

Diagnosis and treatment of chronic inducible urticaria

Chronic inducible urticaria (CIndU) is a group of chronic urticarias (all forms of urticaria with a duration of 6 weeks or longer). CIndU is characterized by (a) recurrent wheals, angioedema, or both, which (b) only occur after exposure to definite external triggers, but not spontaneously.^{1,2} The triggers that lead to the urticarial signs and symptoms in CIndU patients are mainly physical or chemical stimuli. The former include pressure (in delayed pressure urticaria [DPU]), radiation (in solar urticaria), friction (in symptomatic dermographism [SD]), temperature (in cold and heat urticaria), and vibration (in vibratory angioedema). Chemical triggers of CIndU reactions are water (in aquagenic urticaria), sweat (in cholinergic urticaria [CholU]), and other urticariogenic chemical compounds (in contact urticaria). CIndUs are common, with about 0.5% of the population affected, and many patients are severely disabled, mainly due to the impact of trigger avoidance. In most types of CIndUs, there is a correlation of the strength of the trigger and the severity of symptoms. Systemic symptoms of mast cell activation may occur. Up to 70% of patients with ColdU or CholU experience systemic reactions including anaphylaxis in severe cases.

CIndU patients often have comorbid chronic spontaneous urticaria (CSU) and vice versa. In contrast to CIndUs, the wheals and angioedema in CSU develop spontaneously, that is, without being induced by a definite trigger. CSU, in some patients, is aggravated by various triggers, stress, for example, or the intake of certain foods or medication, but the effects of these CSU triggers are sporadic. In other words, CIndU patients only develop urticarial signs and symptoms when exposed to the relevant trigger, and they do so every time this happens. CSU patients, in contrast, also develop signs and symptoms in the absence of any triggers, and the presence of triggers does not necessarily make their urticaria worse. Similar to CSU, CIndUs go into spontaneous remission in most patients. The duration of CIndUs is often longer than that of CSU. The duration of individual wheals in most CIndUs, however, is often shorter than in CSU, lasting minutes to a few hours on average.

CIndUs are diagnosed based on the patients' history, and the diagnosis is confirmed by provocation testing (Figure 1). Most but not all CIndU patients present with a clear history of trigger-induced wheals. Patients with CSU may not realize that they also have a CIndU. Therefore, all patients with CSU, in addition to all patients suspected to have a CIndU, should be asked, "Can you make your wheals come?", and, if yes, "How can you bring out your wheals?". Suspected triggers should then be tested for their relevance using established protocols (standardized provocation sites, reading times, criteria for positive reactions, and appropriate instruments and documentation).¹ Negative provocation tests in patients with a clear history of whealing induced by physical or chemical triggers should prompt suspicion of atypical

CIndU and be followed up by (a) further exploration, with the patient, of previous urticarial responses to triggers in real life, and photodocumentation of future ones by the patient, reassessment for the use of any medication that may have suppressed outcomes as well as (b) additional provocation testing that closely resembles real-life triggering situations (eg, provocation at sites which have been usually affected, increased trigger strength and/or prolonged duration of trigger application, use of a combination of triggers). Antihistamines and glucocorticosteroids should be stopped at least 3 and 7 days before provocation testing, respectively, and testing should not be done at skin sites affected by urticaria in the last 24 hours.

As of yet, CIndUs cannot be cured, as their cause is unknown, but they can be managed very well. The management of CIndU should prevent the occurrence of signs and symptoms and control the disease, completely, for as long as it takes for spontaneous remission to occur. This is achieved by measuring and monitoring trigger thresholds and patient-reported outcomes, the use of the mitigation of triggers, and medication (Figure 2).

In all CIndU patients, disease activity, impact (quality-of-life impairment), and control should be assessed, at the first and at all subsequent visits. Disease activity, in CIndU patients, is assessed by trigger threshold testing and the use of activity scores where available. The results of trigger threshold testing are useful for counseling patients on how to avoid triggering situations. When performed before and during therapy, they also serve for monitoring treatment responses, and can help to optimize treatment. Activity scores for CIndUs such as the CholUAS7 for CholU are based on the daily documentation of symptom scores and trigger exposure.³ Tools for measuring disease-specific quality-of-life impairment are available for some but not all CIndUs, for example, the CholU-QoL for CholU.³ Disease control, in all CIndUs, is assessed by use of the UCT.⁴

All CIndU patients should be educated on the importance of avoiding relevant triggers, that is, that modifying or stopping the exposure to eliciting triggers can help. They should also be provided with strategies to do so. For example, patients with DPU should know that soft and loose fitting shoes can minimize the risk of swelling of the feet as compared to tight fitting ones.

The treatment of CIndU is prophylaxis that prevents the effects of the mast cell-mediator histamine (by H1 antihistamines)⁵ or the activation of mast cells, if antihistamines are not effective (eg, by omalizumab).^{6,7} Prophylactic strategies for CIndUs are similar to the ones for CSU, with the difference that patients with some CIndUs such as ColdU, heat urticaria, and solar urticaria can benefit from desensitization to triggers.

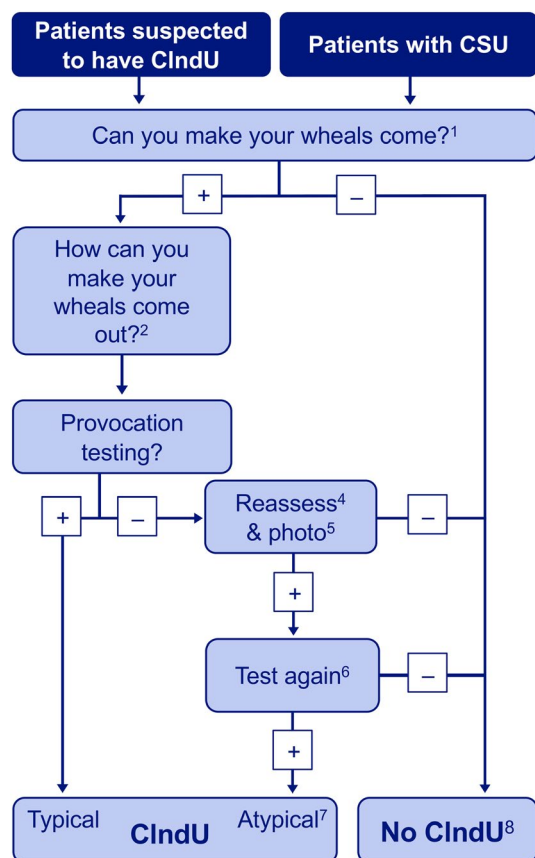


FIGURE 1 How to diagnose chronic inducible urticarias. The diagnosis of CIndU is built on the patient history and provocation testing. Abbreviations: CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria. ¹Patients should be asked whether there is anything they can do to make wheals appear, such as scratching the skin (symptomatic dermographism) or physical exercise (cholinergic urticaria); ²All triggers that are suspected to induce whealing should be assessed for their relevance by provocation testing; ³Provocation testing is done to confirm that suspected triggers induce whealing. Established protocols and appropriate instruments should be used¹; ⁴When provocation tests are negative, patients should be asked to describe, in detail, previous triggering situations that resulted in whealing; ⁵Patients should be asked to take pictures of wheals induced by triggers in real life; ⁶If, despite negative provocation testing, the history strongly suggests trigger-induced whealing, provocation testing should be repeated and modified in accordance with the information obtained from patients, for example, by changing the test site or the trigger strength or duration of exposure or by testing multiple triggers simultaneously; ⁷Atypical cases of CIndU are characterized by negative results in standard provocation tests and positive results in modified provocation testing. Examples of atypical CIndUs include cold-induced cholinergic urticaria, where exercise in cold environments leads to generalized urticaria, and localized cold urticaria, in which only certain areas of the body urticate with cold contact⁴; ⁸Differential diagnoses of CIndUs include CSU, autoinflammatory disorders (vs cold urticaria), exercise-induced anaphylaxis (vs cholinergic urticaria), diseases characterized by trigger-induced itching without whealing, for example, aquagenic pruritus (vs aquagenic urticaria), and diseases with trigger-induced skin inflammatory reactions that are not urticarial, for example, polymorphous light eruption (vs solar urticaria)

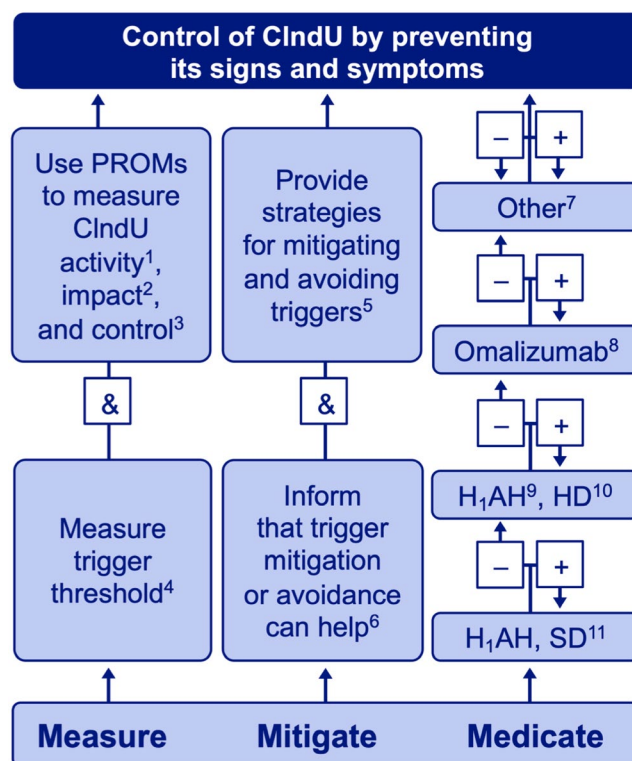


FIGURE 2 The three Ms of managing chronic inducible urticaria (CIndU): Measure, Mitigate, and Medicate. The goal of managing CIndU is to achieve control of the disease by preventing its signs and symptoms until spontaneous remission occurs. This is done by measuring and monitoring disease activity, impact, and control, by mitigating the effects of triggers, and by the prophylactic use of medication. Abbreviations: PROMs, patient-reported outcome measures, H₁AH, H₁ antihistamine; SD, standard dose; HD, high dose. ¹Disease activity should be assessed by the use of standardized tools where available, for example, the ChIUAS7 in cholinergic urticaria³; ²Disease impact should be measured by instruments that assess disease-specific quality-of-life impairment such as the ChIU-QoL for cholinergic urticaria³; ³Disease control, in all CIndUs, should be assessed with the urticaria control test¹; ⁴Trigger thresholds should be assessed using recommended protocols and instruments¹; ⁵Patients should be provided with examples of how they can modify or avoid exposure to relevant triggers²; ⁶Patients should know that trigger mitigation and avoidance can help. On the other hand, quality of life should not be impaired by this; ⁷Treatments other than omalizumab and antihistamines can be effective in some or all CIndUs.^{1,4,5} These include trigger desensitization therapy; ⁸Omalizumab can be of benefit in all CIndUs⁶ and has been shown, in randomized controlled trials, to be effective in cold urticaria and symptomatic dermographism.⁷ As of now, omalizumab is licensed for the treatment of patients with CSU, but not CIndU. ⁹Modern non-sedating antihistamines should be preferred over older sedating ones; ¹⁰Higher than standard doses (up to fourfold the standard dose) have been shown to be more effective than standard doses of antihistamines in the management of CIndU⁵; ¹¹Antihistamines, in the management of CIndU, should be used daily²

The current EAACI/GA²LEN/WAO/EDF guideline for urticaria as well as recent systematic reviews and consensus documents provides detailed recommendations and guidance on the diagnosis

and management of CIndUs.^{1,2,4-6,8} The management of challenging cases may benefit from cooperating with an Urticaria Center of Reference and Excellence, UCARE (www.ga2len-ucare.com).⁹ The UCARE network also offers patients with CIndU to participate in clinical trials and research projects aimed at identifying the underlying causes of CIndUs and the development of novel and better treatment options.

ACKNOWLEDGMENTS

We gratefully acknowledge the support of the urtikaria network e.V. (UNEV, www.urtikaria.net) and of the GA²LEN UCARE network (www.ga2len-ucare.com).⁹ We also thank all of the members of the Charité UCARE.

CONFLICTS OF INTEREST

Dr Weller reports personal fees from Dr R. Pflieger, personal fees from UCB, personal fees from Uriach, personal fees from Moxie, personal fees from Novartis, outside the submitted work. Prof. Magerl reports personal fees from Moxie and personal fees from Novartis, outside the submitted work. Prof. Maurer reports grants and personal fees from Allakos, personal fees from Aralez, personal fees from Alnylam, grants from AstraZeneca, grants and personal fees from BioCryst, grants from Blueprint, personal fees from CSL Behring, grants and personal fees from FAES, grants and personal fees from Genentech, personal fees from Kalvista, grants and personal fees from Menarini, grants from Leo Pharma, grants and personal fees from Moxie, grants and personal fees from MSD, grants from Pharming, personal fees from Pharvaris, grants and personal fees from Roche, grants and personal fees from Sanofi, grants and personal fees from Shire/Takeda, grants and personal fees from UCB, grants and personal fees from Uriach, outside the submitted work. Dr Metz reports personal fees from Moxie, personal fees from Novartis, personal fees from Sanofi, outside the submitted work. Dr Siebenhaar reports personal fees from Novartis, personal fees from Allakos, nonfinancial support from Moxie GmbH, during the conduct of the study. Dr Terhorst-Molawi has nothing to disclose. Dr Hawro has nothing to disclose. Dr Krause reports personal fees from Novartis, personal fees from Moxie, outside the submitted work. Dr Zuberbier reports personal fees from Astra Zeneca, personal fees from AbbVie, personal fees from ALK, personal fees from Almirall, personal fees from Astellas, personal fees from Bayer Health Care, personal fees from Bencard, personal fees from Berlin Chemie, personal fees from FAES, personal fees from HAL, personal fees from Leti, personal fees from MEDA, personal fees from Menarini, personal fees from Merck, personal fees from MSD, grants and personal fees from Novartis, personal fees from Pfizer, personal fees from Sanofi, personal fees from Stallergenes, personal fees from Takeda, personal fees from Teva, personal fees from UCB, grants from Henkel, personal fees from Kryolan, personal fees from L'Oreal, outside the submitted work; and Organizational Affiliations: Committee

member, WHO-Initiative "Allergic Rhinitis and its Impact on Asthma" (ARIA) Member of the Board, German Society for Allergy and Clinical Immunology (DGAKI) Head, European Centre for Allergy Research Foundation (ECARF) Secretary General, Global Allergy and Asthma European Network (GA²LEN) Member, Committee on Allergy Diagnosis and Molecular Allergology, World Allergy Organization (WAO). Dr Altrichter reports personal fees from Moxie GmbH, other from Allakos, Inc, outside the submitted work.

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REFERENCES

1. Magerl M, Altrichter S, Borzova E, et al. The definition, diagnostic testing, and management of chronic inducible urticarias - The EAACI/GA² LEN/EDF/UNEV consensus recommendations 2016 update and revision. *Allergy*. 2016;71(6):780-802.
2. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73(7):1393-1414.
3. Ruft J, Asady A, Staubach P, et al. Development and validation of the Cholinergic Urticaria Quality-of-Life Questionnaire (ChIU-QoL). *Clin Exp Allergy*. 2018;48(4):433-444.
4. Maurer M, Fluhr JW, Khan DA. How to Approach Chronic Inducible Urticaria. *J Allergy Clin Immunol Pract*. 2018;6(4):1119-1130.
5. Dressler C, Werner RN, Eisert L, Zuberbier T, Nast A, Maurer M. Chronic inducible urticaria: A systematic review of treatment options. *J Allergy Clin Immunol*. 2018;141(5):1726-1734.

6. Maurer M, Metz M, Brehler R, et al. Omalizumab treatment in patients with chronic inducible urticaria: A systematic review of published evidence. *J Allergy Clin Immunol*. 2018;141(2):638-649.
7. Metz M, Schütz A, Weller K, et al. Omalizumab is effective in cold urticaria-results of a randomized placebo-controlled trial. *J Allergy Clin Immunol*. 2017;140(3):864-867.
8. Maurer M, Magerl M, Metz M, Siebenhaar F, Weller K, Krause K. Practical algorithm for diagnosing patients with recurrent wheals or angioedema. *Allergy*. 2013;68(6):816-819.
9. Maurer M, Metz M, Bindslev-Jensen C, et al. Definition, aims, and implementation of GA(2) LEN Urticaria Centers of Reference and Excellence. *Allergy*. 2016;71(8):1210-1218.