

C1 inhibitor deficiency: 2014 United Kingdom consensus document

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Introduction

C1 esterase inhibitor deficiency (C1 inhibitor deficiency) is a rare disorder that may be genetic (hereditary angioedema, HAE) [1] or less commonly acquired (acquired angioedema, AAE) [2]. The disease has an estimated prevalence of 1 : 50 000; any ethnic group may be affected, and many cases are undiagnosed [3–5]. C1 inhibitor deficiency manifests with episodic attacks of bradykinin-mediated localized subcutaneous and/or submucosal swellings, with a predilection for the face, extremities, gut, genitals, oropharynx and upper respiratory tract [6]. Abdominal attacks are extremely painful and disruptive, while laryngeal swelling is

Summary

C1 inhibitor deficiency is a rare disorder manifesting with recurrent attacks of disabling and potentially life-threatening angioedema. Here we present an updated 2014 United Kingdom consensus document for the management of C1 inhibitor-deficient patients, representing a joint venture between the United Kingdom Primary Immunodeficiency Network and Hereditary Angioedema UK. To develop the consensus, we assembled a multi-disciplinary steering group of clinicians, nurses and a patient representative. This steering group first met in 2012, developing a total of 48 recommendations across 11 themes. The statements were distributed to relevant clinicians and a representative group of patients to be scored for agreement on a Likert scale. All 48 statements achieved a high degree of consensus, indicating strong alignment of opinion. The recommendations have evolved significantly since the 2005 document, with particularly notable developments including an improved evidence base to guide dosing and indications for acute treatment, greater emphasis on home therapy for acute attacks and a strong focus on service organization.

Keywords: C1 inhibitor deficiency, guidelines, HAE, hereditary angioedema

life-threatening and accounts for the very significant life-time mortality reported from historical data [6–8].

The evidence base for disease management has expanded significantly since the first UK consensus document was published in 2005 [9]. For acute therapy, extensive data are now available for two new drugs that target the bradykinin pathway [10–17], for two established plasma-derived C1 inhibitor replacement products [18–20] and for a novel recombinant C1 inhibitor concentrate product [21–23]. Further evidence supports the use of home therapy for acute attacks, an approach with clear benefits for patients and the wider health economy [24–28]. The effectiveness of regular C1 inhibitor concentrate injections for long-term

prophylaxis is now established more firmly, presenting an alternative to attenuated androgens for selected patients [19,29]. In parallel with these advances in medical management, focused research efforts have revolutionized our understanding of the impact of C1 inhibitor deficiency on the physical, emotional and economic health of patients and their families [5,30–34], thus informing the application of this improved evidence base.

A number of documents have translated these data into evidence-based guidelines [24,35–41], but none fully reflect the priorities and organization of services for C1 inhibitor-deficient patients in the United Kingdom. With these considerations in mind, the United Kingdom Primary Immunodeficiency Network (UK PIN – a cross-disciplinary professional association) and the patient group Hereditary Angioedema UK (HAE UK) jointly commissioned this project to update the 2005 UK consensus document.

Several considerations are particularly pertinent to the context of this document. The UK National Health Service (NHS) is dealing with unprecedented financial pressure, and while successive governments have continued to pledge commitment to a health-care system that is free at the point of demand, traditional hospital-based models of health care are unlikely to be affordable for the United Kingdom in the long term. Recent government initiatives have focused on community and patient-centred ‘integrated’ care, both as a means to ensure long-term affordability and to improve social and medical outcomes [42]. There has also been increased awareness of more rare diseases, with the needs of affected patients recognized in UK initiatives [43]. Finally, there is a perception that the provision of specialist services for C1 inhibitor-deficient patients varies geographically [44], with possible underlying factors including the availability of funding for high-cost drugs and the location of major centres of expertise.

In England, these considerations have contributed to radical reform of specialist services for patients with C1 inhibitor deficiency and other rare diseases: centralized funding has been devolved to NHS England, with the commissioning specification encouraging expert patient-centred care, coordinated by specialist centres that fulfil predefined standards [45]. The organization of services in other UK nations differs: in Wales, all patients access services at the Immunodeficiency Centre in Cardiff, with centrally commissioned resources transferred from Health Boards; in Scotland, patients access local services or travel across Unitary Health Board areas where this is not possible, with high-cost medicines accessed through a Pharmacy Board structure overseen by the Scottish Medicines Committee; in Northern Ireland, services are centralized to the Regional Immunology Service in Belfast, with a local process for the approval of high-cost drugs.

It was not felt appropriate to replicate the excellent work that has produced a plethora of recent evidence-

based guidelines in the field of C1 inhibitor deficiency [24,35–41]. Instead, we sought to produce a UK-specific document that is complementary to existing guidelines. To achieve this aim, the guidelines have been produced using the Delphi method, a structured process that aims to produce consensus among a group of experts. We report here the consensus process and statements that were ultimately approved. This document, together with standards for specialist services issued by UK PIN [46], provides a framework for the management of C1 inhibitor-deficient patients in the United Kingdom.

Methods

The research design for the consensus was based on the Delphi method: respondents are presented with a series of statements, each of which is scored for agreement using a four-point Likert scale, as follows: strongly agree, tend to agree, tend to disagree, strongly disagree. Following the first round of responses, any statements considered contentious (typically less than 66% of respondents agree) may be reviewed, with the final list of statements representing the consensus.

The questionnaire was developed by the HAE Consensus Steering Group, which included a patient representative, eight physicians with a specialist interest in the disease and three specialist nurses. Throughout a day of discussion on 26 September 2012, the Steering Group agreed a total of 48 consensus statements across 11 themes. When developing these statements, the Steering Group considered developments in the evidence base, published guidelines for specialist services [45,46] and personal experiences. The statements were incorporated into a consensus questionnaire, with a slightly modified plain-language version generated for patient use. Questionnaires were sent to all UK-based physicians and specialist nurses known to be involved in the management of C1 inhibitor-deficient patients, and additionally to the membership of key professional organizations (Table 1). Patients were invited to express their opinion by HAE UK. Two subsequent opportunities to complete the questionnaire were provided by

Table 1. Professional societies invited to participate in the consensus process.

Professional organization
Association of Clinical Pathologists
British Association of Dermatologists
British Dental Association
British Society for Allergy and Clinical Immunology
British Society for Immunology
College of Emergency Medicine
Institute of Biomedical Science
Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of Pathologists

electronic mail, and additional paper copies were distributed at professional and academic meetings.

The process was facilitated by Triducive Ltd, who collated the anonymized data for consideration by the panel. A second meeting was held on 18 November 2013 to discuss the findings and approve the consensus statements.

Results

Ninety-one health-care workers (51 consultant immunologists and/or allergists, 10 specialist registrars training in clinical immunology or allergy, 14 immunology specialist nurses, 16 other or unknown designations) responded, representing the majority of health-care professionals who care actively for this patient group. A total of 36 patients with C1 inhibitor deficiency responded. All four nations within the United Kingdom were represented among respondents.

The consensus statements are listed in Table 2. A high degree of consensus was obtained during the first round, with more than 90% of respondents indicating 'strongly agree' or 'tend to agree' to all the statements and few abstentions (Supporting information, Table S1). As all statements achieved consensus in excess of 90%, no iterative amendment was required. Consensus was highest among patient respondents, with more than 97% agreement to all statements. Among health-care workers, agreement of >90% was achieved in response to 47 of 48 questions; statement 20 – concerning use of anti-fibrinolytics in prophylaxis – achieved 88.8% agreement. In general, most statements elicited 'strong agreement', with 'tend to disagree' and 'strongly disagree' rarely observed. Consensus remained extremely high when analysed by occupation or speciality, although small numbers limit the interpretation of subgroup analysis. Alignment of these statements to accreditation standards for specialist centres published by UK PIN is described in Supporting information, Table S2.

A facility for freetext comments was utilized by a minority of respondents to comment on the statements and study process: one respondent criticized the document for being too 'centralist' and another suggested that the definition of 'specialist centre' should be kept flexible enough to allow for different models of care. Some questions (for example, concerning children or new medications) were indicated as inappropriate for those without specific expertise. We note that some respondents did not comment on all statements, presumably denoting lack of expertise or opinion with regard to a particular statement (see Supporting information, Table S1).

Discussion

We present here an updated UK consensus for the management of patients with C1 inhibitor deficiency. The consensus was developed using the Delphi method, an established process for the collation of opinion from a

group of experts. According to this process, respondents indicate agreement with statements in rounds; after each round, facilitators collate and anonymize the responses to guide amendment of the statements for future rounds. The process is completed when predefined levels of consensus are reached. This method was pursued in order to produce guidelines that are complementary to recent publications [24,35–41] and with an emphasis on UK services.

The consensus has evolved significantly since the previous 2005 UK document. A particularly important development is an improved evidence base to guide the management of acute attacks. The dosing of C1 inhibitor concentrate (statement 17) was particularly emphasized, given the availability of guidance from robust trial data [18–21]. However, clinical experience suggests that individualized dosing is appropriate, including higher doses where treatment is delayed and lower doses when treatment is immediately available (statement 18). In keeping with other recent guidelines [24,35–41], the document supports the wider use of acute treatment for disabling attacks (statement 3) rather than limiting treatment to severe episodes. Statement 2 (treatment of HAE should follow international guidance and standards, while considering the resources available in the United Kingdom) and statement 12 (patients should take medication according to clinical need rather than financial considerations) could perhaps be considered to conflict. We would emphasize, however, that as currently worded, the consensus for statements 2 and 3 does not mandate treatment for all attacks – rather, less serious attacks are considered to be potentially treatable. Consideration of treatment costs will form part of the decision process when weighing up whether or not symptoms are sufficiently disabling to warrant therapy within the parameters of statement 12. Regarding long-term prophylaxis, the value of closely monitored androgens with appropriate monitoring is endorsed (statements 21–25). A greater emphasis is placed on long-term prophylaxis with C1 inhibitor concentrate (statement 27), reflecting an improved evidence base [19,29] and increased experience among clinicians and patients. Long-term prophylaxis with tranexamic acid continues to be supported in the paediatric setting where options are limited (statement 46). A more guarded statement was supported (with 88.9% consensus among health-care workers) for the general use of this agent for long-term prophylaxis (statement 20); this was the only statement to achieve consensus below 90%, reflecting a weak evidence base and mixed practice.

Saule and colleagues published an observational series including 16 women with hereditary angioedema, describing modest benefit from progestagens in long-term prophylaxis [47]. The authors recommended either desogestrel 75 mg daily (Cerazette), medroxyprogesterone acetate (Depo-Provera) or norethisterone 10 mg daily. The latter two options provide a higher dose and possibly a higher

Table 2. 2014 C1 inhibitor deficiency consensus statements.

A: Treatment objectives

1. Each C1 inhibitor-deficient patient should be able to manage his or her symptoms proactively in such a way that they maintain personal safety and minimal disruption in living a healthy and productive life
2. Treatment of HAE should follow international guidance and standards, whilst considering the resources available in the UK
3. All disabling attacks irrespective of location are eligible for treatment as soon as they are clearly recognized
4. Patient self-treatment is the ideal service model in line with government policy

B: Access to expertise

5. Every patient should be under the supervision of a specialist hub centre for HAE, either directly or via a spoke centre
6. A specialist centre has appropriate resources and a sufficient cohort of patients to maintain appropriate expertise in the treatment of HAE
7. Informative educational literature and support should be made available to every HAE patient
8. People with suspected HAE need to have access to a specialist centre expert
9. Every patient (including children) should be offered the option of home administration with appropriate monitoring, training and governance

C: Access to medication

10. Every patient should hold a safe quantity (minimum of one) of acute treatment doses at home dependent on individual needs
11. It is important that arrangements are in place to facilitate speedy replacement of acute attack medication after use so that the patient may proactively manage their symptoms safely with minimum disruption to living a healthy and productive life
12. Patient should take their medication according to clinical need rather than financial considerations

D: Acute treatment

13. Plasma-derived C1 inhibitors (Berinert, Cinryze), recombinant C1 inhibitor (Ruconest) and Icatibant (Firazyr) are all acceptable options for acute treatment
14. Icatibant may be particularly useful in enabling self-administration as intravenous access is not necessary
15. Regular prophylactic treatment with C1 inhibitor may be appropriate for patients requiring treatment for two or more attacks per week
16. Plasma-derived C1 inhibitor is the treatment of choice for acute attacks of HAE for children, pregnant and breast-feeding women, and those trying to conceive

E: Dosing of C1 inhibitor

17. We recommend that patients use the licensed dose of C1 inhibitor. In certain circumstances, the dose may need adjustment according to clinical response
18. A higher dose may be required if treatment is delayed. For early treatment via self administration, lower doses may be appropriate
19. If a second dose is needed, then the full dose will be required. It may therefore be a false economy to dose inappropriately low in the first instance

F: Long-term prophylaxis

20. Evidence for the efficacy of anti-fibrinolytics is poor; however, a minority of patients may find them helpful
21. Attenuated androgens are effective in long-term prophylaxis for most people
22. The lowest effective dose of attenuated androgen should be used to minimize side effects
23. High doses of androgens may provoke severe side effects without added benefits
24. Doses of danazol above 200 mg daily should be exceptional
25. Doses of stanozolol above 4 mg daily should be exceptional
26. Treatment registries should be completed to allow better understanding of new products
27. Exceptionally, C1 inhibitor prophylaxis may be required when control of acute attacks is not possible by other means (including for children). This should be reviewed at regular intervals

G: Treatment plans

28. All patients should have a treatment plan for acute and elective surgery, including dentistry
29. All patients should have an additional treatment plan in place to ensure their safety when away from home or abroad
30. Treatment plans should be developed according to individual need and updated regularly

H: Role of the specialist nurse

31. The specialist immunology nurse is pivotal in patient care
32. All patients should have timely access to a specialist immunology nurse
33. The specialist immunology nurse has a key role in supporting the patient and their family in the practicalities of living with HAE to achieve the best quality of life

I: Patient support

34. Because HAE is a rare condition, patient information should be comprehensive and consistent
35. HAE patients benefit from direct contact with others with the same condition
36. Advocacy is important in ensuring equality of access and benefit
37. Patients may have inappropriately low expectations of QoL with HAE, which may limit their life options. This should be addressed
38. Patient information should be provided in an easily accessible and up-to-date format including electronic media
39. Specialist HAE patient support groups such as HAE UK have an important role in disseminating best practice in partnership with health care professionals

J: Commissioning

40. Central funding of HAE treatments will allow equality of access
41. Central funding of HAE treatments will allow affordability through a shared financial risk
42. A national approach to commissioning of HAE services enables accurate estimation of likely costs, based on mean resource utilization
43. Commissioning of home therapy will reduce utilization of hospital services

K: Children and adolescents

44. Children require exceptional treatment plans, which need to be developed according to individual need and updated regularly
45. The use of attenuated androgens should be avoided in pre-adolescent children
46. Tranexamic acid is the drug of choice for prophylaxis in children
47. Treatment registries should be completed to allow better understanding of unlicensed products
48. Treatment plans for children and adolescents should address planning for issues such as school trips and examinations

HAE = hereditary angioedema; QoL = quality of life

response rate. A statement about the role of progestagens as long-term prophylaxis was not included in this document because the relevant paper was not published at the time of the steering group meeting.

The results also indicate strong consensus on aspects of service organization and delivery, showing overwhelming support for specialist services (statements 5–9), and patient self-management and home therapy (statement 4). We welcome the principle of patient-centred, community-based care, supported by easily accessible specialist expertise and, where appropriate, local centres. The haemophilia model of self-administration of intravenous medications by patients and their families demonstrates that this model is feasible and cost-effective. The net financial effects of such an approach as applied to C1 inhibitor deficiency in the United Kingdom have not been defined, but data from Denmark demonstrate the benefits of the approach in reducing hospital attendance and the burden of disease [48]. The results of the consensus indicate clearly that both patients and health-care workers endorse this model for C1 inhibitor deficiency, in order to ensure that patients can achieve their full potential by early education and training in the prevention and management of acute attacks.

Some important performance characteristics of the Delphi method should be considered. The consensus involves scientific evidence, but does not involve rigorous review of scientific evidence in order to produce guidance. This has produced a document that is complementary to existing guidelines from other bodies. It does not seek to replicate or replace their work, but rather adds another form of expert opinion evidence to the literature. Compared to the generation of evidence-based guidelines by small panels of experts, the Delphi method is more inclusive and gathers opinion from a larger number of professionals. The anonymity of respondents may temper domination of the process by opinion leaders and encourages free expression. However, the issue is not completely resolved, as the question set is determined by a steering group.

Another key difficulty is selection of the panel members: a very inclusive process may produce an invalid

consensus by including responses from respondents who lack expertise in the field, whereas an overly exclusive process may not reflect a true consensus. We attempted to engage with a wide variety of stakeholders outside the clinical immunology and allergy community by collaborating with relevant professional bodies, distributing paper copies at professional meetings and permitting peer-to-peer distribution of questionnaires. A significant number of responses was obtained from outside the immunology and allergy community which, in addition to 51 responses from clinical immunologists and/or allergists, is felt to capture the large majority of health-care workers involved directly in the management of this disease. As these respondents work independently in specialist centres throughout the United Kingdom, we can be confident that the remarkably high consensus does not reflect training or service led by small number of opinion leaders. However, it must be acknowledged that the UK allergy and immunology community constitutes a small group with a long-standing tradition of cooperation through organizations such as UK PIN. In addition, the methodology does not permit the calculation of a defined response rate. Compared to the health-care worker data set, results from patient respondents are less robust due to relatively small numbers ($n = 36$) and the risk of ascertainment bias.

The assumption that all participants are equal in terms of knowledge and experience represents another weakness of the methodology. This probably accounts for a relatively high number of abstentions among respondents for several more technical statements, notably 24, 25, 45 and 46. Finally, where successive rounds are utilized, the risk is that the process may mould, rather than simply collate, opinion; this was not a concern in this project, as consensus was reached within a single round. Despite the shortcomings, the very high level of consensus among health-care workers and a small sample of patients indicate strong alignment of opinion.

This project has not addressed explicitly hereditary bradykinin-mediated angioedema that is not related to C1 inhibitor deficiency [49], but many of the statements would be applicable to this group, whose specific needs

Table 3. Respondents who publicly declare their support for the document.

Ms Karen Abrams, Specialist Nursing Practitioner in Immunology, Oxford University Hospitals NHS Trust
 Dr Hana Alachkar, Consultant Immunologist, Salford Royal NHS Foundation Trust
 Dr Peter Arkwright, Senior Lecturer and Honorary Consultant Paediatric Immunologist, University of Manchester
 Dr Gururaj Arumugakani, Specialist Registrar in Immunology, Leeds Teaching Hospitals NHS Trust
 Mrs Fran Ashworth, Clinical Nurse Specialist in Immunology, Sheffield Teaching Hospitals NHS Trust
 Dr Amolak S Bansal, Consultant in Immunology and Allergy, Epsom and St Helier University Hospitals NHS Trust
 Dr Claire Bethune, Consultant Immunologist, Plymouth Hospitals NHS Trust
 Dr Malini Bhole, Consultant Immunologist, The Dudley Group NHS Foundation Trust
 Dr Matthew Buckland, Consultant Immunologist, Barts Health NHS Trust, London
 Dr Catherine Cale, Consultant Paediatric Immunologist, Great Ormond Street Hospital NHS Foundation Trust
 Dr Anita Chandra, Clinical Immunologist, Cambridge University Hospitals NHS Foundation trust
 Dr Ignatius Chua, Specialist Registrar in Immunology, Barts Health NHS Trust
 Dr Sheila Clark, Consultant Dermatologist, Mid Yorkshire and Leeds Teaching Hospitals NHS Trusts
 Professor Christopher Corrigan, Professor of Allergy, Asthma and Respiratory Science, Kings College London
 Mr John Dempster, Immunology Nurse Specialist, Barts Health NHS Trust
 Dr Tina A Dixon, Consultant Allergist, Royal Liverpool and Broadgreen University Hospital NHS Trust
 Dr Philip Dore, Consultant Immunologist, Hull and East Yorkshire Hospitals NHS Trust
 Dr Michael Duddridge, Consultant Clinical Immunologist, University Hospitals of Leicester NHS Trust
 Dr David Edgar, Consultant Immunologist, The Royal Hospitals, Belfast
 Dr Efreem Eren, Consultant Immunologist, University Hospital Southampton NHS Foundation Trust
 Mrs Alex Farragher, Immunology Specialist Nurse, Central Manchester University Hospitals NHS Foundation Trust
 Dr TJ Flood, Consultant in Paediatric Immunology, The Newcastle upon Tyne Hospitals NHS Trust
 Dr Tomaz Pereira Garcez, Consultant Immunologist, Central Manchester University Hospitals NHS Foundation Trust
 Dr Mark Gompels, Consultant Immunologist, North Bristol NHS Trust
 Dr Clive Grattan, Consultant Dermatologist, Norfolk and Norwich Hospitals NHS Trust
 Dr Elizabeth Griffiths, SpR in Allergy, Guys and St Thomas's NHS Trust, London
 Dr Sofia Grigoriadou, Consultant Immunologist, Barts Health NHS Trust
 Professor Tim Harris, Professor of Emergency Medicine, Barts Health NHS Trust
 Dr Grant Hayman, Consultant Clinical Immunologist, Epsom and St Helier University Hospitals NHS Trust
 Dr Richard Herriot, Consultant Immunologist, Aberdeen Royal Infirmary
 Dr Archana Herwadkar, Consultant Immunologist, Salford Royal NHS Foundation Trust
 Dr Aarnood Huissoon, Consultant Immunologist, Heart of England NHS Foundation Trust
 Dr Rashmi Jain, Consultant Immunologist, Oxford University Hospitals NHS Trust
 Dr Stephen Jolles, Consultant Immunologist, University Hospital of Wales
 Dr M Yousuf Karim, Consultant Immunologist, Frimley Park Hospitals NHS Foundation Trust and The Royal Surrey County Hospital NHS Foundation Trust
 Dr DS Kumararatne Consultant Immunologist, Cambridge University Hospitals NHS Trust
 Dr Hilary Longhurst, Consultant Immunologist, Barts Health NHS Trust
 Ms Lorena Lorenzo, Immunology Specialist Nurse, Barts Health NHS Trust
 Dr Joanna Lukawska, Locum Consultant Allergist, Royal National Throat Nose and Ear Hospital
 Dr John Maher, Senior Lecturer in Immunology and Honorary Consultant Immunologist, King's College London
 Miss Clare Malcolmson, Clinical Nurse Specialist in Immunology, Great Ormond Street Hospital NHS Foundation Trust
 Dr Ania Manson, SpR in Clinical Immunology, Barts Health NHS Trust
 Ms Gail Menzies, Immunology Nurse Specialist, Ninewells Hospital Dundee
 Dr Joanne Miller, Specialist Registrar in Clinical Immunology, Oxford University Hospitals NHS Trust
 Dr Vasantha Nagendran, Consultant Immunologist, Epsom and St Helier University Hospitals NHS Trust
 Dr Iman Nasr, SpR in Immunology, Barts Health NHS Trust
 Dr Sadia Noorani, Consultant Immunologist, Sandwell and West Birmingham NHS Trust
 Dr D G Paige, Consultant Dermatologist, Barts Health NHS Trust, London
 Dr Andrew Riordan, Consultant in Paediatric Infectious Diseases and Immunology, Alder Hey Children's NHS Foundation Trust
 Ms Carol Ross, Specialist Nursing Practitioner in Clinical Immunology, Oxford University Hospitals NHS Trust
 Dr Sinisa Savic, Consultant Clinical Immunologist, Leeds Teaching Hospitals NHS Trust
 Dr Suranjith Seneviratne, Consultant Immunologist, Royal Free London NHS Foundation Trust
 Dr Ravishankar Sargur, Consultant Immunologist, Sheffield Teaching Hospitals NHS Foundation Trust
 Dr Anna Shrimpton, Consultant Immunologist, Sheffield Teaching Hospitals NHS Foundation Trust
 Mr Craig Simon, Immunology Nurse Specialist, Royal Liverpool and Broadgreen University Hospitals NHS Trust
 Dr Catherine Stroud, Consultant Immunologist, The Newcastle upon Tyne Hospitals NHS Foundation Trust
 Mrs Christine Symons, Nurse Consultant in Immunology, Plymouth Hospitals NHS Trust

Dr Michael Tarzi, Senior Lecturer and Honorary Consultant Immunologist, Brighton and Sussex Medical School
 Dr Moira J Thomas, Consultant Immunologist, Gartnavel General Hospital Glasgow
 Dr Andrew P Volans, Consultant in Emergency Medicine, York Teaching Hospital NHS Foundation Trust
 Ms Ruth Weldon, Clinical Nurse Specialist Immunology and Allergy, Nottingham University Hospitals NHS Trust
 Dr Paul Williams, Consultant Clinical Immunologist, University Hospital of Wales
 Dr Philip Wood, Consultant Immunologist, Leeds Teaching Hospitals NHS Trust
 Dr Patrick FK Yong, Consultant Clinical Immunologist, Frimley Health NHS Foundation Trust

are also addressed in a separate consensus document [50]. Although the document is UK-centric, the themes of quality improvement, patient-centred care and increasing health-care costs are a focus and challenge for most higher-income nations at the current time.

While responses are confidential and not individually available to the steering committee, those responding have been invited to support this paper publically. Sixty-four of 91 health-care professionals indicated their publicly declared support and are listed (Table 3) as the UK 2014 C1 Inhibitor Deficiency Consensus Group.

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Disclosures

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CSL-Behring. M. G. has been a member of advisory panels for Shire, CSL-Behring and Viropharma. S. S. has received travel grants to attend scientific meetings and attended advisory boards hosted by Shire, SOBI Biovitrum and Viropharma. S. J. reports consulting, speaker, travel, advisory board and research support from CSL Behring, Baxter, BPL, Biotest, SOBI, Shire, Viropharma and Octapharma.

Author contributions

All authors contributed to the consensus process as members of the Steering Committee. The manuscript was written by H. J. L. and M. D. T. and critiqued by all authors.

References

- 1 Longhurst H, Cicardi M. Hereditary angio-oedema. *Lancet* 2012; **379**:474–81.
- 2 Cugno M, Castelli R, Cicardi M. Angioedema due to acquired C1-inhibitor deficiency: a bridging condition between autoimmunity and lymphoproliferation. *Autoimmun Rev* 2008; **8**:156–9.
- 3 Roche O, Blanch A, Caballero T, Sastre N, Callejo D, Lopez-Trascasa M. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. *Ann Allergy Asthma Immunol* 2005; **94**:498–503.
- 4 Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. *Br J Dermatol* 2009; **161**:1153–8.
- 5 Jolles S, Williams P, Carne E *et al.* A UK national audit of hereditary and acquired angioedema. *Clin Exp Immunol* 2014; **175**:59–67.
- 6 Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore)* 1992; **71**:206–15.
- 7 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.
- 8 Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol* 2012; **130**:692–7.
- 9 Gompels MM, Lock RJ, Abinun M *et al.* C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; **139**:379–94.
- 10 Cicardi M, Banerji A, Bracho F *et al.* Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med* 2010; **363**:532–41.
- 11 Lumry WR, Li HH, Levy RJ *et al.* Randomized placebo-controlled trial of the bradykinin B(2) receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. *Ann Allergy Asthma Immunol* 2011; **107**:529–37.

- 12 Zanichelli A, Bova M, Coerezza A, Petraroli A, Triggiani M, Cicardi M. Icatibant treatment for acquired C1-inhibitor deficiency: a real-world observational study. *Allergy* 2012; **67**: 1074–7.
- 13 Bas M, Greve J, Hoffmann TK *et al.* Repeat treatment with icatibant for multiple hereditary angioedema attacks: FAST-2 open-label study. *Allergy* 2013; **68**:1452–9.
- 14 Cicardi M, Levy RJ, McNeil DL *et al.* Ecallantide for the treatment of acute attacks in hereditary angioedema. *N Engl J Med* 2010; **363**:523–31.
- 15 Levy RJ, Lumry WR, McNeil DL *et al.* EDEMA4: a phase 3, double-blind study of subcutaneous ecallantide treatment for acute attacks of hereditary angioedema. *Ann Allergy Asthma Immunol* 2010; **104**:523–9.
- 16 Sheffer AL, Campion M, Levy RJ, Li HH, Horn PT, Pullman WE. Ecallantide (DX-88) for acute hereditary angioedema attacks: integrated analysis of 2 double-blind, phase 3 studies. *J Allergy Clin Immunol* 2011; **128**:153–9 e4.
- 17 Sheffer AL, MacGinnitie AJ, Campion M, Stolz LE, Pullman WE. Outcomes after ecallantide treatment of laryngeal hereditary angioedema attacks. *Ann Allergy Asthma Immunol* 2013; **110**:184–8 e2.
- 18 Craig TJ, Levy RJ, Wasserman RL *et al.* Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol* 2009; **124**:801–8.
- 19 Zuraw BL, Busse PJ, White M *et al.* Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med* 2010; **363**:513–22.
- 20 Craig TJ, Bewtra AK, Hurewitz D *et al.* Treatment response after repeated administration of C1 esterase inhibitor for successive acute hereditary angioedema attacks. *Allergy Asthma Proc* 2012; **33**:354–61.
- 21 Zuraw B, Cicardi M, Levy RJ *et al.* Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. *J Allergy Clin Immunol* 2010; **126**:821–7 e14.
- 22 Riedl MA, Bernstein JA, Li H *et al.* Recombinant human C1-esterase inhibitor relieves symptoms of hereditary angioedema attacks: phase 3, randomized, placebo-controlled trial. *Ann Allergy Asthma Immunol* 2014; **112**:163–9 e1.
- 23 Riedl MA, Levy RJ, Suez D *et al.* Efficacy and safety of recombinant C1 inhibitor for the treatment of hereditary angioedema attacks: a North American open-label study. *Ann Allergy Asthma Immunol* 2013; **110**:295–9.
- 24 Longhurst HJ, Farkas H, Craig T *et al.* HAE international home therapy consensus document. *Allergy Asthma Clin Immunol* 2010; **6**:22.
- 25 Cicardi M, Craig TJ, Martinez-Saguer I, Hebert J, Longhurst HJ. Review of recent guidelines and consensus statements on hereditary angioedema therapy with focus on self-administration. *Int Arch Allergy Immunol* 2013; **161** (Suppl. 1):3–9.
- 26 Bygum A, Andersen KE, Mikkelsen CS. Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. *Eur J Dermatol* 2009; **19**: 147–51.
- 27 Levi M, Choi G, Picavet C, Hack CE. Self-administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency. *J Allergy Clin Immunol* 2006; **117**:904–8.
- 28 Longhurst HJ, Carr S, Khair K. C1-inhibitor concentrate home therapy for hereditary angioedema: a viable, effective treatment option. *Clin Exp Immunol* 2007; **147**:11–7.
- 29 Zuraw BL, Kalfus I. Safety and efficacy of prophylactic nanofiltered C1-inhibitor in hereditary angioedema. *Am J Med* 2012; **125**:938 e1–7.
- 30 Bernstein JA. HAE update: epidemiology and burden of disease. *Allergy Asthma Proc* 2013; **34**:3–6.
- 31 Nordenfelt P, Dawson S, Wahlgren CF, Lindfors A, Mallbris L, Bjorkander J. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. *Allergy Asthma Proc* 2014; **35**:185–90.
- 32 Bouillet L, Launay D, Fain O *et al.* Hereditary angioedema with C1 inhibitor deficiency: clinical presentation and quality of life of 193 French patients. *Ann Allergy Asthma Immunol* 2013; **111**:290–4.
- 33 Lumry WR, Castaldo AJ, Vernon MK, Blaustein MB, Wilson DA, Horn PT. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc* 2010; **31**: 407–14.
- 34 Banerji A. The burden of illness in patients with hereditary angioedema. *Ann Allergy Asthma Immunol* 2013; **111**:329–36.
- 35 Zuraw BL, Banerji A, Bernstein JA *et al.* US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. *J Allergy Clin Immunol Pract* 2013; **1**:458–67.
- 36 Craig T, Aygoren-Pursun E, Bork K *et al.* WAO guideline for the management of hereditary angioedema. *World Allergy Organ J* 2012; **5**:182–99.
- 37 Caballero T, Farkas H, Bouillet L *et al.* International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency. *J Allergy Clin Immunol* 2012; **129**:308–20.
- 38 Bowen T, Cicardi M, Bork K *et al.* Hereditary angioedema: a current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. *Ann Allergy Asthma Immunol* 2008; **100**:S30–40.
- 39 Cicardi M, Bork K, Caballero T *et al.* Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy* 2012; **67**:147–57.
- 40 Bowen T, Cicardi M, Farkas H *et al.* 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol* 2010; **6**:24.
- 41 Betschel S, Badiou J, Binkley K *et al.* Canadian hereditary angioedema guideline. *Allergy Asthma Clin Immunol* 2014; **10**:50. doi: 10.1186/1710-0000-0000-0000. eCollection 2014.
- 42 Transforming participation in health and care. Patients and Information Directorate, NHS England, Ref 00381. Available at: <http://www.england.nhs.uk/wp-content/uploads/2013/09/trans-part-hc-guid1.pdf>. Accessed March 10, 2015.
- 43 The UK strategy for rare diseases. Department of Health. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/260562/UK_Strategy_for_Rare_Diseases.pdf. Accessed March 10, 2015.
- 44 Manson AL, Price A, Dempster J *et al.* In pursuit of excellence: an integrated care pathway for C1 inhibitor deficiency. *Clin Exp Immunol* 2013; **173**:1–7.

- 45 Clinical commissioning policy: treatment of acute attacks in hereditary angioedema. NHS Commissioning Board 2013. Available at: <http://www.england.nhs.uk/wp-content/uploads/2013/04/b09-p-b.pdf>. Accessed March 10, 2015.
- 46 UK PIN Accreditation Standards. Available at: <http://www.ukpin.org.uk/home/accreditation-standards.html>. Accessed March 10, 2015.
- 47 Saule CI, Boccon-Gibod O, Fain G *et al.* Benefits of progestin contraception in non-allergic angioedema. *Clin Exp Allergy* 2013; **4**: 475–482.
- 48 Bygum A. Hereditary angioedema – consequences of a new treatment paradigm in Denmark. *Acta Derm Venereol* 2014; **94**: 436–441.
- 49 Grigoriadou S, Longhurst HJ. Clinical immunology review series: an approach to the patient with angio-oedema. *Clin Exp Immunol* 2009; **155**:367–77.
- 50 Zuraw BL, Bork K, Binkley KE *et al.* Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel. *Allergy Asthma Proc* 2012; **33** (Suppl 1): S145–56.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Consensus statistics.

Table S2. Alignment of UK C1 inhibitor consensus statements with UK Primary Immunodeficiency Network (UKPIN) accreditation standards.