] (evidence level 2). In the series of Cicardi *et al.* [8] therapy with C1 INH concentrate was necessary in 12 of 28 patients, of whom three became progressively resistant.

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, the authors can accept no legal responsibility or liability for any omissions or errors that may be made.

Consultation process

The standards were developed by the project Advisory Group (see Table 8 for membership) with the project consultants.

Consultation on draft standards was undertaken through:

Table 8. Membership of the advisory group

Chair	Mark M. Gompels	Consultant immunologist	Southmead Hospital, Bristol
Group members	Mario Abinun	Consultant paediatrician	Newcastle General Hospital
	Claire A. Bethune	Consultant immunologist	Derriford Hospital, Plymouth
	Graham Davies	Consultant paediatrician	Great Ormond Street Hospital, London
	Clive Grattan	Consultant dermatologist	Norfolk and Norwich University Hospital
	Anne C. Fay	Consultant immunologist	Royal Victoria Infirmary, Newcastle upon Tyne
	Robert J. Lock	Clinical scientist in immunology	Southmead Hospital, Bristol
	Hilary J. Longhurst	Consultant immunologist	St Bartholomew's Hospital, London
	Leigh Morrison	Specialist immunology nurse	Southmead Hospital, Bristol
	Anne Price	Patient representative	Primary Immunodeficiency Association, Alliance House, Caxton Street, London
	Megan Price	Consultant dermatologist	Brighton and Sussex University Hospitals
	David Watters	Chief executive	Primary Immunodeficiency Association, Alliance House, Caxton Street, London
Writing team	Mark M. Gompels		Southmead Hospital, Bristol
	Robert J. Lock		Southmead Hospital, Bristol
	Leigh Morrison		Southmead Hospital, Bristol

- A 1-day facilitated workshop with representatives of national stakeholder organizations.
- Individual meetings with professional groups, voluntary sector organizations and regional groups of providers.
- Request for written comments from all individuals and organizations invited to the above events.
- Availability of draft standards on Primary Immunodeficiency Association (http://www.pia.org.uk) and Primary Immunodeficiency Network websites (http://www.ukpin.org.uk/News/C1-inhibitor.doc) with request for comment.

Declaration

The final version has been read and approved by all members of the advisory group (Table 8). Members of the advisory group were selected to provide a range of experience and expertise in immunology service provision. The group as a whole advised on the project and the consensus in general. M.M.G., R.J.L. and L.M. comprised the writing team. In addition, each group member co-drafted individual sections.

References

1 Cicardi M, Bergamaschini L, Marasini B, Boccassini G, Tucci A, Agostoni A. Hereditary angioedema: an appraisal of 104 cases. Am J Med Sci 1982; **284**:2–9.

2 Fay A, Abinun M. Current management of hereditary angio-oedema (C1 esterase inhibitor deficiency). J Clin Pathol 2002; **55**:266–70.

3 Tosi M. Molecular genetics of C-inhibitor. Immunobiology 1998; **199**:358–65.

4 Cicardi M, Bergamaschini L, Cugno M *et al.* Pathogenetic and clinical aspects of C1 inhibitor deficiency. Immunobiology 1998; **199**:366–76.

5 Prada AE, Zahedi K, Davis AE. Regulation of C1-inhibitor synthesis. Immunobiology 1998; **199**:377–88.

6 Bork K, Barnstedt S, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. Lancet 2000; **356**:213–7.

7 Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. Medicine (Baltimore) 1992; **71**:206–15.

8 Cicardi M, Zingale LC, Pappalardo E, Folcioni A, Agostoni A. Autoantibodies and lymphoproliferative diseases in acquired C1-inhibitor deficiencies. Medicine (Baltimore) 2003; **82**:274–81.

9 Johnson AM, Alper CA, Rosen FS, Craig JM. C-1 inhibitor: evidence for decreased hepatic synthesis in hereditary angioedema. Science 1971; **173**:553–4.

10 Cugno M, Nussberger J, Cicardi M, Agostoni A. Bradykinin and the pathophysiology of angioedema. Int Immunopharmacol 2003; **3**:311–17.

11 Zahedi R, Bissler JJ, Davis AE, Andreadis C, Wisnieski JJ. Unique C1 inhibitor dysfunction in a kindred without angioedema. II. Identification of an Ala443→Val substitution and functional analysis of the recombinant mutant protein. J Clin Invest 1995; **95**:1299–305.

12 Zahedi R, Wisnieski J, Davis AE. Role of the P2 residue of complement 1 inhibitor (Ala443) in determination of target protease specificity: inhibition of complement and contact system proteases. J Immunol 1997; **159**:983–8.

13 Carrer FMJ. The C-1 inhibitor deficiency. Eur J Clin Chem Clin Biochem 1992; **30**:793–804.

14 Moore GP, Hurley WT, Pace SA. Hereditary angioedema. Ann Emerg Med 1988; **17**:1082–6.

15 Sim TC, Grant JA. Hereditary angioedema: its diagnostic and management perspectives. JAMA 1990; **88**:656–64.

16 Starr JC, Brasher GW. Erythema marginatum preceding hereditary angioedema. J Allergy Clin Immunol 1974; **53**:352–5.

17 Williamson DM. Reticulate erythema – a prodrome in hereditary angio-oedema. Br J Dermatol 1979; **101**:549–52.

18 Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. Ann Intern Med 1976; **84**:580–93.

19 Karlis V, Glickman RS, Stern R, Kinney L. Hereditary angioedema: case report and review of management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997; **83**:462–4.

20 Bork K, Fischer B, Dewald G. Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by oral contraceptives or hormone replacement therapy. Am J Med 2003; **114**:294–8.

21 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.

22 Pearson KD, Buchignani JS, Shimkin RM, Frank MM. Hereditary angioneurotic edema of the gastrointestinal tract. Am J Roentgenol Radium Ther Nucl Med 1972; **116**:256–61.

23 Hara T, Shiotani A, Matsunaka H *et al.* Hereditary angioedema with gastrointestinal involvement: endoscopic appearance. Endoscopy 1999; **31**:322–4.

24 Gompels MM, Lock RJ, Morgan JE, Osborne J, Brown A, Virgo PF. A multi-centre evaluation of the diagnostic efficiency of serological investigations for C1 inhibitor deficiency. J Clin Pathol 2002; **55**:145–7.

25 Kunschak M, Engl W, Maritsch F et al. A. randomized, controlled trial to study the efficacy and safety of C1 inhibitor concentrate in treating hereditary angioedema. Transfusion 1998; **38**:540–9.

26 Lockitch G, Halstead AC, Quigley G, MacCallum C. Age- and sex-specific pediatric reference intervals: study design and methods illustrated by measurement of serum proteins with the Behring LN Nephelometer. Clin Chem 1988; **34**:1618–21.

27 Nielsen EW, Johansen HT, Holt J, Mollnes TE. C1 inhibitor and diagnosis of hereditary angioedema in newborns. Pediatr Res 1994; **35**:184–7.

28 Gompels MM, Lock RJ, Unsworth DJ, Johnston SL, Archer CB, Davies SV. Misdiagnosis of hereditary angioedema (Type 1 and Type 2). Br J Dermatol 2003; **148**:719–23.

29 Watson RD, Gershwin ME. Acquired angioedema associated with sinusitis. J Invest Allergol Clin Immunol 2000; **10**:129–34.

30 Cicardi M, Frangi D, Bergamaschini L, Gardinali M, Sacchi G, Agostoni A. Acquired C1 inhibitor deficiency with angioedema symptoms in a patient infected with *Echinococcus granulosus*. Complement 1985; **2**:133–9.

31 Rais M, Unzeitig J, Grant JA. Refractory exacerbations of hereditary angioedema with associated *Helicobacter pylori* infection. J Allergy Clin Immunol 1999; **103**:713–4.

32 Farkas H, Gyeney L, Majthenyi P, Fust G, Varga L. Angioedema due to acquired C1-esterase inhibitor deficiency in a patient with *Helicobacter pylori* infection. Z Gastroenterol 1999; **37**:513–18.

33 Tisch M, Lampl L, Groh A, Maier H. Angioneurotic edemas of the upper aerodigestive tract after ACE-inhibitor treatment. Eur Arch Otorhinolaryngol 2002; **259**:419–21.

34 Berkun Y, Shalit M. Hereditary angioedema first apparent in the ninth decade during treatment with ACE inhibitor. Ann Allergy Asthma Immunol 2001; **87**:138–9.

35 Kleiner GI, Giclas P, Stadtmauer G, Cunningham-Rundles C. Unmasking of acquired autoimmune C1-inhibitor deficiency by an angiotensin-converting enzyme inhibitor. Ann Allergy Asthma Immunol 2001; **86**:461–4.

36 Howes LG, Tran D. Can angiotensin receptor antagonists be used safely in patients with previous ACE inhibitor-induced angioedema? Drug Safety 2002; **25**:73–6.

37 Abdi R, Dong VM, Lee CJ, Ntoso KA. Angiotensin II receptor blocker-associated angioedema: on the heels of ACE inhibitor angioedema. Pharmacotherapy 2002; **22**:1173–5.

38 Cicardi M, Zingale LC, Bergamaschini L, Agostoni A. Angioedema associated with angiotensin-converting enzyme inhibitor use: outcome after switching to a different treatment. Arch Intern Med 2004; **164**:910–3.

39 Sheffer AL, Austen KF, Rosen FS. Tranexamic acid therapy in hereditary angioneurotic edema. N Engl J Med 1972; **287**:452–4.

40 Frank MM, Sergent JS, Kane MA, Alling DW. Epsilon aminocaproic acid therapy of hereditary angioneurotic edema: a double blind study. N Engl J Med 1972; **286**:808–12.

41 Gelfand JA, Sherins RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol. Reversal of clinical and biochemical abnormalities. N Engl J Med 1976; **295**:1444–8.

42 Rothbach C, Green RL, Levine MI, Fireman P. Prophylaxis of attacks of hereditary angioedema. Am J Med 1979; **66**:681–3.

43 Agostoni A, Cicardi M, Martignoni GC, Bergamaschini L, Marasini B. Danazol and stanozolol in long-term prophylactic treatment of hereditary angioedema. J Allergy Clin Immunol 1980; **65**:75–9.

44 Gould DJ, Cunliffe WJ, Smiddy FG. Anabolic steroids in hereditary angiooedema. Lancet 1978; **i**:770–1.

45 Sheffer AL, Fearon DT, Austen KF. Clinical and biochemical effects of stanozolol therapy for hereditary angioedema. J Allergy Clin Immunol 1981; **68**:181–7.

46 Sheffer AL, Fearon DT, Austen KF. Hereditary angioedema: a decade of management with stanozolol. J Allergy Clin Immunol 1987; **80**:855–60.

47 Spaulding WB. Methyltestosterone therapy for hereditary episodic edema (hereditary angioneurotic edema). Ann Intern Med 1960; **53**:739–45.

48 Davis PJ, Davis FB, Charache P. Longterm therapy of hereditary angioedema (HAE). Preventive management with fluoxymesterone and oxymetholone in severely affected males and females. Johns Hopkins Med J 1974; **135**:391–8.

49 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.

50 Bork K, Siedlecki K, Bosch S, Schopf RE, Kreuz W. Asphyxiation by laryngeal edema in patients with hereditary angioedema. Mayo Clin Proc 2000; **75**:349–54.

51 Nilsson IM, Andersson L, Bjorkman SE. Epsilon–aminocaproic acid (E–ACA) as a therapeutic agent based on 5 year's clinical experience. Acta Med Scand Suppl. 1966; **448**:1–46.

52 Agostoni A, Marasini B, Cicardi M, Martignoni G, Uziel L, Pietrogrande M. Hepatic function and fibrinolysis in patients with hereditary angioedema undergoing long-term treatment with tranexamic acid. Allergy 1978; **33**:216–21.

53 Rybo G. Tranexamic acid therapy is effective treatment in heavy menstrual bleeding. Clin Update Safety Ther Adv 1991; **4**:1–8.

54 Agostoni A, Cicardi M, Cugno M, Storti E. Clinical problems in the C1-inhibitor deficient patient. Behring Inst Mitt, 1993; **93**:306–12.

55 Abinun M. Diagnosis and treatment of hereditary angioedema, a genetically determined deficiency of C1 inhibitor. Thesis. University of Belgrade Medical School, 1988.

56 Donaldson VH. Therapy of 'the neurotic edema'. N Engl J Med 1972; **286**:835–6.

57 Van Dellen RG. Long-term treatment of C1 inhibitor deficiency with epsilon-aminocaproic acid in two patients. Mayo Clin Proc 1996; **71**:1175–8.

58 Gwynn CM. Therapy in hereditary angioneurotic oedema. Arch Dis Child 1974; **49**:636–40.

59 Naish P, Barratt J. Hereditary angioedema. Lancet 1979; **i**:611.

60 British Medical Association and the Royal Pharmaceutical Society of Great Britain. Antifibrinolytic drugs and haemostatics. British National Formulary. Oxford, UK: British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2003.

61 Hosea SW, Santaella ML, Brown EJ, Berger M, Katusha K, Frank MM. Long-term therapy of hereditary angioedema with danazol. Ann Intern Med 1980; **93**:809–12.

62 Cicardi M, Bergamaschini L, Tucci A *et al.* Morphologic evaluation of the liver in hereditary angioedema patients on long-term treatment with androgen derivatives. J Allergy Clin Immunol 1983; **72**:294–8.

63 Keele DK, Worley JW. Study of an anabolic steroid: certain effects of oxymetholone on small children. Am J Dis Child 1967; **113**:422–30.

64 Spooner JB. Classification of side effects to danazol therapy. J Int Med Res 1977; **5** (Suppl. 3):15–17.

65 Smith CS, Harris F. Preliminary experience with danazol in children with precocious puberty. J Int Med Res 1977; **5** (Suppl. 3):109–13.

66 Castro-Magana M, Cheruvanky T, Collipp PJ, Ghavarni-Maibodi Z, Angulo M, Stewart C. Transient adrenogenital syndrome due to exposure to danazol *in utero*. Am J Dis Child 1981; **135**:1032–4.

67 Schwartz RP. Ambiguous genitalia in a term female infant due to exposure to danazol *in utero*. Am J Dis Child 1982; **136**:474.

68 Wynn V. Metabolic effects of danazol. J Int Med Res 1977; **5** (Suppl. 3):25–35.

69 Westaby D, Ogle SJ, Paradinas FJ, Randell JB, Murray-Lyon IM. Liver damage from long-term methyltestosterone. Lancet 1977; **2**:262–3.

70 Johnson FL, Lerner KG, Siegel M *et al.* Association of androgenic-anabolic steroid therapy with development of hepatocellular carcinoma. Lancet 1972; **ii**:1273–6.

71 Ziegenfuss J, Carabasi R. Androgen and hepatocellular carcinoma. Lancet 1973; **ii**:262.

72 Cattan D, Vesin P, Wautier J, Kalifat R, Meignan S. Liver tumours and steroid hormones. Lancet 1974; **1**:878.

73 Fermand JP, Levy Y, Bouscary D *et al.* Danazol-induced hepatocellular adenoma. Am J Med 1990; **88**:529–30.

74 Bork K, Pitton M, Harten P, Koch P. Hepatocelluar adenomas in patients taking danazol for hereditary angio-oedema. Lancet 1999; **353**:1066–7.

75 BTG Pharm. Oxandrin Fact Sheet, 2003. Available at: http://www.oxandrin.com/hiv/about/ox_factsheet.html.

76 Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. N Engl J Med 1996; **334**:1630–4.

77 Sheffer AL, Fearon DT, Austen KF, Rosen FS. Tranexamic acid: preoperative prophylactic therapy for patients with hereditary angioneurotic edema. J Allergy Clin Immunol 1977; **60**:38–40.

78 Ward Booth P. Hereditary angioedema. Lancet 1979; **i**:611.

79 Bork K, Hardt J, Schicketanz KH, Ressel N. Clinical studies of sudden upper airway obstruction in patients with hereditary angioedema due to C1 esterase inhibitor deficiency. Arch Intern Med 2003; **163**:1229–35.

80 Agostoni A, Aygoren-Pursun E, Binkley KE *et al.* Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. J Allergy Clin Immunol 2004; **114** (**3** Suppl.):S51–131.

81 Schulte U, Hofmann P. Stability of a new formulation of C1-esterase-inhibitor concentrate at room temperature. International Clinical Practice Series. Tunbridge Wells, Kent: Wells Medical Ltd, 2004.

82 Anthony PP. Liver tumours. Baillieres Clin Gastroenterol 1988; **2**:501–22.

83 Zurlo JJ, Frank MM. The long-term safety of danazol in women with hereditary angioedema. Fertil Steril 1990; **54**:64–72.

84 Kahn H, Manzarbeitia C, Theise N, Schwartz M, Miller C, Thung SN. Danazol-induced hepatocellular adenomas. A case report and review of the literature. Arch Pathol Lab Med 1991; **115**:1054–7.

85 Bork K, Schneiders V. Danazol-induced hepatocellular adenoma in patients with hereditary angio-oedema. J Hepatol 2002; **36**:707–9.

86 Anabolic Steroids (systemic). US National Library of Medicine, 2004. Available at: http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202035html.

87 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.

88 Bork K, Barnstedt S. Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in patients with hereditary angioedema. Arch Intern Med 2001; **161**:714–18.

89 Agostoni A, Bergamaschini L, Martignoni G, Cicardi M, Marasini B. Treatment of acute attacks of hereditary angioedema with C1-inhibitor concentrate. Ann Allergy 1980; **44**:299–301.

90 Inbal A, Epstein O, Blickstein D, Kornbrot N, Brenner B, Martinowitz U. Evaluation of solvent/detergent treated plasma in the management of patients with hereditary and acquired coagulation disorders. Blood Coagul Fibrinolysis 1993; **4**:599–604.

91 Chandra S, Groener A, Feldman F. Effectiveness of alternative treatments for reducing potential viral contaminants from plasma-derived products. Thromb Res 2002; **105**:391–400.

92 De Serres J, Groner A, Lindner J. Safety and efficacy of pasteurized C1 inhibitor concentrate (Berinert P) in hereditary angioedema: a review. Transfus Apheresis Sci 2003; **29**:247–54.

93 Han ED, MacFarlane RC, Mulligan AN, Scafidi J, Davis AE. Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor. J Clin Invest 2002; **109**:1057–63.

94 Wolff MW, Zhang F, Roberg JJ *et al.* Expression of C1 esterase inhibitor by the baculovirus expression vector system: preparation, purification, and characterization. Protein Expr Purif 2001; **22**:414–21.

95 Logan RA, Greaves MW. Hereditary angio-oedema: treatment with C1 esterase inhibitor concentrate. J R Soc Med 1984; **77**:1046–8.

96 Osler W. Hereditary angioneurotic oedema. Am J Med Sci 1888; **95**:362–7.

97 Nielsen EW, Gran JT, Straume B, Mellbye OJ, Johansen HT, Mollnes TE. Hereditary angio-oedema: new clinical observations and autoimmune screening, complement and kallikrein–kinin analyses. J Intern Med 1996; **239**:119–30.

98 British Medical Association and the Royal Pharmaceutical Society of Great Britain. Pregnancy. British National Formulary. Oxford, UK: British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2003.

99 Lindoff C, Rybo G, Astedt B. Treatment with tranexamic acid during pregnancy, and the risk of thrombo-embolic complications. Thromb Haemost 1993; **70**:238–40.

100 Böckers M, Bork K. Kontrazeption und Schwangerschaft beim hereditären Angioödem. Dtsch Med Wochenschr 1987; **112**:507–9.
101 Hopkinson RB, Sutcliffe AJ. Hereditary angioneurotic oedema. Anaesthesia 1979; **34**:183–6.
102 Yip J, Cunliffe WJ. Hormonally exacerbated hereditary angioedema. Australas J Dermatol 1992; **33**:35–8.
103 Bouittet L, Ponard D, Drouet C, Jullien D, Massot C. Angioedema and oral contraception. Dermatology 2003; **206**:106–9.
104 Atkinson JC, Frank MM. Oral manifestations and dental management of patients with hereditary angioedema. J Oral Pathol Med 1991; **20**:139–42.
105 Bork K, Barnstedt SE. Laryngeal edema and death from asphyxiation after tooth extraction in four patients with hereditary angioedema. J Am Med Assoc 2003; **134**:1088–94.
106 Farkas H, Gyeney L, Gidofalvy E, Fust G, Varga L. The efficacy of short-term danazol prophylaxis in hereditary angioedema patients undergoing maxillofacial and dental procedures. J Oral Maxillofac Surg 1999; **57**:404–8.
107 Donaldson VH, Rosen FS. Hereditary angioneurotic edema: a clinical survey. Pediatrics 1966; **37**:1017–27.
108 Bork K, Witzke G. Hereditary angioneurotic edema. Clinical aspects and extended diagnostic and therapeutic possibilities. Dtsch Med Wochenschr 1979; **104**:405–9.
109 Brickman CM, Hosea SW. Hereditary angioedema. Int J Dermatol 1983; **22**:14–7.
110 Agostoni A. Inherited C1 inhibitor deficiency. Complement Inflamm 1989; **6**:112–18.
111 Abinun M, Mikuska M, Milosavljevic J. Problems of longterm prophylaxis in children with hereditary angioedema. Periodicum Biologorum 1986; **88** (Suppl. 1):221–2.
112 Bedford S. Hereditary angio-oedema. Proc R Soc Med 1971; **64**:1049–50.
113 Ohela K. Hereditary angioneurotic oedema in Finland. Clinical, immunological and genealogical studies. Acta Med Scand 1977; **201**:415–27.
114 Tappeiner G, Hintner H, Glatzl J, Wolff K. Hereditary angio-oedema: treatment with danazol. Report of a case. Br J Dermatol 1979; **100**:207–12.
115 Rajagopal C, Harper JR. Successful use of danazol for hereditary angio-oedema. Arch Dis Child 1981; **56**:229–30.
116 Barakat A, Castaldo AJ. Hereditary angioedema: danazol therapy in a 5-year-old child. Am J Dis Child 1993; **147**:931–2.
117 Farkas H, Harmat G, Gyeney L, Füst G, Varga L. Danazol therapy for hereditary angio-oedema in children. Lancet 1999; **354**:1031–2.
118 Farkas H, Harmat G, Fust G, Varga L, Visy B. Clinical management of hereditary angio-oedema in children. Pediatr Allergy Immunol 2002; **13**:153–61.
119 Cicardi M, Castelli R, Zingale LC, Agostoni A. Side effects of long-term prophylaxis with attenuated androgens in hereditary angioedema: comparison of treated and untreated patients. J Allergy Clin Immunol 1997; **99**:194–6.
120 Fraser IS, Allen JK. Danazol and cholesterol metabolism. Lancet 1979; **1**:931.
121 Allen JK, Fraser IS. Cholesterol, high density lipoprotein and danazol. J Clin Endocrinol Metab 1981; **53**:149–52.
122 Oliver MF. Hypercholesterolaemia and coronary heart disease: an answer. Br Med J (Clin Res Ed) 1984; **288**:423–4.
123 Champion RH, Lachmann PJ. Hereditary angio-oedema treated with E-aminocaproic acid. Br J Dermatol 1969; **81**:763–5.
124 Bork K, Witzke G. Long-term prophylaxis with C1-inhibitor (C1 INH) concentrate in patients with recurrent angioedema caused by hereditary and acquired C1-inhibitor deficiency. J Allergy Clin Immunol 1989; **83**:677–82.
125 Abinun M, Mikuska M. Hereditary angioedema in children: treatment with C1 inhibitor concentrate. 7th International Congress of Immunology, Berlin, 144A. Berlin: Gustav Fischer Verlag, 1989.
126 Abinun M. Hereditary angio-oedema in children. Lancet 1999; **353**:2242.
127 Agostoni A, Cicardi M. Replacement therapy in hereditary and acquired angioedema. Pharmacol Res 1992; **6** (Suppl. 2):148–9.
128 Cicardi M, Mannucci PM, Castelli R, Rumi MG, Agostoni A. Reduction in transmission of hepatitis C after the introduction of a heat-treatment step in the production of C1-inhibitor concentrate. Transfusion 1995; **35**:209–12.
129 Klarmann D, Kreuz W, Joseph-Steiner J, Ehrenforth S. Hepatitis C and pasteurized C1-inhibitor concentrate. Transfusion 1996; **36**:84–5.
130 Cicardi M, Agostoni A. Hereditary angioedema. N Engl J Med 1996; **334**:1666–7.
131 United Kingdom Haemophilia Centre Directors' Organisation Executive Committee. Guidelines on therapeutic products to treat haemophilia and other hereditary coagulation disorders, 2004. Available at: http://www.medicine.ox.ac.uk/ohc.
132 Pickering RJ, Good RA, Kelly JR, Gewurz H. Replacement therapy in hereditary angioedema. Successful treatment of two patients with fresh frozen plasma. Lancet 1969; **1**:326–30.
133 Beck P, Willis D, Davies GT, Lachmann PJ, Sussman M. A family study of hereditary angioneurotic oedema. Q J Med 1973; **42**:317–39.
134 Jaffe CJ, Atkinson JP, Gelfand JA, Frank MM. Hereditary angioedema: the use of fresh frozen plasma for prophylaxis in patients undergoing oral surgery. J Allergy Clin Immunol 1975; **55**:386–93.
135 Gibbs PS, LaSosso AM, Moorthy SS, Hutton CE. The anesthetic and perioperative management of a patient with documented hereditary angioneurotic edema. Anaesth Analg 1977; **56**:571–3.
136 Lieberman A. The use of fresh-frozen plasma in hereditary angioedema. JAMA 1994; **272**:518.
137 Galan HL, Reedy MB, Starr J, Knight AB. Fresh frozen plasma prophylaxis for hereditary angioedema during pregnancy. A case report. J Reprod Med 1996; **41**:541–4.
138 Kyle RA, Therneau TM, Rajkumar SV et al. A. long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med 2002; **346**:564–9.