

C1 Inhibitor deficiency: Consensus Document

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1 Terms of reference

“Consensus 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 and 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 reference is limited by a paucity of data. The levels of evidence used are listed in appendix B.

2 Background

C1 esterase inhibitor deficiency (C1 INH deficiency – Hereditary or Acquired angio-oedema (HAE/AAE)) is characterised by 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 review see Cicardi et al, 1982)(1).

2.1 Genetics & 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(2). 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(3). 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(3).

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(4). Increased catabolism of C1 INH, even in asymptomatic patients, and possibly decreased production, are likely factors(2;4). 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(2).

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(4). 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 Arg 444, but may also result from changes at several positions outside the reactive site loop.

HAE type III has been described by Bork *et al*(5). 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 affects a tenth as many patients as HAE, presents in older patients, has no family history and is associated with lymphoproliferative disease or, less commonly, autoimmunity(6;7).

2.2 Immunology

C1 INH is the main regulator of the early activation steps of the classical complement pathway. This protein is mainly produced in the liver, but also by activated monocytes and other cell types(8). 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 C2,4

(C3). Formation of this new complex (and associated C3 activation) leads to the production of anaphylactoid-like substances and vasoactive peptides (C2a, C3a, C4a). 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. In the fibrinolytic system, C1 INH regulates conversion of plasminogen to plasmin, and factor XI activation deficiency leads to an increase in fibrin split products. The coagulation pathway is affected by premature activation of factor XI. The end result is increased vascular permeability and massive local uncontrolled oedema, but the precise chemical responsible for the oedema is still unknown(3).

Whilst 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(9)(10;11).

3 Diagnosis

3.1 Clinical

A diagnosis of C1 INH inhibitor deficiency is suspected by a history of recurrent attacks of angio-oedema and of abdominal pain. 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(12). 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(13). 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(14). 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(15;16).

Classically, the oedema and swelling gradually develop over several hours, slowly increasing for 12–36 hours, and then subside after two to five days. However, patients may experience 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 only happen once or twice a year.

Angio-oedema can be precipitated by minor trauma to the tissue, such as dental work(17)(said to be a cause in up to 50% of all cases(18)), by certain drugs such as oestrogen(19), by angiotensin converting enzyme inhibitors, by emotional stress or by infection(20).

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(3). Barium studies, carried out during an acute attack, have been reported to show signs of massive submucosal oedema, spiculation, and fold thickening or effacement(21). 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(22). Histological examination of the bulging area merely showed moderate inflammatory cell infiltration of the lamina propria(22). 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(3).

3.2 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 good screening test for C1 INH deficiency as serum C4 is invariably low in untreated HAE. It has been shown that a combination of low C4 and low C1 INH function has a 99% specificity and a 100% negative predictive value for untreated C1 INH deficiency and is thus an effective test(23). All patients with untreated C1 INH deficiency had a C4 <30% of mean normal level. All patients who are suspected of having C1 INH deficiency should have a C4 level measured. If C4 is

normal it is not necessary to proceed to C1 INH analysis(23). If the C4 level is low then C1 INH level and function should be performed.

The diagnosis of Type I HAE (85% of cases) is by low amounts of C1 inhibitor protein, as assessed by immunochemistry. If C1 inhibitor values appears normal or raised (and C4 is low), a test of C1 inhibitor function should be carried out(17;24). 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 four hours 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(23). All testing should be undertaken off treatment for more than a week, including the administration of C1 INH concentrate or fresh frozen plasma. The presence of a positive test in a child under 1 year confirms the diagnosis. A negative test should be repeated when >1 year.

There is evidence that pitfalls in the diagnosis are common with 11 out of 42 cases recently reviewed found to have a questionable diagnosis (25). 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 and, where possible, by genetic tests (evidence level 4). In cases where the diagnosis is established, C4 and levels of C1 INH and function may be useful to monitor treatment effect.

4 Management

4.1 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(26;27). Eradication of *H. pylori* may be beneficial(28;29)(evidence level 3).

Advice on use of contraceptives and hormone replacement therapy should emphasise avoidance of oestrogen (see section 6.2). Angiotensin-converting enzyme (ACE) inhibitors need to be avoided because of their effects on the kallikrein-bradykinin pathway(30). Both HAE and AAE may be manifest for the first time after treatment with ACE inhibitors(31;32)(evidence level 3). Angiotensin-II receptor antagonists may also induce angioedema and should be used with caution(33;34). No evidence exists for 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 minimising adverse effects. Nevertheless, there will be a group of patients who will require intermittent or continuous, long-term prophylaxis.

4.2 Long term prophylaxis

The regimen for each affected individual should be guided by the severity of their disease. Frequent attacks of peripheral angio-oedema (extremities, trunk), although unpleasant and annoying, are not dangerous and may not require (contingent upon patient's judgement) long term prophylaxis. However, prophylactic administration of antifibrinolytic agents (tranexamic acid(35) or epsilon-aminocaproic acid (EACA; not licensed in the UK)(36)), synthetic, attenuated androgens (danazol(37),(38),(39) or stanazolol(39),(40),(41),(42)) has proved useful in reducing the frequency or severity of attacks (evidence level 2/3). Other androgens (methyltestosterone(43), fluoxymesterone(44), and oxymetholone(44),(45)) 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(39). We advocate a graded approach to the level of treatment in a given individual. In a confirmed case of C1 INH deficiency requiring treatment, consideration should be given to a course of tranexamic acid before attenuated androgens. Maintenance treatment should be considered in any patient who 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 only had mild or benign attacks(46)(evidence level 2).

4.2.1 Antifibrinolytic agents

Antifibrinolytic agents inhibit plasminogen activation with consequent "sparing" of C1 inhibitor usage. They decrease the number and the severity of attacks(18), but are not as effective in this as the attenuated androgens(36)(evidence level 2). Their side effects include nausea, vertigo, diarrhoea, menorrhagia, postural hypotension, tachyphylaxis, fatigue, and muscle cramps with an increase in muscle enzymes concentrations(1;35;36;47-49)(evidence level 2/3), and theoretical concerns about thrombus formation and thrombotic episodes(17). However, recent reports have suggested that these side effects are less common than previously thought; long term use in menorrhagia has shown no evidence for increased thrombus formation(49). The finding of tumours of the retina and liver in experimental animals after long term use of tranexamic acid(17) has limited its use in the USA(14), but not in Europe(50;51). Although a teratogenic effect of EACA has been postulated in the period of embryonic growth and development(17;52), it is being used in the USA(53), it has been used in children(54), and, surprisingly, has been recommended during pregnancy(55).

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. 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 BNF indicates that regular eye examinations and liver function tests (LFT) should be performed, whilst recognising 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 six months.

4.2.2 Attenuated androgens

Anabolic steroids increase the hepatic production of C1 inhibitor protein(17). Danazol, stanozolol and oxandrolone are most commonly used. 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(42;56;57)(evidence level 3). Decreased growth rate in children(58-60)is the main contraindication for their use in this age group. Androgens can cause masculinisation of the female fetus(61;62) and thus are contraindicated during pregnancy. Androgens, particularly the 17-alpha alkylated androgens, may have hepatic side effects, including cholestatic jaundice(63), peliosis hepatis(64), and hepatocellular adenoma(65-68). The observed cases of hepatocellular adenomas developing in patients with C1 INH deficiency on long term prophylaxis with danazol have caused particular concern(69)(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(6)(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 5mg once or twice daily can be used where available(42). To facilitate more accurate titration of dosage a 2mg tablet has been introduced. Stanozolol is available in the UK only by importation and on a 'named patient' basis. The recommended adult dose for oxandralone is 2.5mg to 20mg given in 2 to 4 divided doses(70). Again 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 regime, to discuss fully possible side effects with the patient and to regularly monitor the acceptability of such side effects.

4.3 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 contra-indicated. 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 optimised, by home therapy training if necessary. In exceptional cases where this

approach does not provide sufficient symptom control, regular C1 inhibitor infusions of 500-1000U twice weekly may be required.

4.4 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 six to 12 hours before the procedure, or just prior depending on the individual circumstances(51;71). 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 500 to 1500IU 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.

We believe that correction with C1 INH is to be preferred for more invasive dental procedures. It is more physiological than treatment with attenuated androgens and is more likely to achieve reliably normal levels of C1 INH. Furthermore, use of C1 INH overcomes any potential doubt regarding adherence with attenuated androgens (evidence level 4).

Administration of antifibrinolytics or attenuated androgens, starting five days before the procedure and the following two days thereafter(50), is an alternative. There is 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(72;73) or 2 g (500 mg four times daily) for children(51), given 48 hours before and after surgery. However, it seems that most authors prefer attenuated androgens even in children(17;50) at a dose of 100–600 mg/day for danazol or 2–6 mg/day for stanazolol, given 48 hours before and after surgery(1;17;42;50). See section 5.3 for further information on dental care.

4.5 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 75% have a life threatening attack at some time {Bork, Hardt, et al. 2003 137 /id}.

A UK audit has shown that home possession could reduce the number of avoidable adverse effects from the disorder(74)(evidence level 2). In order to be effective good local links to Accident and Emergency and a care management plan are also essential.

4.5.1 Home possession – patient directed administration

The management of patient-administered C1 INH concentrate is in need of standardisation. 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 Appendix 1).

Home therapy requires the issuing of concentrate and the training of participants of all eligible patients with C1 INH deficiency (see protocol). It provides a quick, convenient and probably safe method of dealing with acute attacks of angio-oedema. 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 suitably cool environment for the storage of the product. There are issues concerning the safety of the patient in the event of any adverse event and the presence of another individual at the time of the infusion, for what is likely to be an emergency event. There is also a requirement to maintain competence in the administration of home infusions, which may be difficult if insufficient practice is undertaken.

No home therapy should occur without a well-compiled protocol, see appendix. Where provided, home therapy programs should automatically include systematic audit to acquire evidence on the safety and efficacy of such a program.

4.5.2 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 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(74)(evidence level 2).

Any such program should be accompanied by appropriate information to be carried with the patient and advice as to strategies for re-supply of concentrate.

4.6 Monitoring of Treatment

4.6.1 Tranexamic Acid

The British National Formulary (BNF) recommends that patients who receive long-term tranexamic acid have a regular eye examination, but notes that this is based on unsatisfactory evidence(75). 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 relevant thrombophilia screen should be performed before commencing treatment (evidence level 4).

4.6.2 Attenuated Androgens

Liver function tests should be performed every six 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 only need testing where initial screen is abnormal. Thereafter we

recommend checking at six months and one year. Where patients are 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).

4.6.3 Hepatic ultrasound

The report of hepatocellular adenomas developing in patients with C1 INH deficiency on long term prophylaxis with danazol (69)(Evidence level 3) has indicated that ultrasound may be a useful test to undertake. As yet there is no data to indicate the extent of the problem or the frequency of screening required.

Danazol and other 17α -alkylated steroids are associated with increased risk of peliosis hepatis and hepatic adenoma(76). 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. However this recommendation is based on insufficient evidence (level 4)(77-80).

4.7 Emergency care

Treatment of acute attacks depends on their severity. Episodes of peripheral swelling only usually do not require treatment, but Stanozolol (up to 6 mg/day) or Danazol (up to 1g /day) given early during an attack may shorten its duration. Involvement of the upper airway usually begins slowly but cases of progression within 20 minutes have been reported(46); 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. Dose requirement will vary between individuals, dependent on body mass and the seriousness of the condition. In a life threatening situation we would recommend 1000-1500 IU. In other situations 500-1000 IU 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(24).

For acute attacks of abdominal oedema, pain relief should be given at an appropriate level and 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 closely observed because the median time to the beginning of the relief of symptoms after concentrate infusion is

0.5-1.5 hours, with complete resolution after 24 hours(24). If symptoms persist at a high intensity 2 hours after infusion, additional C1 inhibitor concentrate should be given, and alternative diagnoses should be considered.

C1 inhibitor concentrate is available throughout Europe. It has been available since the early 1980s(81), and shown to be effective in case series and a controlled trial(71;82;83).(evidence level 2/3)

If concentrate is not available then FFP or solvent detergent treated plasma may be given (evidence level 3), although this may worsen symptoms during the acute phase(14;17;52) because it contains high concentrations of complement components. A solvent/detergent treated plasma (Octaplas) has been evaluated for use in HAE, but there are few data regarding efficacy(84).

There are no randomised trials comparing plasma with C1 INH concentrate or with placebo. The risk of pathogen transmission may be increased if plasma is used(85;86). Therefore, plasma is not an acceptable alternative where emergency treatment is foreseeable. Adrenalin may be a useful adjunct to therapy but is typically not efficacious in aborting acute attacks.

4.8 Potential new therapies

New inhibitors of the fibrinolytic system, such as the kallikrein inhibitor DX88 (Dyax) and the bradykinin B2 inhibitor Icatibant (Jerini AG), hold promise for use in the treatment of C1 INH deficiency(87). Recombinant C1 inhibitor (Pharming) has been developed and should be available in the near future(88).

5 Special situations

5.1 In pregnancy & delivery

Treatment of the disease during pregnancy has special problems. Of published reports, some anecdotes report worsening of the disease(89)(evidence level 3), but few attribute premature labour or stillbirths to the disease(90). 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(17)(evidence level 2). Ideally, all prophylactic drugs should be stopped during pregnancy and, if possible, before conception. Of particular note, attenuated androgens are contra-indicated during pregnancy(91). 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(92)(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 no evidence to suggest that vaginal delivery requires special precautions. There may be local swelling of the vulva and infusion sites but this would not be treated unless urethral obstruction was a problem. Many patients deliver safely without prophylaxis, but this should be considered on an individual basis and the clinician should consider the postpartum period one of higher risk of acute attacks. If an operative delivery is, or may be, required, concentrate should be given if endotracheal intubation is to be carried out but, if possible, regional analgesia should be used (20;93)(level of evidence 3).

5.2 Contraception

Oestrogens should be avoided where possible. Use of an oral contraceptives exacerbate symptom's in HAE patients(94;95)(evidence level 3). A recent study reported that over 60% of HAE type I and III patients have more frequent attacks on oestrogens(19)(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 intra-uterine devices.

5.3 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(82). However attacks are unpredictable. Extensive dental work may be carried out without complication and conversely minor work may sometimes precipitate an attack(96). Danazol, C1 INH concentrate and FFP have all been recommended for prophylaxis(82;96;97).

All patients should be warned of the increased risk of an attack in the 36 hours following dental procedures and should have rapid access to C1 INH replacement in the event of an attack(98), 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.

We believe that correction with C1 INH is to be preferred for more invasive dental procedures. 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).

5.4 Travel

The following advice is taken from the Primary Immunodeficiency Association (PIA) advice for HAE patients when travelling in the UK and abroad. Further advice can be obtained via the PIA website. The advice falls into two broad categories; general administrative advice and that related to emergency treatment.

5.4.1 General Advice

Wear a Medic Alert bracelet. Obtain form E111 from you 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. Medications should be carried as hand luggage in a cool bag.

5.4.2 Emergency Advice

Carry a consultant's letter giving instructions about emergency treatment and a 24-hour emergency advice phone 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.

5.5 Children

Attacks are seen during childhood in most patients(17;99). Although the diagnosis is usually made in the 2nd or 3rd decade of life(17;100;101), 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 kindred) and followed over a period of more than 20 years(1;3;6;50;102) 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(54;103). Occasional patients will have their first symptoms even earlier, before the age of one year(102;104-106). 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(51;54;99).

It is important to note that attacks of laryngeal oedema can occur at any age and may be life threatening(107). For this reason, particularly where there is a strong 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.

5.5.1 Long term prophylaxis of attacks in children

This is a relatively unexplored issue(54;103), and most references state that the use of antifibrinolytics and androgens are not recommended because of the serious side effects of these drugs(24;71).

Because severe or life threatening attacks of C1 INH deficiency are less common during childhood, it is rarely necessary to start long term prophylaxis in children(14;51). 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 (>1/month), recurrent attacks of colicky abdominal pain causing distress and disability. In this situation, antifibrinolytics are preferred to androgens(50;54;103). 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.

5.5.2 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(108;109), particularly its potential effect on development, is a cause for concern, even when used with caution(110;111). Maintaining the lowest effective dose and an intermittent regime is very important (112). Anabolic steroids may be helpful in children with frequent abdominal attacks (>1/month). In this case steroids 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 (77;113) and the long term use of androgens has been reported to decrease the concentration of high density lipoproteins(14;114-116).

5.5.3 Antifibrinolytics in children

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(54). Tranexamic acid at a dose of 50 mg/kg/day(50) or 1.5 g/day(48;51) has been used long term with similar benefit and no side effects.

It has been proposed that the long term use of antifibrinolytics, by plasmin inhibition, could also predispose to arteriosclerosis(54;117). This is of particular importance if long term prophylaxis is to be started during childhood because several decades of treatment may be needed.

5.5.4 C1 inhibitor concentrate in children

C1 inhibitor concentrate has been used successfully for long term replacement in selected adult patients(118), and more recently it has been shown to be superior to a placebo in a double blind controlled study(71). 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 IU of C1 INH 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 occasions because laryngeal oedema continued to progress. Concentrations of C1 INH 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.

Based on the clinical benefit seen in these patients, a role for C1 inhibitor concentrate in long term prophylaxis for children has been suggested(71), supporting the few earlier proposals(14;119). In children, progression of an acute attack is usually slow and generally home therapy is not recommended. However, 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 INH concentrate(71;119;120). The disadvantages to this approach to the management are expense(111) and the possibility of viral transmission(121). Despite the lack of evidence of viral transmission with current pasteurised 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 cardinal feature of abdominal oedema in these cases is significant abdominal pain, usually with vomiting, which lasts several hours. Early treatment of symptoms is effective and may reduce the requirement for further treatment. 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 section 4.5 for further detail 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.

6 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(102;122;123). Several studies confirmed the safety of a heat treatment step in the production of a C1 inhibitor concentrate(24;71;123;124) 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(121), surveillance of patients treated with concentrate is essential(125).

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.

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 pre-treatment 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.

FFP is effective in the treatment of acute attacks(126;127) and in short term prophylaxis(93;128;129),but carries significant risks of viral transmission, anaphylactoid reactions, alloimmunisation, and excessive intravascular volume(14;24). FFP is used when C1 INH is unavailable but is not acceptable where emergency treatment is foreseeable or as prophylactic treatment(101;130;131).

7 Service specification

7.1 Diagnosis

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

7.2 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 include the diagnosis of patients and development of a management plan. Remote patients could then be monitored locally by the dermatologist or other designated physician following a protocol with reference back to the regional centre if there is a problem.

7.3 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.

7.4 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 General Practitioners (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.

7.5 Emergency care: Accident and emergency, Primary care and Home therapy

7.5.1 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 prioritising these patients, for example nurse-led protocol-driven treatment with medical review if necessary.

Immunology Nurse/ Nurse Specialist to 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.

7.5.2 General Practitioners (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 deficiency patient registered with their practice. If the patient intends to infuse concentrate at home, the patient's GP should be informed of this and consent obtained to provide emergency cover when therapy given.

Immunology Nurse/Nurse Specialist to liaise with GP regarding concerns or problems with home therapy, or other relevant issues relating to management of C1 INH deficiency patients.

7.6 Other Medical specialists required

Genetics advice, should be offered

Specialist obstetric care

Specialist dental care

7.7 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 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.

7.8 Register of patients

In order to further improve the understanding of HAE and to improve service to patients it is recommended that all patients join the European register. A form for this is provided on the Internet at www.haeregister.org.

8 Patients perspective

8.1 The key aims of C1 esterase inhibitor deficient patients:

For each C1 INH deficient patient to be able to manage their 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.

8.2 This can be achieved by:

Disseminating information to both health professionals and patients.

The referral of all patients to a specialist who has experience of C1 INH deficiency treatment.

Recognising 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.

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.

8.3 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.

9 Acquired Angio-oedema

The recent paper by Cicardi *et al.* 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)(7). This is important because approximately 1% of MGUS per year progress to myeloma or a related disorder(132). 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(27;29)(evidence level 3). Otherwise, the treatment is similar to HAE. Antifibrinolytics are more effective than attenuated androgens in this group(7)(evidence level 2). In the series of Cicardi *et al.* therapy with C1 INH concentrate was necessary in 12 of 28 of whom 3 became progressively resistant(7).

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11 Appendix A: Home Therapy program

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 prophylactic therapy should be optimal.
- In order to maintain required infusion skills, the patient should require infusion of C1 INH or else practice (i.e. self-infusion of intravenous saline) at least every three 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.

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 pre-injection/infusion.
- Administration of injection/management of infusion.
- Management of adverse reactions.
- Automatically injectable adrenaline/epinephrine training.
- 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 Consultant Immunologist/Specialist Nurse 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.

12 Appendix B: 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. Randomised controlled trial.

Level 2. Non-randomised trial or case series.

Level 3. Case reports.

Level 4. Expert opinion.

Level 5. None.

13 Appendix c: 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 in adults and summarises the advice given in the test.

Intervention	Therapy	Dosage (Adult)	Dosage (Children)	Monitoring tests
Long-term prophylaxis	Attenuated androgens	Danazol 200mg once or twice per day. Up to 400mg/day in <20% of cases. Stanozolol up to 5mg once or twice per day Oxandrin 2.5mg-20mg divided dose 2-4 times per day	[Only if indicated, see text] Danazol 100-200 mg/day (Use lowest effective maintenance dose, Consider alternate day or 2x weekly regime)	Six monthly: Liver function tests Annual: Lipid profile Biennial: Hepatic Ultrasound (annual after 10 years treatment)
	Tranexamic acid	Starting dose 0.5 –1.0g up to 4 times per day, reducing to 0.5g once or twice per day	1-2 g per day (Use lowest effective maintenance dose, Consider alternate day or 2x weekly regime)	Six monthly: Liver function tests
Short-term prophylaxis (e.g. for dental work)	Attenuated androgens	Danazol 100-600mg/day for 48 hours before and after procedure. Stanozolol 2-6mg/day for 48 hours before and after procedure	Danazol 300mg/day for 48 hours before and after procedure	
	Tranexamic acid	1g given 4 times daily for 48 hours before and after procedure	500mg given 4 times daily for 48 hours before and after procedure	
	C1 inhibitor concentrate	500-1500 IU 6-12 hours prior to procedure	500 IU 6-12 hours prior to procedure	
Emergency care for acute attacks	Attenuated androgens	Danazol up to 1g/day. Stanozolol 6mg/day		
	Tranexamic acid	1g given 4 times daily for 48 hours before and after procedure		
	C1 inhibitor concentrate	500-1500IU. Addition infusion if symptoms persist for >2hours		Baseline: Liver function tests Hepatitis virology
	Fresh Frozen Plasma			Baseline: Liver function tests Hepatitis virology
	Pain Relief	As appropriate		
Pregnancy	Attenuated androgens	Contra-indicated.		

	Tranexamic acid	May be used with caution		
	C1 inhibitor concentrate	Emergency care as above. Severe cases may require regular replacement		

14 Appendix D: Membership of the advisory group

MEMBERSHIP OF THE ADVISORY GROUP

Chair:

Mark Gompels	Consultant Immunologist	Southmead Hospital, Bristol
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Group members:

Mario Abinun	Consultant Paediatrician	Newcastle General Hospital
Claire Bethune	Specialist Registrar in Immunology	Royal Victoria Infirmary, Newcastle upon Tyne
Graham Davies	Consultant Paediatrician	Great Ormond Street Hospital, London
Clive Grattan	Consultant Dermatologist	Norwich
Anne Fay	Consultant Immunologist	Royal Victoria Infirmary, Newcastle upon Tyne
Robert J Lock	Clinical Scientist in Immunology	Southmead Hospital, Bristol
Hilary Longhurst	Consultant Immunologist	St Bartholomew's Hospital, London
Leigh Morrison	Specialist Immunology Nurse	Southmead Hospital, Bristol
Anne Price	Patient Representative	Primary Immunodeficiency association, Caxton House, London
Megan Price	Consultant Dermatologist	Brighton
David Watters	Chief Executive	Primary Immunodeficiency association, Alliance House, Caxton Street, London

Writing team

Mark Gompels	Southmead Hospital, Bristol
Robert J Lock	Southmead Hospital, Bristol
Leigh Morrison	Southmead Hospital, Bristol

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. In addition, each group member co-drafted individual sections

15 Appendix E: Consultation on development of the standards

15.1 Consultation process (to be undertaken)

The draft standards were developed by the project Advisory Group (see Appendix C for membership) with the project consultants.

Consultation on draft standards will take place through:

- A one-day facilitated workshop with representatives of national stakeholder organisations (see below).
- Individual meetings with, professional groups, voluntary sector organisations, and regional groups of providers.
- Request for written comments from all individuals and organisations invited to the above events.
- Availability of draft standards on Primary Immunodeficiency Association and ? Primary Immunodeficiency Network websites with request for comment.

Following consultation on the first draft, the Advisory Group will consider comments in detail and the standards will be redrafted.

15.2 Stakeholder consultation

The following national groups and organisations were invited to participate in the consultation process.