1. Introduction and Who Guideline applies to

This policy is intended to optimise the investigation of suspected C1 inhibitor deficiency including Hereditary Angioedema and Acquired Angioedema to enable timely and accurate diagnosis. It covers the key principles of management including pharmacological therapies and special considerations to aid assessment of risk and benefit of treatment and ensure that management follows current evidence base.

This policy is designed as guidance for Immunology medical and nursing staff involved in the care of patients with C1 Inhibitor (C1-INH) deficiency. It may be used as guidance for other medical and nursing staff who are involved in the care of these patients in conjunction with the input of specialist immunologists.

This policy is for adult and paediatric patients, differences between the two populations are clearly highlighted within the text. Emergency management of HAE in children can be found in "Hereditary Angioedema UHL Children Guideline" (Trust Ref D7/2019). This policy does not cover management of other forms of angioedema such as allergy/anaphylaxis, idiopathic angioedema and ACE Inhibitor induced angioedema.

C1 Inhibitor Deficiency is a rare condition with significant morbidity and mortality requiring specialist care.

2. Guideline Standards and Procedures

C1-INH deficiency includes patients who have both a genetic deficiency in the form of Hereditary Angioedema (HAE) and those who develop a secondary form of Acquired Angioedema (AAE). HAE divides to three main types, HAE1 where there is a lack of C1 inhibitor protein, HAE2 where the C1 inhibitor protein is present but non-functional and HAE3 which is a rare separate entity with similar symptoms but a normal C1 inhibitor protein where mutations have been described in other regulators of bradykinin. The C1 Inhibitor protein has an important role not just in the complement pathway but also as a regulator of a number of other protein cascade pathways including aspects of the clotting cascade and regulation of bradykinin. It is in the bradykinin pathway where a lack of control due to deficiencies of C1-INH causes symptoms.

Symptoms occur due to capillary leak and the build-up of oedema in tissues and can include swellings of peripheries, abdominal viscera and of the airway. There is a significant mortality associated with untreated HAE of up to 30-40% and significant morbidity including lost work time and anxiety from attacks. Many patients go undiagnosed for many years and have multiple invasive investigations which could be avoided if the diagnosis of C1-INH deficiency was made more quickly. AAE is associated with autoimmune and lymphoproliferative disease and AAE symptoms can pre-date identification of lymphoma by a number of years and therefore early confirmation of AAE can speed up diagnosis of other associated conditions.

2.1 Diagnosis of C1 Inhibitor Deficiencies

Testing for C1-INH deficiency should be directed by an appropriate clinical history. Patients present with angioedema without urticaria, this can be peripheral swellings of limbs/genitals, swelling of the airways/face presenting with shortness of breath and stridor or wheeze or abdominal attacks of oedema which causes abdominal pain and vomiting. These attacks can have a prodrome and in some cases erythema marginatum can be seen before the onset of attacks. The attacks do not respond to anti-histamines, steroids or adrenaline. It should be noted that 25% of cases arise de novo and so will not have a family history. Symptoms usually begin in later childhood or early adolescence.

For patients suspected to have HAE, initial tests should include blood levels of C1-INH function, C1-INH protein and C4. The combined use of these three tests has higher diagnostic accuracy for identifying HAE-1/2 than with the use of any of the three alone. This requires the sample to arrive

in the immunology laboratory and be frozen within 6 hours due to in vitro consumption of the protein. C1 inhibitor protein and function have different pattern in different HAE types as per the table. C4 levels are usually low in HAE-1/2 patients, but the sensitivity and specificity of C4 as a marker for HAE are limited. Because of this, its use for screening patients and its use as only parameter to diagnose HAE-1/2 are not recommended. Testing of other complement components/function is not routinely indicated. A low C1 inhibitor protein and/or function and low C4 result should be repeated to confirm.

Diganosis	C4 level	C1-INH protein	C1-INH function	C1q
HAE1	Low	Low	Low	Normal
HAE2	Low	Normal	Low	Normal
HAE3	Normal	Normal	Normal	Normal
AAE	Low	Low	Low	Low

Genetic testing is available for the SERPING gene which causes HAE1 and HAE2 and is inherited in an autosomal dominant manner however this should be done in selected patients with proven biochemical HAE as it may miss some cryptic splice sites and rare mutations in up to 10%. The main utility is for pre-natal diagnosis and genetic counselling. On diagnosis consideration should be given to screening family members or seeing them in an immunology clinic for review.

In rare selected patients with a strongly suggestive history but normal C1 inhibitor protein and function consideration by speciality immunologists can be given to the availability of testing for mutations implicated in HAE3, this is of limited availability and not routinely done.

In older patients with low C1 Inhibitor and no family history of HAE, AAE should be considered and in these patients C1q levels which are low in most cases of AAE (although can be normal in patients taking anabolic androgens) should be checked. In patients shown to have AAE consideration based on Symptoms should be given to testing for an underlying cause including checking ANA/ENA for connective tissue disease and Immunoglobulins and lymphocyte subsets +/- CT scanning for lymphoproliferative disease. Patients who are diagnosed with ACEI-AE should be tested for HAE-1/2, as the occurrence of angioedema attacks after the initiation of treatment with an ACE-inhibitor may point to previously asymptomatic HAE.

All HAE patients should ideally be under immunology follow up, the frequency of this is dependent on the clinical severity. Patients with minimal attacks may only be seen annually. Patients should be given access to patient information either in paper or online format and given advice regarding HAE support/patient groups they may wish to join.

2.2 Treatment options for hereditary angioedema:

There is significant overlap in the treatment of HAE and AAE. The major difference is that in AAE treatment of the underlying disorder, especially lymphomas, may lead to a cessation of angioedema symptoms and normalisation of C1-inhibitor levels.

a) On demand therapy

The initial therapy offered to C1ID patients is on demand therapy for attacks. All attacks affecting the upper airway should be treated. Patients should be taught that attacks affecting the airway, painful abdominal attacks and function limiting peripheral/genital attacks should be treated. Early treatment on demand improves attack resolution.

Within the UK the licenced options for on demand treatment are plasma derived C1 inhibitor concentrate as Berinert or Cinryse delivered IV, recombinant C1 Inhibitor (Ruconest) as IV or subcutaneous bradykinin B2 receptor antagonist (Icatibant). Icatibant has only recently in 2019 acquired a licence for use in patients under 12 years, dosing is weight based and an adaptor device is supplied with the product to draw up an appropriate dose. See table below for dosing. Patients can be trained to deliver therapy at home if they are suitable, otherwise they should be provided with the appropriate medication and a treatment letter and advised to seek medical attention for administration for appropriate attacks. Self-administration improves time to treatment.

In rare cases where none of the above are available treatment should be provided with solvent detergent treated plasma or fresh frozen plasma.

Drug	Mechanism	UK licence	Route	Dose
Berinert	Plasma derived C1Inh	Adults and children	IV	20units/kg
Cinryse	Plasma derived C1Inh	Adults and Children >2years	IV	1000units or 500 units For ages 2-11 with weight 10-25kg
Ruconest	Recombinant C1Inh	Adults >12years	IV	50units/kg up to 84kg 4200units above 84kg
Icatibant	Bradykinin receptor antagonism	Adults and children	S/C	30mg/dose
Ecallantide	Kallikreine inhibitor	Not licenced	S/C	30mg/dose

Dosage regimen for Icatibant for paediatric patients (Icatibant is only for those who are unable to do IV Berinert**)**

Body Weight	Dose (Injection Volume)
12 kg to 25 kg	10 mg (1.0 ml)
26 kg to 40 kg	15 mg (1.5 ml)
41 kg to 50 kg	20 mg (2.0 ml)
51 kg to 65 kg	25 mg (2.5 ml)
>65 kg	30 mg (3.0 ml)

Within UHL there is a policy for the emergency department for administration of C1 Inhibitor to patients presenting to emergency care with attacks of C1ID. Berinert is kept stocked in A&E mediwell automated drug storage unit. There should be 6x 500unit vials in stock. If there is a supply issue with Berinert then both Cinrzye and Ruconest are on the UHL formulary for use. Ideally Berinert will be used for acute attacks however if it is unavailable an alternative will be stocked in the ED mediwell automated drug storage unit. If it is the only product available, Ruconest can be used off licence for paediatric patients under 12 years old. Ruconest should not be given to those with known Rabbit allergy.

For upper airway attacks progressing despite treatment, early consideration should be given to intubation or surgical airway management. It should be noted that airway manipulation and examination may exacerbate the angioedema and should only be undertaken if there are facilities to secure a definitive airway.

Patients under the UHL immunology team will be trained by our specialist nurses or through a homecare company for self-administration of on demand therapy where indicated. Patients will be given advice on storage of their treatment. As any attack may be followed by another one in short succession, It is preferable that patients have sufficient medication for on-demand treatment of at least two attacks and carry them at all times.

All UHL patients will have details of management plans in their clinic letters and if required can request “to whom it may concern” letters regarding their treatment. They should be offered advice regarding medic alert bracelets.

Patients should be vaccinated via their GP or immunologist against Hepatitis B in line with the green book protocol given the risk of frequent exposure to blood products. If having frequent use of Berinert consideration should be given to monitoring liver function and storing serum in case of need to monitor for blood borne viruses such as Hepatitis B/C and HIV.

b) Short-term prophylactic treatment

Trauma puts C1-INH deficiency patients at increased risk of attacks of angioedema local to the area of treatment. This is especially relevant in work around the upper airway which may cause life threatening laryngeal oedema, most notably dental work, ENT surgery and upper GI endoscopy. All patients should be advised to make the clinician undertaking the work aware of their condition and to contact immunology for advice well in advance. The patient should also let immunology know. Immunology will either undertake this themselves on the LGH day unit or fully advise the treating team on how to administer an appropriate dose for weight of the medication. Immunology will advise on the timing relative to the procedure and if special monitoring is required post procedure, this will depend on the specific procedure. It is important to be aware that although this reduces the risk of angioedema it does not eliminate it. Patients requiring dental work their General Dental Practitioner cannot offer in the community can be referred to the Westcotes Community Dental Practice who have a guideline for C1-INH deficiency patients.

Intravenous pdC1-INH is the first line short-term prophylaxis. It should be used for pre-procedural prophylaxis, as close as possible to the start of the procedure. The usual dosage is 1000 units for adults , check the BNF for Paediatric doses. Fresh frozen plasma (FFP) may be used as a second-line agent. Pre-procedural attenuated androgens have been used as prophylaxis in some circumstances. They are used for 5 days before and 2 to 3 days post event. Use of Tranexamic acid is not recommended.

With all pre-procedural prophylactic treatments, break-through attacks can occur, so patients and treating physicians should be aware of this increased risk and on demand treatment needs to be available. Patients who have home Icatibant should ensure they carry this with them to their procedure.

c) Long-term prophylactic treatment

For patients with either frequent attacks or with airway attacks consideration should be given to prophylactic agents. Oral prophylaxis should be the first line of treatment for individuals at risk of attacks.

Attenuated androgens such as danazol, oxandralone and stanazalol have the best evidence but their use is off license. These are contraindicated in children before Tanner stage V barring exceptional circumstances under specialist direction, and during pregnancy. Adequate contraception in women of childbearing age is required and the attenuated androgen should be discontinued in advance of trying to conceive. Androgens have a significant side effect profile that can limit their use, patients should have LFTs, FBC, U&E and triglycerides monitored every 6 months and an annual liver ultrasound due to the risk of hepatic impairment and liver tumours. Blood pressure should be checked at each clinic visit.

Berotralstat is recommended only if patient is having at least 2 attacks per month, and it is stopped if the number of attacks per month does not reduce by at least 50% after 3 months.

Another prophylactic agent is **tranexamic acid**, the evidence for this in HAE is weaker however AAE patients may respond better than to attenuated androgens. This is contraindicated in patients with risk factors for thromboembolic disease. It can be used in children and is preferred to attenuated androgens in these patients.

Drug	Mechanism	Usage	Dosage	Route	Side effects	Monitoring
Danazol	Attenuated androgen	Non-pregnant Adults only	100 – 200 mg daily	Oral	Virilisation menstrual disorders Mood Disturbance headache Hepatic adenoma	6 monthly FBC, LFT and cholesterol Annual liver ultrasound
Oxandralone	Attenuated androgen	Non-pregnant Adults only	2.5-10mg daily			
Stanazolol	Attenuated androgen	Non-pregnant Adults only	(not Currently available)			
Tranexamic acid	Antifibrinolytic	Adults And children	1 – 1.5g bd/tds. Max: 6 g/ day 15 - 25 mg/kg bd/tds Max: 1.5 g/dose	oral	GI- upset Risk of VTE	
Pd C1-INH	Replacement therapy	Adults and children	IV	1000 units for adults , check the BNF for Paediatric doses	Risk of blood product administration	Hep B vaccination Monitoring LFTs every 3 months Annual save serum
Berotralstat	plasma kallikrein inhibitor	Adults and Children > 12years	oral	150 mg daily	GI reactions (self-resolved with time)	LFT and ECG should be done before initiation
Lanadelumab	anti-kallikrein monoclonal antibody	Adults and Children > 12 years	S/C	300 mg every 2 weeks (every 4 weeks if attack free)		

Lanadelumab is recommended as a prophylactic option in people with HAE who continue to experience two or more clinically significant attacks per week, over 8 weeks despite oral preventive therapy, or oral therapy is contraindicated or not tolerated.

In exceptional cases regular prophylactic C1 inhibitor can be administered IV, usually twice a week with a weight based dosing, dependent on the product used. Cinryse currently has the only UK license for prophylaxis. Patients must meet the current NHS England criteria of at least 2 attacks a week despite oral prophylaxis or intolerance of oral prophylaxis and must be approved by a panel of immunologists outside of the treating team.

Patients should be maintained on the lowest dose of prophylaxis possible and if they remain with a low attack frequency consideration on a case by case basis should be given to withdrawing prophylaxis with clinical response monitored.

2.3 Special considerations in C1-INH deficiency:

a) C1-INH deficiency in pregnancy and breast-feeding:

Progress is variable during pregnancy and attack frequency may increase, decrease or remain unchanged. Labour and delivery can precipitate attacks and C1 inhibitor prophylaxis should be given under immunology advice on the day of delivery (either vaginal or Caesarean) and it is recommended to deliver in hospital.

Diagnosis of C1 inhibitor deficiency in a pregnant patient is difficult. Plasma levels of C1-INH decrease during pregnancy and return to normal after delivery. Therefore, measurements of levels of C1-INH level and function and C4 for the purpose of diagnosing HAE during pregnancy should be interpreted with caution and it should be repeated after childbirth to confirm the diagnosis.

Attenuated androgens and Icatibant are contraindicated in pregnancy and thus on demand or prophylactic C1 inhibitor concentrate is the preferred therapy. Routine administration of pre-procedural prophylaxis is not mandatory and can be considered on a case to case basis as per clinical judgment, but C1-INH concentrate should be available for immediate on-demand use. Pre-procedural prophylaxis with C1-INH is recommended before a caesarean section and it is mandatory if intubation is planned.

For LTP during pregnancy, C1-INH is considered a safe and effective prophylactic treatment. It is provided for under the NHS England commissioning document in discussion with additional immunologists from outside the treating team as described in section 3.2.2, a Bluteq form is required for these patients. Androgens are contraindicated.

Breastfeeding may be associated with an increased number of maternal attacks, with abdominal symptoms and facial oedema, but is recommended based on benefits provided to the infant. Pd C1-INH is considered the best therapy for on-demand treatment, short-term prophylaxis and long-term prophylaxis during lactation. Tranexamic acid was found to be safe during breastfeeding but breast-feeding should be discontinued before androgens are introduced.

b) C1-INH deficiency in children

Childhood/neonatal testing – Measuring C4 at less than 1 year old is not helpful, C1-INH protein and function measurement at <1 year old may not be reliable and should be repeated after 1 year of age for confirmation. Genetic testing may be of benefit and consideration should be given to referral to clinical genetics for discussion for patients planning a family or where conception has occurred. Pre-natal diagnosis of HAE is not currently common.

C1-INH and icatibant are the only approved on-demand treatments for children with HAE-1/2 (see doses in 2.2.1). For short-term prophylaxis- Pd C1-INH is the first-line pre-procedural prophylactic option, and short courses of attenuated androgens should only be used second line, only when C1-INH concentrate is not available. For long-term prophylaxis- pdC1-INH is the preferred therapy in children younger than 12 years of age. When C1-INH concentrate is not available tranexamic acid is preferred to androgens. Androgens are not recommended (see 2.2.3).

c) Travel

It is possible to travel abroad with C1ID however it is important to ensure that the patient makes their insurance company aware of the condition. They should take their on-demand therapy with them and this will necessitate a flight letter to enable carrying medications and needles onto the flight and a “to whom it may concern” letter in case they need to seek medical attention. They should be advised to ensure that they can store their therapy adequately during their travel considering the temperature requirements for each product.

2.4 Patient consenting

All HAE patients should be educated about the risks and benefits of C1-INH and consented for its use as it may be required in an emergency.

2.5 Patient’s Monitoring

It is recommended that HAE patients have a medical evaluation at least annually. Newly diagnosed patients and those on long-term prophylaxis should be seen in shorter intervals, until control is achieved. Patients on androgens should continue to be seen twice a year. Evaluation at follow-up visits should include a review of patient’s disease activity, impact and control and of the frequency of use and effectiveness of on-demand treatment for swelling attacks. There are validated Patient-reported Outcome Measures (PROM) which can be used for monitoring disease activity in selective patients.

2.6 Family screening in HAE

There is a risk that the first HAE attack may affect the airway or the abdomen and could cause asphyxia or unnecessary surgery Therefore, family members of HAE-1/2 patients should be offered screened for C1-INH protein and function and C4 plasma levels. Once HAE is diagnosed further discussion could be considered including genetic testing.

2.7 Patient Education and Training

All patients should have an individualized treatment plan carefully developed by shared decision-making. It should include clear instructions about on-demand therapy, short-term and long-term prophylaxis.

All patients who are provided with on-demand treatment licensed for self-administration should be taught to self-administer. All patients with HAE should be educated about triggers that may induce attacks. This include trauma (accidental, dental, medical, and surgical procedures) and the use of oestrogen-containing oral contraceptive agents and oestrogen hormone replacement therapy (progesterone-only pills may be beneficial for many women with HAE-1/2). Antihypertensive agents containing ACE inhibitors should be strictly avoided. Other reported triggers include psychological stress, fatigue, febrile illness, and the menstrual cycle.

All patients should be offered contact details of patient support groups such as www.haeuk.org who can provide support and advice to patients and families.

3. Education and Training

Training for HAE is given to registrars and nurses by the consultant. Staff who treat patients are asked to be familiar with the guidelines.

4. Monitoring Compliance

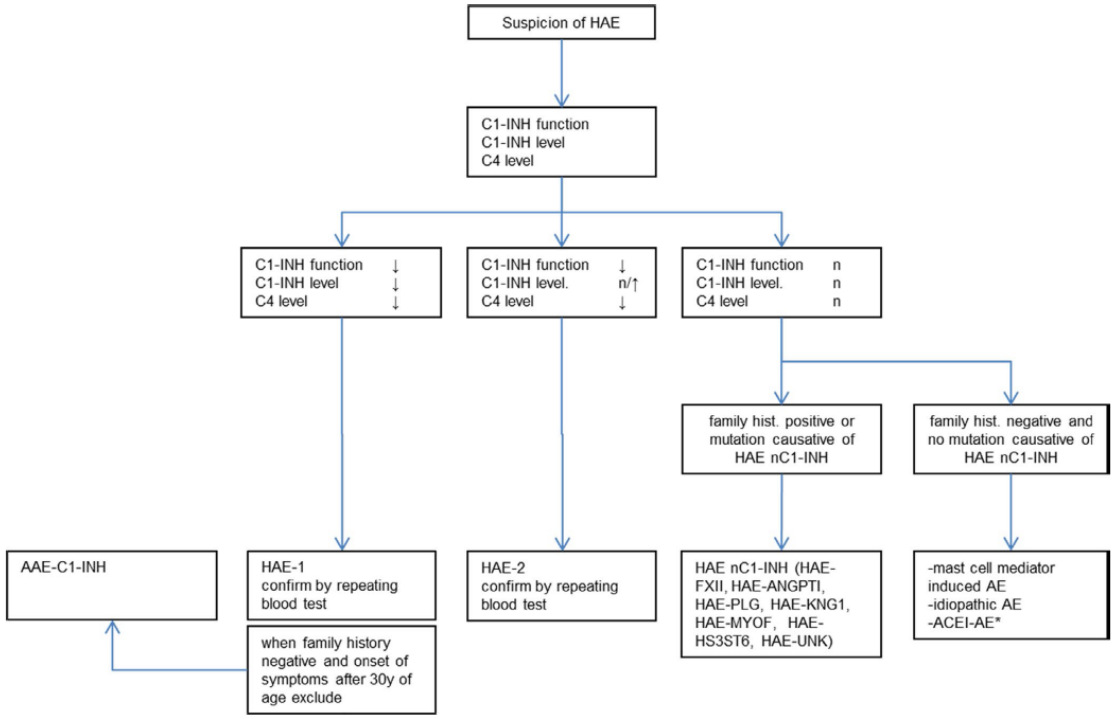
What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Monitoring blood and USS test compliance	Notes Audit	AP	Annual	Local MDT

5. Supporting References

The international WAO/EAACI guideline for the management of hereditary angioedema—The 2021 revision and update; Maurer,Markus et al; European Journal of Allergy and Clinical Immunology 10 January 2022 https://doi.org/10.1111/all.15214

Longhurst HJ, Tarzi MD, Ashworth F, et al. C1 inhibitor deficiency: 2014 United Kingdom consensus document [published correction appears in Clin Exp Immunol. 2015 Dec;182(3):346]. Clin Exp Immunol. 2015;180(3):475–483. doi:10.1111/cei.12584

Diagnostic work up in patients suspected to have C1-INH deficiency



10. Key Words

List of words, phrases that may be used by staff searching for the Guidelines on PAGL. If none – state none.

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) **Dr Arthur Price & Dr Intisar Abdelhakam**	**Executive Lead** **Medical Director – Andrew Furlong**
Details of Changes made during review:	