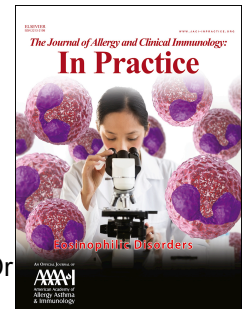


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Managing Chronic Urticaria and Recurrent Angioedema Differently with Advancing Age

Dr Hilary J. Longhurst, MA FRCP PhD FRCPATH, Dr Margarida Gonalo, MD, PhD, Dr Kiran Godse, MD, PhD, FRCP, Dr Luis F. Ensina, MD, PhD



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Authors: Dr Hilary J. Longhurst MA FRCP PhD FRCPath^{1,2}, Dr Margarida Gonçalo, MD, PhD³, Dr Kiran Godse, MD, PhD, FRCP⁴, Dr Luis F. Ensina, MD, PhD⁵.

1. Auckland District Health Board

2. Department of Medicine, University of Auckland

hlonghurst@doctors.org.uk, hilarylo@adhb.govt.nz

Phone: (+64) 9 307 4949 Ext 22971

3. Department of Dermatology, University Hospital and Faculty of Medicine, University of Coimbra, Coimbra, Portugal

(mgoncalo@fmed.uc.pt)

4. Department of Dermatology, D Y Patil University School of Medicine, Navi Mumbai, India

(drgodse@gmail.com)

5. Department of Pediatrics, Federal University of São Paulo, São Paulo, Brazil

(100alergia@gmail.com)

Corresponding author: Hilary J. Longhurst, Department of Immunology, 6th floor, Support Building, Auckland City Hospital, 2 Park Road, Grafton, Auckland 1023, New Zealand. hlonghurst@doctors.org.uk, hilarylo@adhb.govt.nz

Phone: (+64) 9 307 4949 Ext 22971

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34

35 **Key words:** Angioedema, urticaria, older people, histamine, bradykinin, leukotriene,
36 treatment, diagnosis.

37

38 **Abbreviations:**

39 AAS7: angioedema activity score measured over 7 days

40 ACE: angiotensin converting enzyme

41 AECT: angioedema control test

42 AH: antihistamine

43 C1,2,3,4: 1st, 2nd, 3rd, 4th component of the complement system

44 EAACI: European Allergy and Clinical Immunology association

45 GA²LEN: Global Allergy and Asthma European Network

46 EDF: European Dermatology Forum

47 HAE: hereditary angioedema

48 Ig: Immunoglobulin

49 NSAID: Nonsteroidal anti-inflammatory drug

50 UAS7: urticaria activity score measured over 7 days

51 UCT: urticaria control test

52 sgAH second-generation antihistamine

53 TPO: thyroid peroxidase

54 WAO: World Allergy Organisation

55 WHO: World Health Organization

56

Abstract

Angioedema and urticaria affect people of all ages. Accurate diagnosis and optimum management is essential for healthy ageing. Older people continue to experience mast cell-mediated urticaria and angioedema, with a higher prevalence of autoimmune and lower prevalence of autoallergic disease. Bradykinin-mediated angioedemas are more common in the elderly because of their association with ACE inhibitor treatment. Acquired C1-inhibitor deficiency, another bradykinin-mediated angioedema, occurs predominantly in older people, while hereditary angioedema due to C1 inhibitor deficiency continues to cause symptoms, even in old age. Drug-induced angioedemas disproportionately affect older people, the most frequent users of ACE inhibitors, aspirin and non-steroidal anti-inflammatory drugs. Accurate diagnosis and targeted treatment prevents unnecessary morbidity and mortality. Second generation antihistamines with omalizumab if required are effective and well tolerated in older people with mast cell-mediated urticaria. For bradykinin-mediated angioedemas, these drugs are ineffective. C1 inhibitor replacement or blockade of kallikrein or the bradykinin B2 receptor of the contact pathway is required to treat hereditary angioedema and may be considered in other bradykinin-mediated angioedemas, if supportive treatment is insufficient. For aspirin-related angioedema and urticaria, alternative medications or, exceptionally, desensitization may be required.

Introduction

With increased life expectancy and lower fertility rates, the population of older people is rapidly expanding in all but a handful of 'outlier' countries. The World Health Organization (WHO) estimates that the proportion of over 60s will have increased from 12% in 2015 to 22% in 2050¹. Although the majority of older people currently live in high-income countries, the rate of increase in the older population is greatest in middle and lower income countries. Healthy ageing, allowing older people to continue to contribute to society and to enjoy an independent life is therefore more important than ever.

Treatment of elderly patients presents several challenges associated with age-related changes in physiology, pharmacokinetics, and pharmacodynamics. Comorbidities are frequent, leading to increased risk of treatment-related adverse events, requiring the use of various drugs simultaneously and resulting in a greater chance of drug-drug interaction. Variations in drug absorption, distribution, metabolism, and excretion may additionally affect the safety profile of drugs in this population, particularly in rare diseases, where the number of older patients subject to formal study is likely to be low².

Chronic urticaria and angioedema syndromes can be long-term conditions. Over 10% of patients with chronic urticaria and 52% with autoimmune urticaria may require treatment for longer than 5 years³⁴. Hereditary angioedemas are lifelong and prophylaxis may be required for decades. Adverse events from very long-term treatments are poorly studied for many drugs. Therapeutic decisions need to consider risks as well as benefits of long-term treatment, since any cumulative long-term effects are likely to manifest at an age of physical vulnerability and diagnostic challenge.

Here we discuss the specific challenges of chronic urticaria and angioedema syndromes for the older population.

Management of chronic spontaneous urticaria and mast cell driven angioedema in older people

Chronic urticaria (CU), namely chronic spontaneous urticaria (CSU), affects mainly young adults but a significant proportion of patients are aged ≥65 years (4-

18.1%)^{5,6,7,8}. One Korean study found a second peak of CSU prevalence between 70 and 79 years⁹. Estimated point prevalence after ≥ 60 years in the US was 0.23% (230 cases/100.000 individuals)¹⁰.

There are few studies concerning CSU in the elderly¹¹. Compared with young adults, there is lower predominance of females^{5,6,7}, shorter duration albeit with comparable severity, and less frequent association with angioedema or inducible urticaria^{6,7,8}. Concerning comorbidities, there is less association with atopy but higher frequency of high blood pressure, diabetes and autoimmune thyroiditis^{6,7,8}, diseases that may impact on treatment choice. Aggravation by NSAIDs is less frequent in the aging population^{6,7}, but exacerbation by other drugs, such as opioids, is more frequently reported⁸. Significantly lower IgE and eosinopenia, and more frequent thyroiditis⁸, as well as other markers that suggest type IIb: autoimmune urticaria¹², seem to affect preferentially older patients¹³.

As in younger populations, CSU diagnosis is based on the clinical history of ~~evanescent~~ wheals and/or angioedema for more than six weeks. In this setting angioedema is not usually associated with upper airway, digestive or other internal swellings. In addition to the few recommended diagnostic tests (complete blood cell count, C-reactive protein and/or erythrocyte sedimentation rate, total serum IgE and IgG anti TPO)¹⁴, other laboratory investigations might be important in elderly patients in order to look for comorbidities and functioning of organs that may interfere with treatment protocols, e.g. renal and liver function. Particularly in the case of non-pruriginous lesions, the diagnosis of urticarial vasculitis and Schnitzler syndrome should be excluded. Apart from skin biopsy, showing respectively, leukocytoclastic vasculitis or neutrophilic urticaria, additional testing for complement levels and serum electrophoresis is advocated^{15,16,17}.

As in younger populations, patient reported outcomes (PRO) should be used to assess disease activity and control, namely UAS7 (Urticaria Activity Score 7 days) and UCT (Urticaria Control Test) when urticaria predominates or AAS -Angioedema activity score - for 28 days and AECT - Angioedema Control Test when angioedema is associated¹⁴.

In the management of CSU, including in this age group, it is often impossible to eliminate underlying causes and triggers are not easily avoided¹⁴. It is necessary to

proceed to pharmacologic treatment with the aim of controlling symptoms until urticaria remits¹⁴. According to the current EAACI/GA²LEN/EDF/WAO guideline for the management of urticaria, all patient populations should be treated according to the same proposed algorithm: second-generation H1-antihistamines (sgAH) at the standard dose, followed by up dosing up to four-fold (1st and 2nd line therapy), followed by omalizumab and cyclosporine, respectively (3rd and 4th line)¹⁴. Nevertheless, in elderly individuals some drugs need to be adapted to the individual patient, depending on comorbidities, polypharmacy and altered pharmacokinetics and pharmacodynamics.

H1-anti-histamines control CSU in less than 50% of patients^{18,19}, but response rates have not been evaluated in the elderly population. Angioedema and chronic inducible urticaria, associated with poorer response to antihistamine therapy^{20,21}, are less frequent in the aging population, therefore response rate may be slightly superior. However, type IIb autoimmune urticaria that responds poorly to 1st and 2nd line therapy seem to affect older individuals¹³. Current guidelines recommend avoiding first-generation H1-antihistamines in the treatment of CSU, and this is of utmost importance in the elderly population who suffer more frequent and severe adverse events. Due to their capacity to cross the blood-brain barrier these antihistamines are associated with impairment of cognition, memory, and psychomotor function, drowsiness, sedation and fatigue and their additional anticholinergic, antiserotonergic and antidopaminergic effects may cause urinary retention, blurred vision and postural hypotension, particularly in older people^{22,23}. Second generation H1-antihistamines are well-tolerated, although few studies have been conducted with up dosing in this population. Somnolence is very occasionally reported and in some patients it is worse with up dosing²⁴, but there is no reference to any relation with increasing age. Cardiotoxicity is not reported for higher dose bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, mizolastine or rupatadine, but as there are no studies in elderly, we recommend special attention in patients who already have a long QT interval, previous cardiac disease or are using drugs that prolong QT interval (anti-arrhythmics, tricyclic anti-depressants, neuroleptics)²⁵. Also, interactions may be of concern when antihistamines that require hepatic metabolism (desloratadine, fexofenadine and ebastine) are used

concomitantly with drugs competing for the same cytochromes (antifungal azoles, macrolides, grapefruit juice and St. Johns Wort)²⁶.

Omalizumab, an anti-IgE monoclonal antibody is effective and safe in H1-antihistamine refractory CSU. It significantly reduces or clears wheals and angioedema in over 60% of patients^{27,28}, and improves quality of life^{29,30,31}. Omalizumab has been used in elderly individuals both in clinical trials, which included individuals up to 75 years^{32,33}, and in many published case-series^{34,35}, with good response and safety profile. In a real-life setting, Nettis et al. evaluated 32 patients with CSU aged 65 to 83 years. In comparison with the younger patients, they found no difference in response rate; the frequency of minor adverse events was lower (6.2 vs 11.7%)³⁶. Efficacy and safety of omalizumab has also been shown in patients with hypertension, dyslipidemia, ischemic heart disease, hepatic or renal disease, cancer, autoimmune and some infectious diseases³⁵, comorbidities that are more frequent in elderly patients.

Cyclosporine is recommended as the 4th line (off label) therapy¹⁴. Cyclosporine is efficacious, particularly in patients with low IgE^{37,38,39}. Frequent contraindications and adverse events (arterial hypertension, kidney damage, hirsutism, gingival hyperplasia, dyslipidemia) limit its use, particularly in the elderly.

Although mast cell-mediated angioedemas are most common, it is important to accurately diagnose bradykinin-mediated angioedemas, which disproportionately affect older people (figure 1)

Management of hereditary angioedema in older people

Hereditary angioedema (HAE) due to C1-esterase inhibitor (C1INH) deficiency (HAE-C1INH) is a rare, autosomal-dominant disease characterized by bradykinin-mediated recurrent angioedema. Onset of symptoms usually begins in childhood and adolescence, but attacks may occur at any age and recur throughout the patient's life⁴⁰. Attacks affect sites like the face, extremities, genitalia, digestive tract, and upper airways, impacting the patient's activities and well-being. Although laryngeal edema occurs in less than 1% of attacks, over 50% of patients have experienced this life-threatening symptom at least once⁴¹. Prevention of attack progression and long-term prophylaxis are the main goals of treatment when considering patient's survival and

quality of life. However, current consensus guidelines do not address any specific recommendation for HAE-C1INH treatment in the elderly^{40,42}.

Presence of comorbidities in this age group is frequent and challenging, since HAE-C1INH patients with concomitant diseases have a higher number of attacks per year than those without other medical issues⁴³ and may have contraindications to commonly used HAE medications.

HAE attacks can be treated on an “on-demand” basis. Home therapy is encouraged as early treatment shortens the time to resolution of symptoms regardless of attack severity. However, drug self-management can be a challenge for some older adults, especially those with physical or mental disabilities. Among the drugs recommended for attack treatment, C1INH concentrates, and icatibant are available for self-administration^{40,42}. A study on the use of intravenous plasma-derived C1INH concentrate in adults ≥ 65 years of age showed that almost 95% of infusions could be administered outside of a healthcare setting. Furthermore, no evidence of difficulties with home administration was reported⁴⁴.

Concerns regarding self-administration treatment include the occurrence and management of adverse events (AE). In this same study, the rate of adverse events (0.83 events per subject and 0.02 events per infusion) in older adults was similar to those observed in younger ones. None of the AE were related to the drug, and 90% were mild or moderate⁴⁴. Icatibant, a bradykinin B2 receptor antagonist, is indicated for treating HAE attacks as well. The percentage of patients treated with this drug presenting at least one possibly/probably drug-related AE were similar for the elderly (2.0%) when comparing to younger patients (2.7%)⁴³. In general, both drugs available for self-treating HAE attacks are safe for use in patients ≥ 65 years of age, despite their more frequent comorbidities and concomitant medications^{43,44}.

There is no specific data on the use of ecallantide (kallikrein inhibitor), solvent detergent-treated, or fresh frozen plasma in the treatment of HAE attacks in older adults.

Long-term prophylaxis aims to reduce the overall number, severity, and burden of angioedema attacks. All patients should be evaluated for long-term prophylaxis in every visit, at least once a year under an individualized treatment plan. Patients under

long-term prophylaxis should also have on-demand treatment for breakthrough attacks^{40,45}.

Plasma-derived C1INH or lanadelumab are currently preferred for long-term prophylaxis. Subcutaneous twice weekly administration of doses varying from 40 to 60UI/kg (C1INH) or 30mg every 2 to 4 weeks (lanadelumab) is safe and effective, improving patients' quality of life compared to on-demand treatment alone^{40,42, 45}.

Bernstein et al. evaluated ten patients ≥ 65 years of age with at least four attacks for more than two consecutive months treated with prophylactic subcutaneous C1INH for 52 to 140 weeks. Most of them had multiple comorbidities and were taking at least five different non HAE-related drugs. No patient discontinued the study because of an AE. Mild local injection site reactions occurred in 50% of patients. Six of nine patients were classified as responders with a reduction equal to or greater than 50% in the number of attacks. The mean number of attacks per month decreased from 2.71 to 0.86. In general, subcutaneous C1INH was safe, effective, and well-tolerated by older patients in long-term prophylaxis for HAE⁴⁶.

Lanadelumab is a human monoclonal antibody that binds and inhibits active plasma kallikrein. A phase-III clinical trial in which just three patients older than 65 years had received the active treatment showed that subcutaneous lanadelumab significantly reduced attack rate compared to placebo with a good safety profile⁴⁷. Androgens are considered second-line for long-term prophylaxis and should be used with caution in older patients because of their potential side effects, particularly hypertension, but also hyperlipidemia, hepatic abnormalities and theoretical concerns about promoting thrombosis. Antifibrinolytic agents are no longer recommended for long-term prophylaxis. There is a lack of specific studies for treating HAE patients over 65 years of age with these drugs⁴⁰.

In conclusion, current limited data support the use of C1INH concentrate and icatibant for treating HAE attacks in the elderly, as well as subcutaneous C1INH or lanadelumab for long term prophylaxis. All drugs have been demonstrated to be well-tolerated and effective in this particular population.

Acquired C1 inhibitor deficiency in older people

Acquired C1-inhibitor (C1INH) deficiency, previously known as acquired angioedema, is largely a disorder of older people^{48,49}. As with hereditary angioedema, those affected experience episodic angioedema without wheals (urticae), which can affect any part of the body. Lips, face and in particular tongue, are more commonly affected than in the hereditary angioedemas, and death from laryngeal oedema has been reported^{50,51}. Erythema marginatum prodromes rarely occur, although a 'pricking sensation' at the site prior to onset and occasionally extreme fatigue can herald an attack⁵¹. Onset of C1INH deficiency in an older person, without family history of angioedema should therefore raise suspicion of acquired disease. The condition may be unmasked by use of ACE inhibitors^{52,53}. Failure of the angioedema to resolve within a few months of stopping ACE inhibitors should trigger evaluation for C1INH deficiency.

Acquired C1INH deficiency results from over-activation of classical, contact or fibrinolytic pathways, with consumption of C1INH⁵⁴. It is associated with presence of paraproteins and with B-cell lymphoproliferative disorders, particularly marginal lymphoma^{48,51,55}; autoimmunity, particularly connective tissue disease⁴⁹ or chronic infection^{56,57}. Interestingly, diagnostic delay is shorter, with a mean delay of 12 months compared with 112 months for hereditary angioedema in one case series⁵⁸. Diagnosis is confirmed by low C4, normal or low C3 and low C1INH protein and function⁵⁹. Over-activation of the early classical complement pathway results in low C1q in the majority of cases and C1INH antibodies may be present^{48,50,51}. However, the angioedema itself results from excess local bradykinin, occurring as a result of reduced contact pathway inhibition due to deficiency of C1INH.^{49,60}

Diagnosis of acquired C1INH deficiency should trigger enquiry about systemic symptoms such as night sweats, weight loss, diarrhea, fatigue or symptoms of connective tissue disease or chronic infection, and physical examination, including for lymphadenopathy and hepatosplenomegaly. Investigations should include blood count, paraproteins, lymphocyte immunophenotype where appropriate, and screening for chronic infections, including hepatitis C and HIV. Imaging of the chest, abdomen and pelvis is necessary^{59,61}.

Although there are no randomized clinical trial data, treatments are broadly similar to treatment of hereditary angioedema. Targeted treatments that inhibit

contact or fibrinolytic pathways appear to be more effective than those which replace or increase levels of C1INH⁶². C1INH is effective, although higher doses may be required for acute attacks, and patients occasionally become refractory, particularly when C1INH is used prophylactically^{50,51}. An indirect comparison of patients with hereditary and acquired C1INH deficiency suggested that icatibant, a bradykinin B2 receptor blocker, resulted in more rapid attack resolution in patients with acquired C1-INH deficiency⁵⁸.

For prophylaxis, tranexamic acid, given in doses of 1g twice daily (or up to 1.5g thrice daily) appears more effective than attenuated androgens^{50,51}. A trial of lanadelumab, a human monoclonal anti-kallikrein antibody, is ongoing⁶³.

Treatment of the underlying cause can lead to hematological and clinical remission of the C1INH deficiency⁶⁴. Numerous case reports describe response to B-cell ablation with rituximab^{48,49,60}, which can lead to long-term remission⁶⁵. However, late antibody deficiency is a concern⁶⁶. Efficacy of rituximab suggests that the source of the paraprotein in most acquired C1INH cases is B-cell rather than plasma cell.

Uncontrolled angioedema can cause major detriment to quality of life and, although there is no age-specific data, older people are often severely affected⁶⁷ [Longhurst personal communication]. For this reason, effective treatment should not be withheld because of undue concerns of adverse effects.

Icatibant is contraindicated in acute stroke or myocardial infarction, but outside these very limited restrictions, both C1 inhibitor and icatibant have proved well-tolerated in the elderly, including in those with cardiovascular disease or hypertension^{43,44,62}. Tranexamic acid, while theoretically of concern in thrombotic diseases is well tolerated in short-term use^{68,69} and in long-term use in younger women, without increase in thrombosis in either case⁷⁰. While it is not recommended in those with seizures, there is no evidence that it can promote seizures in those who may be at risk because of age-related brain disorders⁶⁸.

Drug-related angioedema in older people: ACE inhibitor angioedema

Adverse drug reactions (ADR), including hypersensitivity reactions, are generally common in the elderly, accounting for up to 1.5% of emergency hospitalization among older adults in the USA⁷¹. The presence of common chronic

conditions in the elderly increases the likelihood of being exposed to drugs that are potential triggers for adverse reactions⁷². Angiotensin-converting enzyme inhibitors (ACEIs) are among the most commonly prescribed drugs to treat different diseases such as hypertension, heart failure, diabetic nephropathy, among others. Observational studies show that 19-30% of patients treated with ACEIs have to discontinue treatment because of adverse reactions⁷³.

ACEI therapy is a relevant cause of drug-induced angioedema and has a significant role in hospitalizations due to angioedema. Approximately 0.1 to 0.7% of patients receiving ACEIs experience angioedema, but the numbers were higher in a nation-wide prevalence survey in Japan (8%)⁷⁴. On the other hand, ACEIs are responsible for just 1% of all reported drug-induced angioedema, according to data from a Latin-American registry⁷⁵.

There is a lack of data on ACEI-induced angioedema (ACEI-AE) in older adults. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) evaluated the incidence and predictors of angioedema in hypertensive patients older than 55 years of age at high risk for cardiovascular disease. More than 42,000 participants were enrolled in the study and were randomized into four different groups of treatment with an ACEI (lisinopril), a calcium channel blocker (amlodipine), an alpha-blocker (doxazosin), or a diuretic (chlorthalidone). Angioedema was reported in 0.12% of total participants and 0.41% in those treated with ACEI. Angioedema occurred on the first day of treatment with lisinopril in 6% of patients, within the first week in 23%, and during the first month in 34%. Two-thirds of those affected experienced angioedema in the year following starting the ACEI⁷⁶. In a retrospective study using the French Pharmacovigilance National Database, the median duration of treatment before the occurrence of the first attack was 720 days (1-5400)⁷⁷.

Mahmoudpour et al. reported data from a cohort of almost 278,000 ACEI users aged over 45 years or older that initiated therapy between 2007 and 2014. Angioedema was experienced in 416 patients. Patients older than 65 years had a higher risk, as well as those with a history of allergy, use of antihistamines, corticosteroids, and calcium-channel blockers⁷³. Alharbi et al. reported a significant risk of ACEI-AE in patients over 65 years of age compared with an 18-65 years-old

group⁷⁸. Other age-independent risk factors include black and Hispanic ethnicity, history of smoking, and female gender. Diabetes has been associated with a higher risk of ACEI-induced angioedema in some studies but not in others⁷⁹.

ACEI-AE is likely mediated by bradykinin. Thus, antihistamines, corticosteroids, and epinephrine have little or no effect in controlling the symptoms. The most common affected sites are lips (65%), tongue (55%), and larynx/pharynx (29%), but abdominal involvement may also occur. It is important to note that the recurrence rate is high if the ACEI is not withdrawn⁷⁹. Up to 70% of the reactions were considered moderate/severe in patients admitted in an Israeli hospital, where 26% of them needed intensive care and 13% intubation. Obesity and antidiabetic medication, but not age or comorbidities, were considered risk factors for severe angioedema and intubation⁸⁰.

The first action when ACEI-AE is suspected should be stopping ACEI treatment and provide a safe alternative. Angiotensin II receptor blockers (ARBs) have no direct effect on the inhibition of bradykinin breakdown and are well tolerated by most patients with ACEI-AE⁷⁹.

Different drugs targeting bradykinin have been studied, but none of the studies focused on patients ≥ 65 years. A systematic review analyzed 21 studies describing acute attack treatment in 154 patients with drugs such as icatibant, fresh frozen plasma, and C1INH concentrate. The median time to initial response ranged from a few minutes up to 2.5 hours, and to complete response from 0.5 to 48 hours. Another two randomized clinical trials compared ecallantide with placebo to treat ACEI-AE attacks, but no significant differences were observed⁸¹.

Data on the efficacy of icatibant in treating ACEI-AE is controversial. Some case series and a small randomized controlled trial suggest a beneficial effect in reducing the time to resolution of symptoms. On the other hand, two other randomized controlled trials, including 33 and 121 patients, showed that the time to complete response was not statistically different when comparing icatibant and placebo⁷⁹.

In conclusion, age over 65 years is a risk factor for ACEI-AE, and, despite the lack of high-quality evidence, therapies targeting bradykinin are currently the only ones available to treat attacks independently of the age group.

Figure 2 summarizes the main types of angioedema and their management.

Drug-related angioedema in older people

Antihypertensives, non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics are the most common drugs associated with emergency room attendance^{82,83,84}. With the exception of antibiotics, these drugs are most commonly prescribed for older people, resulting in diagnostic and management challenges when wheals or angioedema occurs (Table 1). Drug-induced angioedema occurs in up to 43% of elderly patients with drug hypersensitivity reactions⁷⁵.

Aspirin or NSAIDs-related urticaria/angioedema may occur in relation to a single NSAID only or to multiple classes of NSAIDs, which can also non-specifically exacerbate CSU or may be associated with nasal polyps and asthma exacerbations (Samter's triad)⁸⁵. Although true IgE-mediated anaphylaxis can occur, in most cases the mechanism is via COX1 inhibition, which increases leukotriene production via "diversion" from prostaglandin to leukotriene synthesis. This results in loss of the mast cell stabilizing effect of prostaglandin D2, leukotriene-induced delayed histamine release from mast cells and direct vasodilatation and vascular leakage induced by leukotrienes⁸⁶. Although the clinical history can be highly suggestive of NSAIDs hypersensitivity, drug provocation tests are often necessary to confirm the diagnosis⁸⁷. Alternatives to aspirin such as clopidogrel can be used in cardiovascular disease⁸⁸ but where aspirin is considered essential, desensitization should be considered⁹⁰. After successful desensitization, it is necessary to continue daily aspirin to avoid recurrence of the hypersensitivity⁹⁰. For pain relief, paracetamol is usually tolerated but where NSAIDs are considered essential, an alternative class of NSAID or a preferential/selective Cox-2 inhibitor may be tolerated^{88,91}.

Apart from ACE inhibitors, no antihypertensives have been definitively associated with angioedema^{79,92,93,94,95}. However other drugs which may cause bradykinin-mediated angioedema are commonly used in older people. Gliptins, used for maturity onset diabetes and sacubitril, used for heart failure inhibit dipeptidyl peptidase IV and nephrolysin respectively. Both these enzymes play a role in bradykinin degradation and their inhibition would be expected to promote angioedema. Sacubitril, in combination with valsartan, an angiotensin-receptor blocker, was found to be associated with angioedema in 0.45% of cases, compared

with 0.25% of patients treated with ACE inhibitor (enalapril), over 0-5 years in a double-blind comparative study⁹⁶. When combined with ACE inhibitor the incidence was 2.7%⁹⁷. Gliptins appear to cause angioedema relatively rarely^{98,99} except when in combination with ACE inhibitors¹⁰⁰.

Plasminogen activators, widely used for thrombolysis can enhance bradykinin production via the potentiating effect of plasmin on the bradykinin-producing contact pathway. In a prospective observational study, 7.9% of patients receiving thrombolysis for stroke experienced angioedema, with ACE inhibition conferring higher risk¹⁰¹. In most cases no treatment was required. However, several cases required intubation to prevent airway obstruction.

Statins may increase expression of bradykinin B2 receptors¹⁰² and occasional case reports have linked statins to angioedema^{103,104}.

Estrogens and anti-androgens, used in hormone replacement therapy and treatment of hormone-responsive cancers can occasionally promote angioedema in those with genetic or environmental susceptibility. This occurs via increased activity of factor XII, which promotes kallikrein-mediated bradykinin release and by inhibition of bradykinin metabolism^{105,106}.

Since bradykinin-mediated angioedema arises because of a 'threshold' effect rather than immediate consequence, angioedema may occur after months or even years of treatment, making it difficult to assign causality. Onset and resolution over hours or days, absence of wheals, occasional involvement of peripheries or intra-abdominal structures and resistance to conventional antihistamine or corticosteroids should raise suspicion of bradykinin-mediated angioedema. This in its turn should prompt withdrawal of medication known to potentiate bradykinin, where possible, as well as investigation for C1 inhibitor deficiency¹⁰⁷.

CONCLUSION

Angioedema, with or without urticaria is common in the elderly. Recommended treatments are well tolerated and, as with younger people, complete symptom control should be the aim. Mast cell-mediated angioedema may occur at any age, including older people and respond to antihistamines in most cases. Bradykinin-mediated angioedemas are more common in the elderly. Accurate diagnosis is essential to avoid

airway obstruction, ineffective treatment with antihistamines and to recognize and manage the underlying cause, whether that be drug-related, lymphoproliferative, autoimmunity or infection. Likewise, timely recognition and management of aspirin or non-steroidal anti-inflammatory drug-related wheals and angioedema is essential for optimum control of common age-related disorders, such as cardiovascular or inflammatory disease.

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806 **Figure legends**

807 **Figure 1.** Schematic classification of chronic / recurrent angioedema without wheals.

808 **Figure 2:** Clinical and laboratory evaluation of angioedema in the acute setting and
809 main treatment procedures.

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Table 1. Drugs associated with angioedema

Drug	Management	Etiology
ACE inhibitors	Stop ACE inhibitor, substitute alternative, such as Angiotensin receptor blocker	Bradykinin-mediated
Aspirin	Substitute alternative anti-platelet agent such as clopidogrel Desensitisation	Leucotriene or histamine-mediated)
Non steroidal anti-inflammatory agents	Substitute alternative Such as paracetamol, alternative Cox-1 inhibitor (if tolerated) or Cox-2 inhibitor	Leucotriene or histamine-mediated
Gliptins (usually in association with ACE inhibitor)	Substitute alternative antidiabetic or antihypertensive	Bradykinin-mediated
Sacributil (usually in association with ACE inhibitor)	Substitute alternative anti-heart failure drug or antihypertensive	Bradykinin-mediated
Statins?	Substitute alternative lipid-lowering agent	Bradykinin-mediated?
Oestrogens and anti-androgens (usually in those with predisposition to angioedema)	Stop or substitute alternative (depending on indication)	Bradykinin-mediated
Tissue plasminogen activators	Supportive (benefit usually outweighs risk; single dose)	Bradykinin-mediated
Opioids	Substitute alternative painkiller	Histamine-mediated

Clinical and laboratory evaluation of angioedema in the acute setting and main treatment procedures

Diagnosis	Very acute Laryngeal edema Bronchospasm Hypotension Bradycardia Exposure: drugs, food Venom, insect bites High serum tryptase	Recurrent Possibly urticaria No abdominal/upper airway symptoms No family history No known cause Possibly NSAIDs	Recurrent No urticaria Familial history Abdominal attacks Possibly asphyxia ↓ C1-INH, C4* US: bowel edema, peritoneal effusion	Recurrent No urticaria Abdominal attacks Possibly asphyxia No family history Exposure to ACEI (other drugs)** No other cause	Recurrent No urticaria No family history Onset > 40 years Lymphoproliferative/autoimmune disease
	Anaphylaxis	MCD-AAE	HAE	ACEI-AAE**	C1-Inh-AAE
Treatment	Immediate Epinephrine IV antihistamine, high dose corticosteroid . (fluids, B2 agonist)	H1 antihistamines Omalizumab Ciclosporin A Oral corticosteroid (short course)	C1-INH replacement BKB2R antag (icatibant) Kallikrein antagonist (Ecallantide) Prophylaxis: C1-INH Kallikrein inhibitors (Lanadelumab, Berotralstat)	ACEI (other drugs)** withdrawal BKR2 antagonist (icatibant)***	C1-INH BKR2 antagonist (icatibant) Kallikrein inhibitor (Ecallantide) Prophylaxis: Tranexamic acid

MCD-AAE: Mast-cell derived Acquired angioedema; **C1-INH:** C1-inhibitor; US – ultrasonography; **HAE:** hereditary angioedema; **ACEI-AAE:** Acquired angioedema related to ACEI; **C1-Inh-AAE:** Acquired angioedema with C1-Inh deficiency; **BKR2antag** – Bradikinin receptor 2 antagonist; NSAIDs – Non-steroidal anti-inflammatory drugs

*HAE with normal C1-INH and C4 are related with other mutations, namely in *Factor XII*, plasminogen and angiotensin-1

**Apart from ACE, other drugs, namely gliptins, have been associated with drug-induced angioedema possibly mediated by Kinins

*** Controversial, since 2 of 3 randomized controlled trials failed to show benefit.

