

REVIEW ARTICLE

Controversies and challenges in the management of chronic urticaria

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Abstract

This supplement reports proceedings of the second international Global Urticaria Forum, which was held in Berlin, Germany in November 2015. Despite the clear international guideline, there remain a number of controversies and challenges in the management of patients with chronic urticaria (CU). As a result of major advancements in urticaria over the past 4 years, the current EAACI/GA²LEN/EDF/WAO urticaria guideline treatment algorithm requires updating. Case studies from patients with chronic spontaneous urticaria (CSU) [also called chronic idiopathic urticaria (CIU)], chronic inducible urticaria (CIndU) or diseases and syndromes related to CU are useful in describing and exploring challenges in disease management. Case studies of specific CSU patient populations such as children with CU or patients with angioedema but no hives also require consideration as potentially challenging groups with unmet needs. The current EAACI/GA²LEN/EDF/WAO urticaria guideline provides a general framework for the management of patients with CU but, as these cases highlight, a personalized approach based on the expert knowledge of the physician may be required.

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Conflicts of interest

- Petra Staubach has acted as a consultant or speaker for Abbvie, Allergika, Allmirall, Celgene, Karrer, LaMer, Leti, LEO Pharma, MSD, Procter & Gamble, Shire, Viropharma, Pharming and Novartis.
- Torsten Zuberbier has acted as a consultant for Ansell, Bayer Schering, DST, FAES, Fujisawa, HAL, Henkel, Kryolan, Leti, Menarini, Merck, MSD, Novartis, Procter & Gamble, Ranbaxy, Sanofi-Aventis, Schering Plough, Stallergenes, Takeda and UCB.
- Christian Vestergaard has acted as speaker for Novartis, Abbvie, LEO Pharma, and served on advisory boards for Novartis, Abbvie and Sanofi.
- Frank Siebenhaar is, or was recently, a speaker or advisor for Abbott, Braun, Dr. Pflieger, Moxie, Novartis, Patara Pharma, Procter & Gamble, and Uriach.
- Elias Toubi has acted as a speaker for Novartis.
- Gordon Sussman has recently acted as a consultant and speaker for Novartis, Merck, CSL Behring, Pfizer and Shire.

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Introduction

The first international EAACI/GA²LEN/EDF/WAO urticaria guideline was developed in 2006 following the 2nd International

Consensus Meeting on Urticaria, 'Urticaria 2004'.¹ Since then, there has been an update every four years, taking into account the latest developments and views from the medical and

scientific community. The current 2013 update to the EAACI/GA²LEN/EDF/WAO urticaria guideline is the result of a systematic literature review and outcomes from 4th International Consensus Meeting on Urticaria held in Berlin in 2012. Since then, there have been major advancements in the field of urticaria. For example, in 2014 omalizumab was approved as add-on therapy for the treatment of chronic spontaneous urticaria (CSU) [also called chronic idiopathic urticaria (CIU)], in patients with inadequate response to H₁-antihistamine treatment, making it the only licensed third-line treatment option.^{2–4} The next International Consensus Meeting on Urticaria is scheduled for late 2016.

The current EAACI/GA²LEN/EDF/WAO guideline-recommended treatment algorithm for urticaria is shown in Fig. 1.² The use of H₁-antihistamines for the first- and second-line treatment of urticaria is likely to continue to be recommended. There remain, however, some questions around the optimal treatment selection after second-line therapy. It is clear that the current

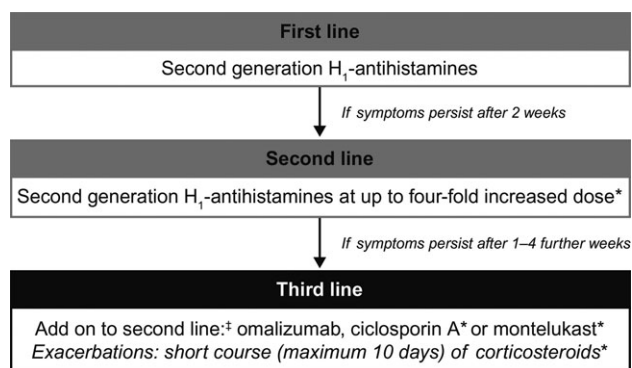


Figure 1 EAACI/GA²LEN/EDF/WAO guideline-recommended treatment algorithm for urticaria.²

*Not licensed for the treatment of urticaria.

†The order of third-line treatments does not reflect preference.

EAACI, European Academy of Allergy and Clinical Immunology; EDF, European Dermatology Forum; GA²LEN, Global Allergy and Asthma European Network; WAO, World Allergy Organization.

First line = high-quality evidence: low cost, worldwide availability (e.g. modern second-generation antihistamines exist also in developing countries; mostly cheaper than old sedating antihistamines), per daily dose as the half-life time is much longer, very good safety profile and good efficacy. Second line = high-quality evidence: low cost, good safety profile, good efficacy. Third line as add-on to antihistamines. Ciclosporin A = high-quality evidence: medium to high cost, moderate safety profile, good efficacy. Omalizumab = high-quality evidence: high cost, very good safety profile, very good efficacy. Montelukast = low-quality evidence: low cost, good safety, low efficacy. Short course of corticosteroids = low-quality evidence: low cost, worldwide availability, good safety profile (for short course only), good efficacy during intake, but very low for lasting efficacy.

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evidence-based treatment algorithm does not fit every urticaria patient. It is important that physicians do not just consult the algorithm but read the guideline line by line and employ an individualized approach to the care of each patient.

The current third-line recommendation of add-on ciclosporin (currently a strong recommendation/high level of evidence) was discussed and feedback from Global Urticaria Forum attendees was mixed, suggesting that its use varies and opinion may have changed. Ciclosporin has been reported to be effective in some studies of CSU, including three double-blind studies,^{5–7} with 40% of patients remaining in full remission at 9 months in one study.⁷ However, many physicians prefer other therapies due to the fear of toxicity with ciclosporin.⁸ Commonly reported adverse events with ciclosporin include hypertension, fatigue, gastrointestinal problems and headache.⁸ There is also a concern regarding the possible development of non-melanoma skin cancer with long-term use.⁹ In general, the risk of side-effects requires physicians to monitor blood pressure and, most importantly, renal function in patients receiving ciclosporin for CSU.¹⁰ Ciclosporin is not licensed for the treatment of urticaria and should only be used for a short number of months.

Compared with omalizumab and ciclosporin, the benefits of add-on montelukast third-line (currently a weak recommendation/low level of evidence) are less convincing. It is unknown whether further evidence will become available to change the low strength of recommendation for the use of leukotriene receptor antagonists (LTRAs) in the future. LTRAs have not been shown to significantly improve urticaria when given alone; however, some benefit has been derived from combination of montelukast with H₁-antihistamines in certain types of chronic urticaria (CU).^{11,12} Montelukast is not licensed for the treatment of urticaria.

The use of add-on omalizumab for the third-line treatment of urticaria (currently a strong recommendation/high level of evidence) is supported by a robust evidence base and this recommendation is likely to remain unchanged in the upcoming update. When the 2013 update of the international urticaria guideline was accepted for publication, omalizumab was not yet licensed for the treatment of CSU and only the results of ASTERIA II and GLACIAL (two out of three of the pivotal phase III studies for omalizumab in CSU) had been published.^{2–4,13,14} Omalizumab has an established safety profile from experience in both moderate-to-severe persistent allergic asthma and CSU. Omalizumab approval in CSU was based on data from three randomized clinical trials (ASTERIA I and II, and GLACIAL).^{13–15} Omalizumab is currently the only agent licensed for the third-line treatment of CSU.^{3,4}

The current international urticaria guideline was unable to provide a recommendation for or against the use of dapsone and its benefits remain unclear. However, results from a double-blind, placebo-controlled trial of dapsone have shown promising efficacy for this therapeutic agent in patients with antihistamine

refractory chronic urticaria.¹⁶ It is worth noting, however, that this trial used the Visual Analogue Scale rather than the recommended 7-day Urticaria Activity Score (UAS7) to assess treatment effectiveness. Recommendations for the use of dapsone in urticaria patients may change if additional good quality supporting evidence becomes available for its use in this setting.

Add-on H₂-antihistamines were suggested at the 4th International Consensus Meeting on Urticaria (November 2012) as a possible alternative treatment but they were not included in the treatment algorithm (*low recommendation/low level of evidence*). A review of the Global Urticaria Forum attendees' opinions suggested that although these agents are old and generally well tolerated by patients, they are unlikely to be used in clinical practice. As such, the next updates to the guidelines may exclude these agents altogether as a therapeutic option.

Additional new therapies such as azathioprine¹⁷ are under investigation for use in urticaria, although the evidence supporting their use is currently limited and not robust enough to warrant a change to current guidance.

The current EAACI/GA²LEN/EDF/WAO guideline recommends add-on omalizumab, ciclosporin or montelukast third line, but in no particular order. Current evidence and experience may lead to updated guidelines specifying a preferred order of the existing third-line agents or perhaps moving some to a fourth line of treatment.

Challenges for the management of urticaria in specific patient groups

Urticaria in children

At present it is recommended (*weak recommendation/clinical consensus*) that in children, the same first-line treatment and up-dosing (weight adjusted) is used as in adults (Fig. 1). Cetirizine, desloratadine, fexofenadine, levocetirizine and loratadine have established long-term safety in the pediatric population.² All further steps should be based on individual considerations. However, there are some differences between childhood and adult urticaria. In children, urticaria frequently presents as an acute episode and is recurrent, often triggered by infections. Chronic spontaneous disease may be the result of an autoimmune reaction and although this remains unclear at present, approximately 30% of children with chronic urticaria present with a positive autologous serum skin test.¹⁸ The diagnosis of childhood urticaria can be challenging as it often presents in the context of a fever or non-cutaneous manifestations. Differential diagnoses ranging from benign to hypersensitive reactions to (auto)inflammatory or autoimmune diseases are possible. Urticarial side-effects to non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, have to be considered.¹⁹ The frequency of subtypes of urticaria in children is unknown and requires further investigation. Treatment of childhood urticaria is presently directed at controlling symptoms; however, H₁-antihistamines are generally

unable to fully ameliorate symptoms in all patients. Unfortunately, the use of first generation H₁-antihistamines is still common. Studies of improvement with dietary intervention are not available. Few studies have been carried out in children suffering from urticaria and as a result the impact of urticaria on quality of life in children remains unknown.²⁰ As such, there is considerable unmet need for treating/managing childhood urticaria.

Further studies are needed to better understand the burden, epidemiology and pathophysiology of urticaria in children, including the clinical significance of functional antibodies in these patients. Methods for better establishing a diagnosis of urticaria and urticarial rash in children are urgently required. Specific instruments for assessing quality of life in children are lacking at present and are needed. Newer, more efficacious treatments are also needed for the treatment of urticaria in patients of all age groups.

Case studies of omalizumab in childhood urticaria

A 12-year-old girl presented with acquired cold-induced urticaria.²¹ Her reactions to the cold became progressively more severe over a period of approximately 2 years, despite therapy with H₁-antihistamines and a cysteinyl leukotriene receptor 1 antagonist. She began to experience systemic symptoms on immersion in ocean water. She was atopic and had moderate persistent asthma. A trial of omalizumab (off-label) resulted in complete resolution of her urticaria and its associated manifestations (Fig. 2).

In a recent publication, four pediatric patients presenting with severe CSU with or without delayed pressure urticaria, achieved complete remission following treatment with omalizumab.²²

CSU patients having angioedema but no hives

Urticaria is characterized by the sudden appearance of hives (wheals), angioedema, or both.² Angioedema is characterized by

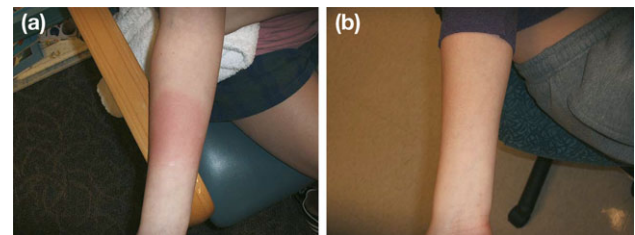


Figure 2 Successful treatment of cold-induced urticaria with omalizumab (off-label) in a 12-year-old girl.²¹ Effect of omalizumab on skin reactivity to locally applied cold stimulus (ice cube test): wheal-and-flare response observed 10 min after a 5-min application of an ice cube to the right forearm before treatment (left) and again after 6 months of treatment with omalizumab (right). Reprinted from Journal of Allergy and Clinical Immunology 117(6), Boyce JA. Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE; 1415–8. Copyright (2016), with permission from Elsevier.²¹

sudden, pronounced erythematous or skin-coloured swelling of the lower dermis and subcutis, often involvement below mucous membranes. The swelling is sometimes characterized by pain rather than itching.² Resolution of histamine-related angioedema is slower than that for hives, sometimes taking up to 72 h.² It should be noted that different non-histamine-related subgroups of angioedema exist. More than 50% of patients with CSU have associated angioedema at baseline.^{23,24} In a subgroup analysis of the phase III GLACIAL clinical trial, omalizumab treatment was associated with a reduction in angioedema compared with placebo (Table 1).²⁴ The X-ACT study of omalizumab treatment for patients with frequent angioedema who were inadequately treated with H₁-antihistamines at up to 4× the licensed dose, found that the chronic urticaria quality of life questionnaire (CU-Q2oL) score significantly improved (60%) during 28 weeks of omalizumab treatment, compared with the placebo group (20%) ($P < 0.001$). In patients treated with omalizumab, the number of angioedema burdened days was 14.6 days, significantly fewer than the placebo group (49.5 days).²⁵

Case study of a patient diagnosed with CSU with angioedema

A 35-year-old female presented with a diagnosis of CSU with angioedema for 2 years. She had been allergy tested, tried various diets and been treated with antihistamines, all without success. Her C1 esterase level and function were normal and no identifiable causative agent was found. Her histamine release test was normal, as were C-reactive protein (CRP) and whole blood count (WBC). The patient had an Angioedema Activity Score over 7 days (AAS7) of 47 and a UAS7 of 26, indicating substantial burden of disease. She was initially treated with H₁-antihistamines at four times the standard dose. After 2–3 days, she reported to the emergency room (ER) with severe angioedema of the eyes, face and upper lip, and was given



Figure 3 35-year-old CSU patient reporting to the emergency room (ER) with severe angioedema of the eyes, face and upper lip. (Photograph courtesy of Dr Christian Vestergaard. Patient consent received).

prednisolone (Fig. 3). She then began treatment with omalizumab at 300 mg every 4 weeks. Her AAS7 was reduced to 3 and her UAS7 to 2. Over the period of 2 years, the interval of omalizumab treatment was gradually increased to 7 weeks and eventually her treatment was stopped. She was still symptom-free after 6 months, but she was in severe pain with urolithiasis, for which she received NSAIDs, a possible inducer of urticaria/angioedema. The conclusion on this case was that if she re-presents with urticaria and angioedema, the treatment of choice will be omalizumab.

There is an identified need to educate urticaria patients who have episodes of angioedema that their condition is not life-threatening and they do not need to attend the ER. In this regard, it is also important to educate patients regarding the difference between angioedema and the symptoms of anaphylaxis. In the absence of the patient's history on presentation, ER physicians may assume that angioedema is anaphylaxis and the treatment they administer may not be appropriate.

Patients with chronic inducible urticaria (CIndU)

Patients with CIndU develop hives in response to a specific physical trigger. CIndU is the most frequent comorbidity in CSU. Studies suggest that in patients with CU, 66–93% have CSU, and 1–33% a physical urticaria or cholinergic urticaria.^{26–31} A limitation of previous studies is that no

Table 1 Reduction in angioedema following omalizumab in the GLACIAL clinical trial²⁴

	Angioedema-free, %		Mean Angioedema days/week, <i>n</i>	
	Omalizumab 300 mg	Placebo	Omalizumab 300 mg	Placebo
Baseline	–	–	3.7	3.3
Week 2	57.5	31.6	–	–
Week 12	70.5	55.2	1.0	1.2
Week 24	77.4	56.0	0.7	1.5
Week 28	–	–	–	–

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Table 2 Response to omalizumab in case studies of patients with CSU or CIndU³⁵

Type of urticaria	Number of cases*	Complete response	Significant improvement	No significant improvement
CSU	30	25 (83%)	3 (10%)	2 (7%)
CIndU	34	24 (71%)	4 (12%)	6 (17%)
Cholinergic urticaria	8	5 (62%)	1	2
Delayed pressure urticaria	8	7 (88%)	1	–
Symptomatic dermographism	7	6 (86%)	1	–
Cold urticaria	6	3 (50%)	–	3
Solar urticaria	4	3 (75%)	1	–
Heat urticaria	1	– (0%)	–	1
Total	64	49 (76%)	7 (11%)	8 (13%)

*51 patients, 11 of whom presented with two and 1 with three types of urticaria.

In CSU, 'complete response' to omalizumab was defined as a reduction of $\geq 90\%$ in UAS7, 'significant improvement' as a 30–90% reduction in UAS7 and 'no significant improvement' as $< 30\%$ reduction in UAS7.

In CIndU, 'complete response' was defined as an absence of wheals after respective provocation testing or absence of symptoms as assessed by patient global assessment, 'significant improvement' as a $\geq 50\%$ reduction in provocation thresholds or $> 50\%$ improvement of symptoms and 'no significant improvement' as a $< 50\%$ reduction in provocation thresholds or improvement of symptoms. CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; UAS7, 7-day Urticaria Activity Score.

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information is given regarding the evaluation of combinations of CSU and CIndUs.³² The aim of treatment is to achieve complete symptom relief² and the international guideline-recommended treatment algorithm for CIndU is the same as that for CSU (Fig. 1). Second generation H₁-antihistamines reduce the symptoms in some, but not all patients with CIndU, and updos-ing second line can lead to further improvements^{33,34} but not always complete symptom relief. No formal clinical trials using omalizumab third line in CIndU have been undertaken; data for omalizumab in patients with CIndU are currently derived from case reports, and these suggest significant improvements with omalizumab can be achieved in CIndU with similar results to CSU (Table 2).³⁵ Omalizumab is not currently indicated for the treatment of CIndUs.^{3,4} If symptoms of CIndU return following the termination of omalizumab, a second response can be safely achieved with re-introduction of omalizumab.³⁶

Several studies in patients with CIndU are expected to report results soon: CUTEX (NCT01580592) is a multicenter, double-blind, placebo-controlled parallel-group study of omalizumab in patients with antihistamine-resistant, cold contact urticaria; UFO (NCT02169115) is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study to demonstrate efficacy and safety of omalizumab in patients with symptomatic dermographism refractory to standard treatment; XOLUS (NCT02262130) is a study of omalizumab in severe and refractory solar urticaria.³⁷ In addition, a number of other studies in CIndU are ongoing: CUN-OMAL-UCOL (NCT02012387), a study of omalizumab in cholinergic urticaria; PAFCUTIII (NCT01605487), a study of rupatadine in cold urticaria; and NCT02171416, a study of rilanocept in cold urticaria.

Case study of a patient with solar urticaria

This case describes a 52-year-old female with severe solar urticaria who experienced hives and pruritus induced by sun- and interior-light, and had a strong positive result in the UVA provocation test.³⁸ H₁-antihistamines at up to 8× the standard dose, histaglobin injections, various diets, *Helicobacter pylori* eradication therapy, and a UVA rush hardening regimen did not significantly reduce her symptoms. The patient then received omalizumab at 150 mg every 4 weeks (off-label). Within 4 weeks following the first injection, the patient reported a dramatic improvement in light-induced symptoms, and the standardized light-provocation test with UVA and UVB was completely negative (Fig. 4).³⁸

Diseases and syndromes that look like urticaria

Certain diseases and syndromes are related to urticaria (i) because they present with hives, angioedema, or both and/or (ii) because of historical reasons, but they are not classified as such. These differential diagnoses include autoinflammatory diseases (AInfDs), urticarial vasculitis and hereditary/acquired or ACE inhibitor-induced angioedema (Fig. 5).²

Hereditary AInfDs include cryopyrin-associated periodic syndromes (CAPS), which can manifest as an urticarial rash, recurrent fever attacks, arthralgia or arthritis, eye inflammation, fatigue and headaches. CAPS include familial cold autoinflammatory syndromes (FCAS), Muckle-Wells syndrome (MWS) and neonatal onset multisystem inflammatory disease (NOMID). Other more rarely seen hereditary AInfDs include hyper-IgD syndrome (HIDS) and tumor necrosis factor alpha receptor-associated periodic syndrome (TRAPS).





Figure 4 Solar urticaria before and after treatment with omalizumab (off-label).³⁸

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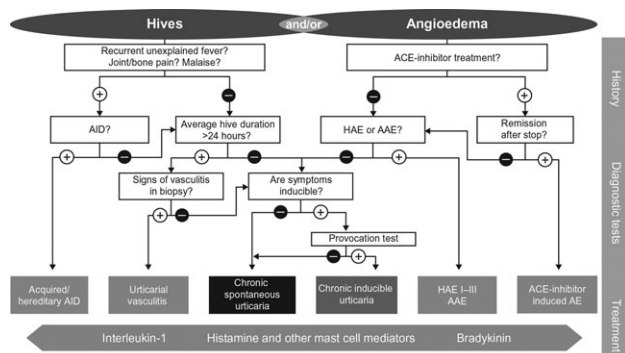


Figure 5 EAACI/GA²LEN/EDF/WAO 2013 guideline-recommended diagnosis algorithm for urticaria.²ACE, angiotensin-converting enzyme; AAE, acquired angioedema due to C1 inhibitor deficiency; AE, angioedema; AID, autoimmune disease; EAACI, European Academy for Allergy and Clinical Immunology; EDF, European Dermatology Forum; GA²LEN, Global Allergy and Asthma European Network; HAE, hereditary angioedema; WAO, World Allergy Organization.

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Acquired AInFDs include Schnitzler's syndrome, which can manifest as a recurrent urticarial rash and monoclonal gammopathy, recurrent fever attacks, bone and muscle pain,

arthralgia or arthritis and lymphadenopathy (Fig. 6). Other AInFDs include systemic-onset juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD).

The following case studies illustrate the presentation of some of these disorders in more detail. Cases have been provided by Global Urticaria Forum faculty or are referenced as published studies.

Case 1: Muckle Wells Syndrome (rare autosomal dominant syndrome associated with overproduction of interleukin [IL]-1 β)

A 45-year-old female presented with lifelong symptoms including cold intolerance, urticaria, periodic fever, conjunctivitis, hearing loss, and bone/joint pain. Half of her family tree was similarly affected. Her laboratory results showed high CRP and serum amyloid A (SAA) levels, and she was positive for genetic markers. She began treatment with canakinumab (anti-IL-1 β) and achieved a complete remission.

Case 2: Familial cold autoinflammatory syndrome (FCAS)

A 62-year-old female had lifelong symptoms including chills, cold-induced painful rashes, bone/joint pain, fever, fatigue and conjunctivitis. Half of her family tree was similarly affected. Laboratory results showed increased SAA and genetic mutation in the NLRP₃ gene. She began treatment with riloncept 9 years ago, which initially led to significant improvement in symptoms, but these have been less controlled over the past 12 months. Her treatment was changed to canakinumab, which appears to be effective to-date.

Case 3: Schnitzler's syndrome (rare condition with sporadic inheritance, associated with elevated IL-1 β) (Fig. 6)

A 71-year-old female presented with a 5-year history of chronic painful urticarial rash, fatigue, malaise, weight loss and bone pain, which were initially treated with prednisone with variable outcomes. She was resistant to H₁-antihistamines, and did not respond after 5 doses of omalizumab 150 mg. She had monoclonal gammopathy of unknown significance (MGUS; IgG κ), elevated SAA [34 410 ng/mL (1000–5000)] and a genetic marker, not expected to be associated with pathology (c.2177T>C (p.Val726Ala) in the MEFV gene). She was diagnosed with Schnitzler's syndrome and was treated with a course of anakinra without improvement.

Case 4: Urticarial vasculitis

A 40-year-old male presented with persistent urticaria for 8 years (Fig. 7). He had a history of spontaneous welts for 1 year, which were also induced by the heat/sun. He had failed to respond to many treatments, including H₁-antihistamines and multiple courses of corticosteroids. He was screened for a possible underlying autoinflammatory disorder. Autoinflammatory markers

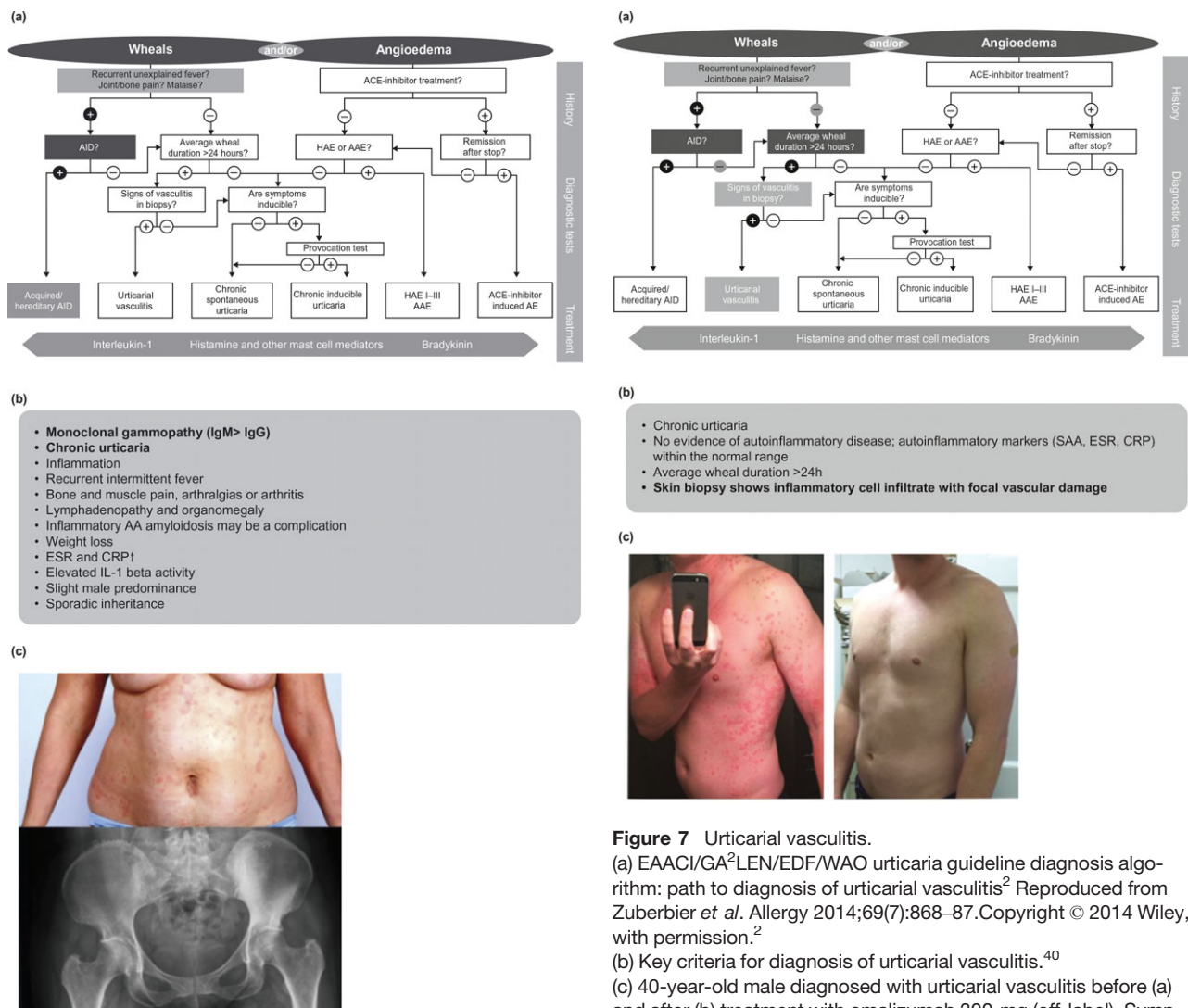


Figure 6 Schnitzler's syndrome, an acquired autoinflammatory disease (AInFD).

(a) EAACI/GA²LEN/EDF/WAO urticaria guideline diagnosis algorithm: path to diagnosis of acquired/hereditary AInFD.² Reproduced from Zuberbier *et al.* Allergy 2014;69(7):868–87. Copyright © 2014 Wiley, with permission²

(b) Key criteria for diagnosis of Schnitzler's syndrome³⁹

(c) Urticaria and sclerosis of the left ilium in a patient with Schnitzler's syndrome.

© 2016 American College of Rheumatology. Used with permission. AA, amyloid A; AAE, acquired angioedema due to C1 inhibitor deficiency; ACE, angiotensin-converting enzyme; AE, angioedema; AID, autoinflammatory disease; CRP, C-reactive protein; EAACI, European Academy for Allergy and Clinical Immunology; EDF, European Dermatology Forum; ESR, erythrocyte sedimentation rate; GA²LEN, Global Allergy and Asthma European Network; HAE, hereditary angioedema; Ig, immunoglobulin; IL, interleukin; WAO, World Allergy Organization.

Figure 7 Urticarial vasculitis.

(a) EAACI/GA²LEN/EDF/WAO urticaria guideline diagnosis algorithm: path to diagnosis of urticarial vasculitis.² Reproduced from Zuberbier *et al.* Allergy 2014;69(7):868–87. Copyright © 2014 Wiley, with permission.²

(b) Key criteria for diagnosis of urticarial vasculitis.⁴⁰

(c) 40-year-old male diagnosed with urticarial vasculitis before (a) and after (b) treatment with omalizumab 300 mg (off-label). Symptoms disappeared within 24 hours, and treatment response continued for a further 3 months to-date. Photograph courtesy of Professor Gordon Sussman. Patient consent received.

AAE, acquired angioedema due to C1 inhibitor deficiency; ACE, angiotensin-converting enzyme; AE, angioedema; AID, autoinflammatory disease; CRP, C-reactive protein; EAACI, European Academy for Allergy and Clinical Immunology; EDF, European Dermatology Forum; ESR, erythrocyte sedimentation rate; GA²LEN, Global Allergy and Asthma European Network; HAE, hereditary angioedema; SAA, serum amyloid A; WAO, World Allergy Organization.

were normal [SAA: 543 ng/mL (1000–5000), CRP < 1.0 mg/L (0.0–8.0)]. A skin biopsy was carried out and showed inflammatory cell infiltrate with focal vascular damage consistent with a diagnosis of urticarial vasculitis. He was treated with omalizumab 300 mg (off-label), resulting in a complete disappearance of

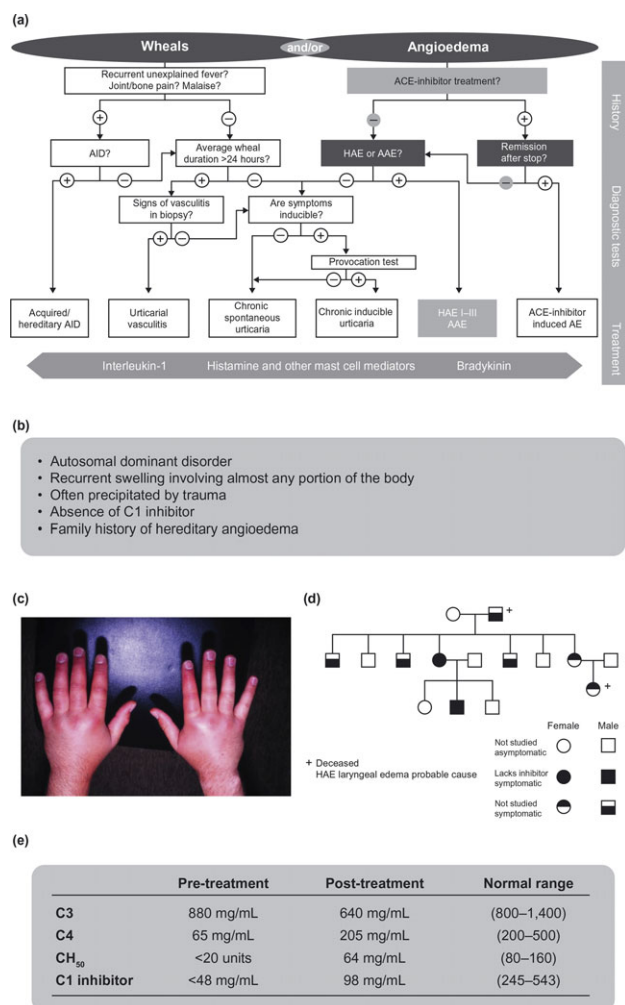


Figure 8 Hereditary angioedema.

(a) EAACI/GA²LEN/EDF/WAO urticaria guideline diagnosis algorithm: path to diagnosis of hereditary angioedema.² Reproduced from Zuberbier *et al.* Allergy 2014;69(7):868–87. Copyright © 2014 Wiley, with permission.²

(a) Key criteria for diagnosis of hereditary angioedema.⁴¹

(c–e) 25-year-old male diagnosed with hereditary angioedema: (c) Recurrent painless, non-pruritic, non-pitting oedema of the hands (photograph courtesy of Professor Gordon Sussman. Patient consent received). (d) Family history: half of his family tree was similarly affected (courtesy of Professor Gordon Sussman. Patient consent received). (e) Laboratory test results: low level of C4 complement and C1 esterase before and after treatment with adrenaline, H₁-antihistamines and corticosteroids (courtesy of Professor Gordon Sussman).

AAE, acquired angioedema due to C1 inhibitor deficiency; ACE, angiotensin-converting enzyme; AE, angioedema; AID, auto-inflammatory disease; EAACI, European Academy for Allergy and Clinical Immunology; EDF, European Dermatology Forum; GA²LEN, Global Allergy and Asthma European Network; HAE, hereditary angioedema; WAO, World Allergy Organization.

urticaria within 24 h, and treatment response continued for a further 3 months to-date.

Case 5: Hereditary angioedema

A 25-year-old male had recurrent painless, non-pruritic, non-pitting edema mainly of the hands and feet since age 12 (Fig. 8). Episodes occurred without warning and subsided within 2–3 days, with a frequency that had increased to weekly. The patient was admitted to the ER with severe swelling of the mouth with laryngeal involvement, hoarseness, dysphagia and pooling of secretions. Following otorhinolaryngology consultation he received adrenaline, H₁-antihistamines and corticosteroids and his angioedema subsided within 72 h. He did not have urticaria, and had no history of pain or swelling following dental work. Half of his family tree was similarly affected. He had a low level of C4 complement and C1 esterase before and after treatment. He was diagnosed with hereditary angioedema. Hereditary angioedema is an autosomal dominant disorder that can manifest as recurrent swelling involving almost any portion of the body. It is often precipitated by trauma and can be characterized by the absence of C1 inhibitor.

Summary

With additional experience and advancements, international guidelines for the treatment of urticaria require periodic discussion and updates. The current EAACI/GA²LEN/EDF/WAO urticaria guideline treatment algorithm is based on the strength of evidence for treatments as was available in 2012–2013. As each patient case is different, experience has shown that a personalized approach based on the expert knowledge of the physician is required in addition to direction provided by the treatment guidelines. Importantly, physicians need to be aware of potential differential diagnoses and factors to consider when evaluating the needs of some special populations, or in certain special situations, to enable them to make informed assessments and treatment decisions. In addition to large randomized trials, data from smaller real-life studies and case series should improve the management of this disease and lead to better prospects for all who suffer with chronic urticaria.

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