Title

Chronic Urticaria Guidelines: 2026 AAAAI/ACAAI Joint Task Force (JTF) on Practice Parameters GRADE- and Institute of Medicine-based recommendations

Authors

AAAAI/ACAAI JTF Chronic Urticaria Guideline Panel

Chairs: Derek K. Chu MD PhD[1,2,17]* Jonathan A. Bernstein MD[3]*, Sarbjit S. Saini MD*[4]

Panel Members: Lisa A Beck MD[5], Kathryn E. Wheeler MD[6], David M. Lang MD[7], Rachel Netahe Asiniwasis MD MSc[8], David A. Khan MD[9], Javed Sheikh MD[10], Eric T Oliver MD[4], Paul Tran PharmD[9], Diane R. Baker MD[11], Jeffrey Chan MD[12], Maisie Flindall[13], Moshe Ben-Shoshan MD[14], Zena Jun[13], Sameer K. Mathur MD[15], Lauren Runyon MSN[9], Emily F. Cole MD[16], Susan Waserman MD MSc[17], Jamie Tattrie[13], Kathryn P. Trayes MD[18], Gordon H. Guyatt MD MSc OC[1,2]

Patient Groups: AAFA - Sanaz Eftekhari BA[19], AAN - Donna D. Gardner DrPH[20], Global Allergy & Airways Patient Platform - Tonya Winders MBA[21]

Evidence in Allergy Group: Alexandro W. L. Chu MD[1,2], Paul Oykhman MD MSc[1,2], Yetiani Roldan-Benitez MD MSc[1,2], Xiajing Chu[1,2]

The AAAAI/ACAAI Joint Task Force on Practice Parameters: David B.K. Golden MDCM[22], Marcus Shaker MD MS[23], Jonathan A. Bernstein MD[3], Caroline C. Horner MD MSCI[24], Jay Lieberman MD[25], Matthew A. Rank MD[26], Julie Wang MD[27], Giselle Mosnaim[28], Anne K. Ellis MD MSc[29], Elissa Abrams[30], Dennis Ledford MD[31], Aikaterini Anagnostou[32], Anil Nanda[33], Derek K. Chu MD PhD[1,2,17]

*Guideline Co-Chairs and Co-first authors

Collaborators (including patient and caregiver partners)

World Allergy Organization. Kerri Olson, Irene Storteboom, Ikramul Hasan, Yasith Mathangasinghe, Nohora Torres, Elayne Libman, Jamie Tattrie, Tonya Miller, Zain Douba, Yara Abou Saab, Lenny Vasanthan, Michél Smit, Tammie Largent, Maisie Flindall, Zena Jun, Anne Holbook, Jasvinder Singh, Christopher Hillis. Evidence in Allergy group evidence synthesis team members and additional collaborators appear in acknowledgements.

Affiliations

1. Department of Medicine, and Department of Health Research Methods, Evidence & Impact, McMaster University, Hamilton, ON, Canada
2. Evidence in Allergy Group, McMaster University and The Research Institute of St. Joe's Hamilton, Hamilton, ON, Canada
3. Division of Rheumatology, Allergy and Immunology, Department of Internal Medicine, University of Cincinnati, Cincinnati, Ohio
4. Division of Allergy and Clinical Immunology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland
5. Department of Dermatology, University of Rochester Medical Center, Rochester, New York
6. Department of Pediatrics, University of Florida, Gainesville, Florida
7. Department of Allergy and Clinical Immunology, Cleveland Clinic, Cleveland, Ohio
8. Division of Dermatology, Department of Medicine, University of Saskatchewan, Regina, Saskatchewan, Canada
9. Division of Allergy and Immunology, Department of Internal Medicine, The University of Texas Southwestern Medical Center, Dallas, Texas

10. Department of Clinical Immunology and Allergy, Southern California Permanente Medical Group, Los Angeles, California
11. Department of Dermatology, Oregon Health and Sciences University, Portland, Oregon
12. Emergency Medicine, Southlake Regional Health Centre, Newmarket, Ontario, Canada
13. Patient Partner
14. Division of Allergy, Immunology and Dermatology, Department of Pediatrics, McGill University, Montreal, Quebec, Canada
15. Division of Allergy, Pulmonary and Critical Care, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin
16. Division of Dermatology, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri
17. Division of Clinical Immunology & Allergy, McMaster University, Hamilton, ON, Canada
18. Department of Family and Community Medicine, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania
19. Asthma and Allergy Foundation of America, Arlington, Virginia
20. Allergy and Asthma Network, Fairfax, Virginia
21. Global Allergy and Airways Patient Platform, Vienna, Austria
22. Johns Hopkins University School of Medicine, Baltimore, Md
23. Dartmouth Geisel School of Medicine and Dartmouth Hitchcock Medical Center, Section of Allergy, Lebanon, NH
24. Division of Allergy and Pulmonary Medicine, Department of Pediatrics, Washington University School of Medicine, St Louis, Mo
25. University of Tennessee Health Science Center and LeBonheur Children's Hospital, Memphis, Tenn
26. Mayo Clinic in Arizona and Phoenix Children's Hospital, Scottsdale and Phoenix, Ariz
27. Jaffe Food Allergy Institute, Serena and John Liew Division of Pediatric Allergy and Immunology, Icahn School of Medicine at Mount Sinai, New York, NY
28. Department of Medicine, Endeavor Health, Evanston, IL
29. Division of Allergy and Immunology, Department of Medicine, Queen's University, Kingston, Ontario, Canada
30. Section of Allergy and Clinical Immunology, Department of Pediatrics, University of Manitoba, Winnipeg, Manitoba, Canada.
31. Morsani College of Medicine, University of South Florida and James A. Haley Veterans' Affairs Hospital, Tampa, Fla
32. Division of Allergy and Immunology, Department of Pediatrics, Baylor College of Medicine, Houston, Texas.
33. Asthma and Allergy Center, Flower Mound, Texas, and Division of Allergy and Immunology, University of Texas Southwestern Medical Center, Dallas, Texas

Correspondence: AAAAI/ACAAI Joint Task Force on Allergy-Immunology Practice Parameters, 555 E Wells Street, Suite 1100, Milwaukee, WI 53212. https://www.allergyparameters.org/.

Disclosures

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Executive Summary - American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Chronic Urticaria Guidelines

Aims of These Guidelines and Specific Objectives

The updated 2026 AAAAI/ACAAI Joint Task Force Guidelines for Chronic Urticaria (CU) guidelines provide the latest evidence-based recommendations for the management of CU for adults and children. The guidelines address the following 6 main management questions:

1. Which oral H1 antihistamines should be used, and how should they be used, to achieve optimal CU outcomes?
2. Should oral H2 receptor antagonists be added for CU treatment?
3. Should antileukotrienes receptor antagonists be added for CU treatment?
4. Should topical steroids be used for CU treatment?
5. When should systemic steroids be used for CU flares (episodes of acute exacerbation)?
6. What systemic treatments, including biologics, small molecules, conventional immunomodulatory agents and immunosuppressants, and phototherapy (UV light therapy) be used to achieve optimal CU outcomes?

The target audience includes CU specialists (allergists and dermatologists), primary care providers, and other healthcare professionals and other decision-makers with the aim to optimize clinical care of CU, improve patient outcomes, and support clinical decision-making across diverse healthcare settings. This guideline is replete with tables and figures to help the clinician navigate through different sections of the guidelines. This document represents a living guideline intended to evolve with emerging evidence and therapeutic advances. These guidelines may also serve as the basis for adoption or adaptation by local, regional, or national guideline panels and policymakers.

What Is New and Different

These Joint Task Force on Practice Parameters (JTFPP) guidelines represent an evolution in trustworthy allergy guidelines[1, 2] and are distinguished from other guidelines[3] through systematic reviews of the evidence with multidisciplinary panelist engagement, adherence to rigorous guideline development processes, independent (open access) publication of all linked evidence syntheses[4-9], robust use of Grading of Recommendations Assessment, Development and Evaluation (GRADE) that fulfills requirements to report its proper use[10, 11], the core involvement of the patient and caregiver voice from start to finish, focus on equity, diversity, and inclusiveness (including concepts addressing CU in diverse skin tones [skin of color] and health disparities), clear translation of evidence to clinically actionable and contextual recommendations, and novel approaches to facilitate knowledge translation. The guidelines emphasize, in addition to standards of trustworthiness, the third principle of evidence-based medicine: that evidence alone is never enough; that patient values and preferences must be carefully considered when determining optimal treatments for patients and populations[12, 13]. The eAppendix provides 1-2 page patient-friendly handouts to facilitate education, discussion, and shared decision-making.

The current guidelines also differ from our previous guidelines in a few other ways. The 2026 AAAAI/ACAAI Joint Task Force on Practice Parameters (JTFPP) CU Guideline builds on the foundational 2014 JTFPP practice parameter[14] update to the 2000 guidelines[15], which provided a framework for

evaluating and treating urticaria and angioedema across acute and chronic presentations. The 2014 and 2000 parameters established several enduring principles that remain central to contemporary care, including the importance of distinguishing acute urticaria, CU (CU), anaphylaxis, physical/inducible urticarias, urticarial vasculitis, and angioedema without wheals; using a focused history and physical examination to guide diagnostic testing; avoiding routine extensive allergy or laboratory testing when the presentation is typical; selecting second-generation H1-antihistamines as first-line therapy; and using a step-care treatment approach for patients whose symptoms remain uncontrolled.

The 2026 guideline expands on these core concepts by updating and advancing them in light of new evidence, new therapies, newer approaches to guideline development, and greater emphasis on patient-centered implementation. Whereas the 2014 practice parameter addressed both acute and CU and provided a broad approach for urticaria with or without angioedema, the 2026 guideline focuses in greater depth on CU in children and adults, including chronic spontaneous urticaria (CSU), chronic inducible urticaria (CIndU), angioedema associated with CU, disease monitoring, comorbidities, health disparities, special populations, patient and caregiver experience, and sequencing of conventional and advanced therapies.

Some of the important changes in this updated practice parameter include the following (**Figure 1**):

- Uses contemporary GRADE-based methods for all recommendations and meets Institute of Medicine, and other international standards, for trustworthy guideline development.
- Guides shared decision-making and presents factors to consider for each recommendation.
- Provides a clearer diagnostic framework for distinguishing CU from mimics and complicating conditions.
- Reinforces that routine broad allergy or laboratory testing is usually unnecessary in typical CU.
- Updates terminology to emphasize CSU, CIndU, mixed disease, and mast cell-mediated angioedema.
- Promotes validated patient-reported outcome measures for monitoring activity, control, angioedema, and quality of life.
- Updates pathophysiology with newer evidence on mast cells, basophils, autoimmunity, BTK signaling, cytokine pathways, MRGPRX2, and coagulation pathways.
- Recognizes biomarkers and endotypes as promising but not yet ready for routine definitive treatment selection.
- Refines first-line treatment by recommending second-generation H1 antihistamines (SGAH), especially less-sedating options and recommending against first-generation H1 antihistamines.
- Suggests optimizing the same SGAH up to 4 times the licensed rather than the routine addition of H2 receptor antagonists (H2RAs), antileukotrienes, high-dose vitamin D, phototherapy, or topical corticosteroids.
- Recommends against maintenance systemic corticosteroids and suggests short courses to selected SGAH-refractory acute flares.
- Recommends omalizumab as a preferred first-line advanced therapy for H1-antihistamine-refractory CU.
- Suggests add-on dupilumab and remibrutinib as new first-line advanced treatment options.
- Suggests add-on cyclosporine after first-line advanced therapies.
- Provides clearer sequencing after partial, inadequate, or intolerant response to advanced therapy (e.g. omalizumab updosing, switching or adding among those refractory to first-line advanced treatments).
- Suggestions for refractory CU, including selected use of hydroxychloroquine or mycophenolate.

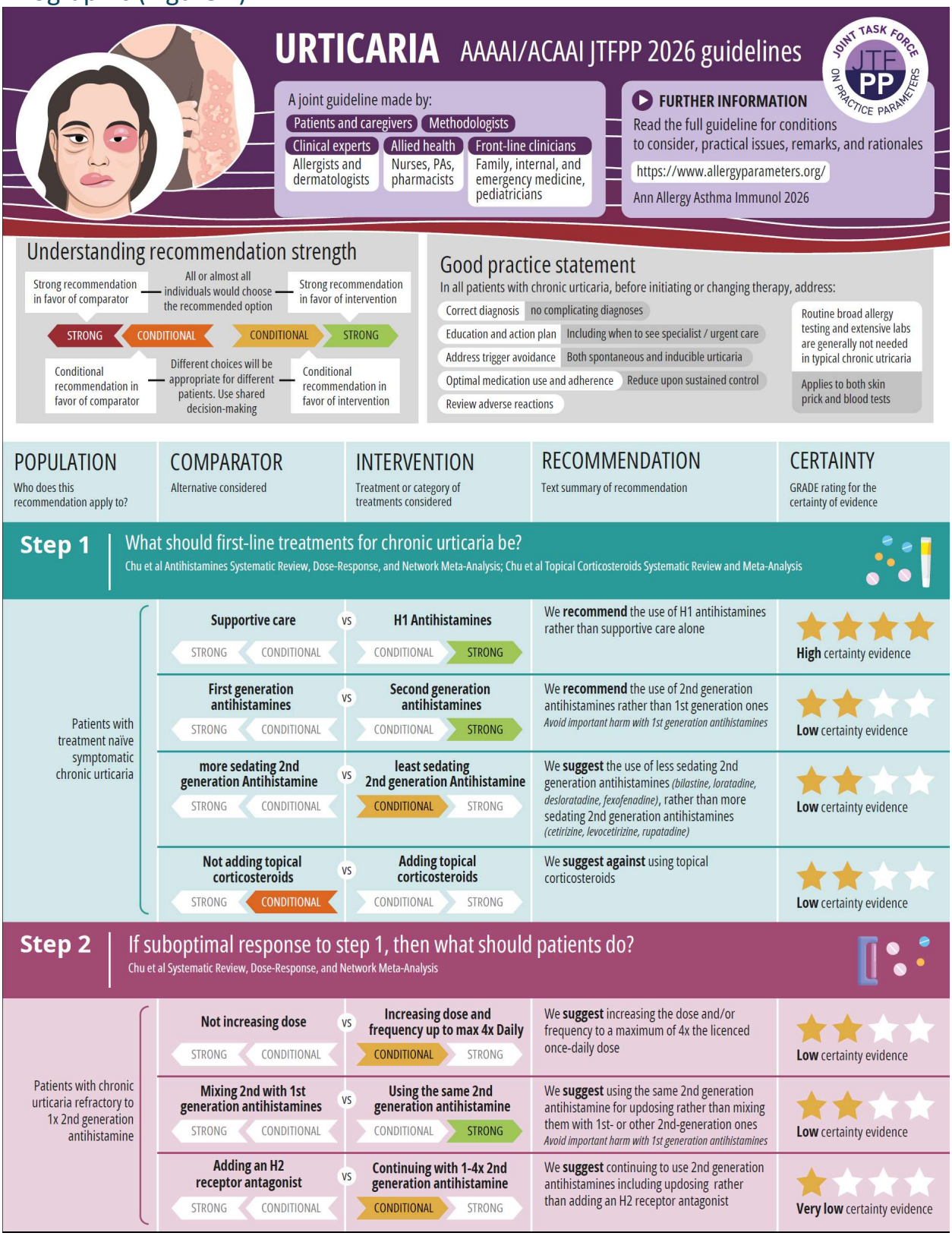
- Suggests against several less favorable immunomodulatory agents (colchicine, dapsone, sulfasalazine, azathioprine, methotrexate) for most patients with refractory CU.
- Expands considerations for children, older adults, pregnancy, conception, and lactation.
- Adds a dedicated focus on health equity, skin of color, treatment access, insurance barriers, and pharmacoequity.
- Emphasizes implementation with action plans, outcome tracking, adherence review, safety monitoring, escalation, and de-escalation to the lowest effective regimen. The eAppendix provides 1-2-page implementation guidance/handouts for each treatment option.
- Makes explicit research recommendations that are critical to transform the field.
- Establishes the guideline as a living document for future evidence updates.

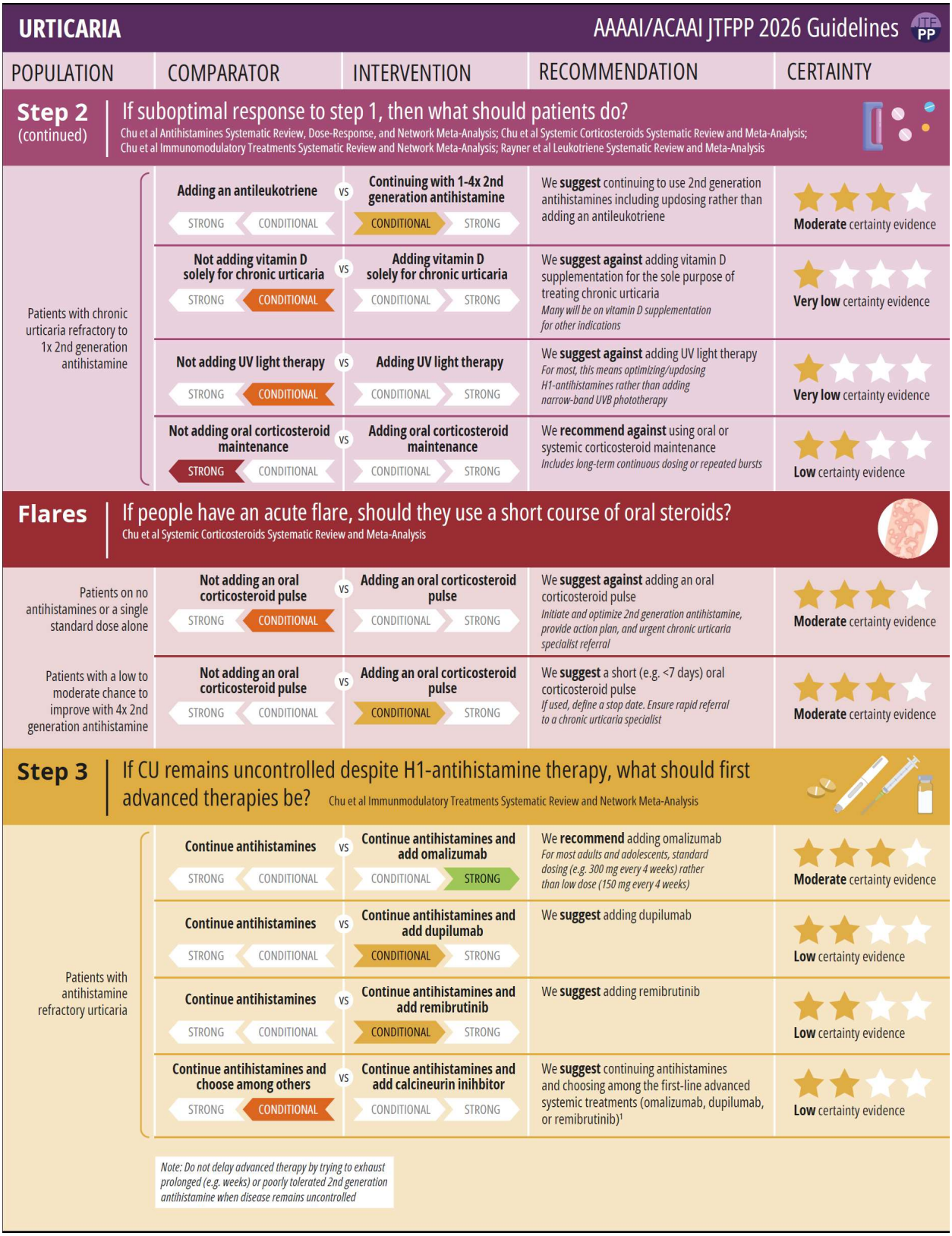
Executive Summary of Recommendations

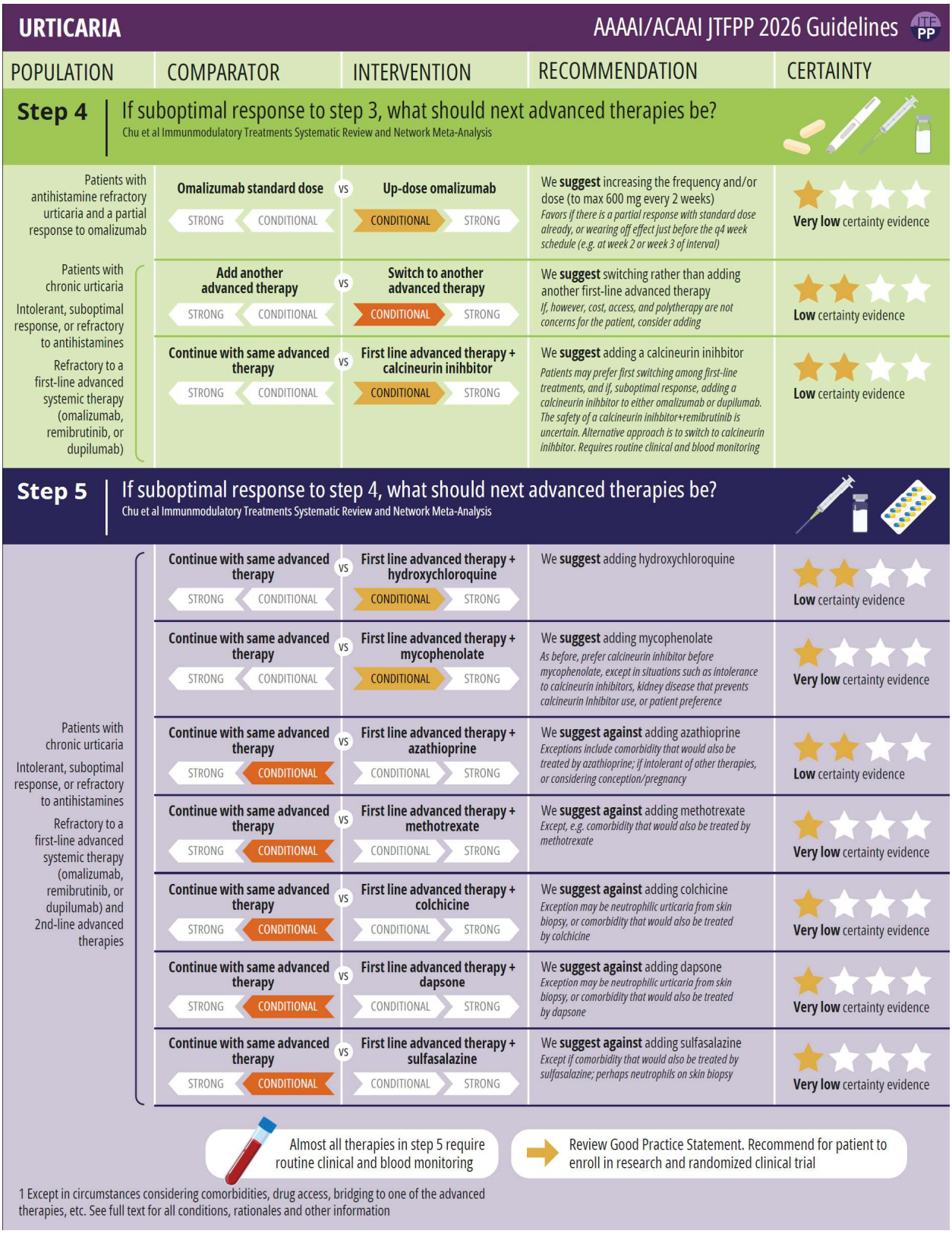
The JTF panel organized treatment around practical clinical states: (1) treatment-naive symptomatic CU; (2) CU that remains uncontrolled with standard-dose SGAHs; (3) CU requiring first-line advanced systemic therapy; (4) CU with inadequate response or intolerance to a first-line advanced systemic therapy; and (5) refractory disease. These steps should be consider as a framework for shared decision-making rather than a rigid mandate to exhaust every option before advancing. In particular, patients who remain uncontrolled after standard-dose, and especially after 2-times dose, SGAHs should be prepared for advanced therapy while clinicians continue to optimize diagnosis, adherence, access, and safety.

The infographic (**Figure 1**) summarizes the recommendations in a format that is easily scalable and shareable, in its unmodified entirety, through social media, flyers, print (eg, 2 pages side by side or a single double-sided page), and as posters (eg, posted in clinician offices). To start, the guidelines provide a Good Practice Statement for care of CU.

Infographic (Figure 1)




URTICARIA
AAAAI/ACAAI JTFPP 2026 Guidelines
POPULATION
COMPARATOR
INTERVENTION
RECOMMENDATION
CERTAINTY
Step 2 (continued)
If suboptimal response to step 1, then what should patients do?
Chu et al Antihistamines Systematic Review, Dose-Response, and Network Meta-Analysis; Chu et al Systemic Corticosteroids Systematic Review and Meta-Analysis; Chu et al Immunomodulatory Treatments Systematic Review and Network Meta-Analysis; Rayner et al Leukotriene Systematic Review and Meta-Analysis
Patients with chronic urticaria refractory to 1x 2nd generation antihistamine
Adding an antileukotriene
STRONG CONDITIONAL
vs
Continuing with 1-4x 2nd generation antihistamine
CONDITIONAL STRONG
We suggest continuing to use 2nd generation antihistamines including updosing rather than adding an antileukotriene
Moderate certainty evidence
Not adding vitamin D solely for chronic urticaria
STRONG CONDITIONAL
vs
Adding vitamin D solely for chronic urticaria
CONDITIONAL STRONG
We suggest against adding vitamin D supplementation for the sole purpose of treating chronic urticaria
Many will be on vitamin D supplementation for other indications
Very low certainty evidence
Not adding UV light therapy
STRONG CONDITIONAL
vs
Adding UV light therapy
CONDITIONAL STRONG
We suggest against adding UV light therapy
For most, this means optimizing/updosing H1-antihistamines rather than adding narrow-band UVB phototherapy
Very low certainty evidence
Not adding oral corticosteroid maintenance
STRONG CONDITIONAL
vs
Adding oral corticosteroid maintenance
CONDITIONAL STRONG
We recommend against using oral or systemic corticosteroid maintenance
Includes long-term continuous dosing or repeated bursts
Low certainty evidence
Flares
If people have an acute flare, should they use a short course of oral steroids?
Chu et al Systemic Corticosteroids Systematic Review and Meta-Analysis
Patients on no antihistamines or a single standard dose alone
Not adding an oral corticosteroid pulse
STRONG CONDITIONAL
vs
Adding an oral corticosteroid pulse
CONDITIONAL STRONG
We suggest against adding an oral corticosteroid pulse
Initiate and optimize 2nd generation antihistamine, provide action plan, and urgent chronic urticaria specialist referral
Moderate certainty evidence
Patients with a low to moderate chance to improve with 4x 2nd generation antihistamine
Not adding an oral corticosteroid pulse
STRONG CONDITIONAL
vs
Adding an oral corticosteroid pulse
CONDITIONAL STRONG
We suggest a short (e.g. <7 days) oral corticosteroid pulse
If used, define a stop date. Ensure rapid referral to a chronic urticaria specialist
Moderate certainty evidence
Step 3
If CU remains uncontrolled despite H1-antihistamine therapy, what should first advanced therapies be?
Chu et al Immunmodulatory Treatments Systematic Review and Network Meta-Analysis
Patients with antihistamine refractory urticaria
Continue antihistamines
STRONG CONDITIONAL
vs
Continue antihistamines and add omalizumab
CONDITIONAL STRONG
We recommend adding omalizumab
For most adults and adolescents, standard dosing (e.g. 300 mg every 4 weeks) rather than low dose (150 mg every 4 weeks)
Moderate certainty evidence
Continue antihistamines
STRONG CONDITIONAL
vs
Continue antihistamines and add dupilumab
CONDITIONAL STRONG
We suggest adding dupilumab
Low certainty evidence
Continue antihistamines
STRONG CONDITIONAL
vs
Continue antihistamines and add remibrutinib
CONDITIONAL STRONG
We suggest adding remibrutinib
Low certainty evidence
Continue antihistamines and choose among others
STRONG CONDITIONAL
vs
Continue antihistamines and add calcineurin inhbitor
CONDITIONAL STRONG
We suggest continuing antihistamines and choosing among the first-line advanced systemic treatments (omalizumab, dupilumab, or remibrutinib)[1]
Low certainty evidence
Note: Do not delay advanced therapy by trying to exhaust prolonged (e.g. weeks) or poorly tolerated 2nd generation antihistamine when disease remains uncontrolled


URTICARIA
AAAAI/ACAAI JTFPP 2026 Guidelines
POPULATION
COMPARATOR
INTERVENTION
RECOMMENDATION
CERTAINTY
Step 4
If suboptimal response to step 3, what should next advanced therapies be?
Chu et al Immunmodulatory Treatments Systematic Review and Network Meta-Analysis
Patients with antihistamine refractory urticaria and a partial response to omalizumab
Omalizumab standard dose
STRONG CONDITIONAL
vs
Up-dose omalizumab
CONDITIONAL STRONG
We suggest increasing the frequency and/or dose (to max 600 mg every 2 weeks)
Favors if there is a partial response with standard dose already, or wearing off effect just before the q4 week schedule (e.g. at week 2 or week 3 of interval)
Very low certainty evidence
Patients with chronic urticaria
Intolerant, suboptimal response, or refractory to antihistamines
Refractory to a first-line advanced systemic therapy (omalizumab, remibrutinib, or dupilumab)
Add another advanced therapy
STRONG CONDITIONAL
vs
Switch to another advanced therapy
CONDITIONAL STRONG
We suggest switching rather than adding another first-line advanced therapy
If, however, cost, access, and polytherapy are not concerns for the patient, consider adding
Low certainty evidence
Continue with same advanced therapy
STRONG CONDITIONAL
vs
First line advanced therapy + calcineurin inihbitor
CONDITIONAL STRONG
We suggest adding a calcineurin inihbitor
Patients may prefer first switching among first-line treatments, and if, suboptimal response, adding a calcineurin inihbitor to either omalizumab or dupilumab. The safety of a calcineurin inihbitor+remibrutinib is uncertain. Alternative approach is to switch to calcineurin inihbitor. Requires routine clinical and blood monitoring
Low certainty evidence
Step 5
If suboptimal response to step 4, what should next advanced therapies be?
Chu et al Immunmodulatory Treatments Systematic Review and Network Meta-Analysis
Patients with chronic urticaria
Intolerant, suboptimal response, or refractory to antihistamines
Refractory to a first-line advanced systemic therapy (omalizumab, remibrutinib, or dupilumab) and 2nd-line advanced therapies
Continue with same advanced therapy
STRONG CONDITIONAL
vs
First line advanced therapy + hydroxychloroquine
CONDITIONAL STRONG
We suggest adding hydroxychloroquine
Low certainty evidence
Continue with same advanced therapy
STRONG CONDITIONAL
vs
First line advanced therapy + mycophenolate
CONDITIONAL STRONG
We suggest adding mycophenolate
As before, prefer calcineurin inhibitor before mycophenolate, except in situations such as intolerance to calcineurin inhibitors, kidney disease that prevents calcineurin Inhibitor use, or patient preference
Very low certainty evidence
Continue with same advanced therapy
STRONG CONDITIONAL
vs
First line advanced therapy + azathioprine
CONDITIONAL STRONG
We suggest against adding azathioprine
Exceptions include comorbidity that would also be treated by azathioprine; if intolerant of other therapies, or considering conception/pregnancy
Low certainty evidence
Continue with same advanced therapy
STRONG CONDITIONAL
vs
First line advanced therapy + methotrexate
CONDITIONAL STRONG
We suggest against adding methotrexate
Except, e.g. comorbidity that would also be treated by methotrexate
Very low certainty evidence
Continue with same advanced therapy
STRONG CONDITIONAL
vs
First line advanced therapy + colchicine
CONDITIONAL STRONG
We suggest against adding colchicine
Exception may be neutrophilic urticaria from skin biopsy, or comorbidity that would also be treated by colchicine
Very low certainty evidence
Continue with same advanced therapy
STRONG CONDITIONAL
vs
First line advanced therapy + dapsone
CONDITIONAL STRONG
We suggest against adding dapsone
Exception may be neutrophilic urticaria from skin biopsy, or comorbidity that would also be treated by dapsone
Very low certainty evidence
Continue with same advanced therapy
STRONG CONDITIONAL
vs
First line advanced therapy + sulfasalazine
CONDITIONAL STRONG
We suggest against adding sulfasalazine
Except if comorbidity that would also be treated by sulfasalazine; perhaps neutrophils on skin biopsy
Very low certainty evidence
Almost all therapies in step 5 require routine clinical and blood monitoring
Review Good Practice Statement. Recommend for patient to enroll in research and randomized clinical trial
1 Except in circumstances considering comorbidities, drug access, bridging to one of the advanced therapies, etc. See full text for all conditions, rationales and other information

Good practice statement: management principles before starting or changing therapy

For all patients with CU, clinicians should first confirm the diagnosis and assess for alternative or complicating diagnoses using a focused history and physical examination. This includes characterizing wheal morphology and duration, itch, angioedema, systemic symptoms, medication exposures, triggers, and features suggesting mimics such as urticarial vasculitis, bradykinin-mediated angioedema, autoinflammatory disease, mast cell disorders, bullous disease, dermatitis, or anaphylaxis. Clinicians should provide structured education and an action plan, including how to monitor control, how to respond to flares, and when to step up therapy. Clinicians should identify and address aggravating factors, review medication adherence, discuss expected adverse effects and safety considerations, and plan de-escalation to the lowest effective regimen once control is sustained. After an otherwise typical history and physical examination, routine broad allergy testing and extensive laboratory testing are generally not needed and should be reserved for situations in which the history suggests a specific alternative diagnosis or clinically relevant trigger.

Treatment-naive symptomatic CU

For patients with newly diagnosed and symptomatic CU, the JTF panel recommends oral H1-antihistamines rather than supportive care alone. The panel further recommends SGAHs rather than first-generation agents because second-generation agents provide effective symptom control with fewer sedating and anticholinergic harms. When choosing among SGAHs, the panel suggests less-sedating options rather than more-sedating options, while recognizing that some patients may reasonably remain on a tolerated agent that is accessible and effective. Selection should consider prior response, sedation, pregnancy and lactation data, age, comorbidities, cost, formulary access, and patient preferences (e.g. occupation, driving, caregiving, or school demands). The panel suggests against using topical corticosteroids as routine add-on or replacement therapy for oral H1-antihistamines in CU because CU lesions are typically migratory and systemic mast-cell mediated. Topical anti-inflammatory therapy may still be appropriate for a coexisting inflammatory dermatosis, such as atopic dermatitis, or a very localized non-sensitive area.

CU uncontrolled with a licensed dose of SGAH

For patients who remain symptomatic on a licensed once-daily SGAH dose, the JTF panel suggests increasing the dose and/or frequency of the same SGAH up to a maximum of 4 times the licensed once-daily dose rather than not updosing. Patients should be counseled that the incremental benefits to urticaria control with higher H1 antihistamine doses may get smaller and smaller, especially beyond 2-times dosing, and that sedation or other adverse effects may increase. For many patients, a double dose twice daily may be easier than four separate daily doses. If updosing is used, the panel suggests using the same SGAH rather than mixing agents, such as combining first- and SGAHs or combining different SGAHs. This approach reduces complexity and avoids unnecessary cumulative adverse effects.

For CU that remains uncontrolled after standard-dose H1-antihistamine therapy, the panel generally favors H1-antihistamine optimization over several commonly used adjuncts. The panel suggests updosing H1-antihistamines rather than adding an H2RA or adding an antileukotriene. The panel also suggests against adding high-dose vitamin D supplementation solely to improve CU in patients who are not already taking vitamin D, while recognizing that vitamin D may still be used for standard non-CU indications. Similarly, the panel suggests updosing H1-antihistamines rather than adding narrow-band ultraviolet light therapy (NB-UVB). These recommendations reflect limited or lower-certainty evidence for the adjunctive strategies and the greater practicality, accessibility, and evidence base for optimized SGAH use.

Systemic corticosteroids and acute flares

The JTF panel recommends against oral or systemic corticosteroids as maintenance therapy for H1-antihistamine-refractory CU. Although systemic corticosteroids may transiently improve urticaria activity, the panel placed high value on avoiding frequent and potentially serious short- and long-term harms, including (cumulative) metabolic, cardiovascular, bone, ocular, infectious, neuropsychiatric, weight-related, and adrenal effects. Repeated short courses should not become a substitute for effective long-term control. Any systemic corticosteroid use should prompt urgent CU specialist evaluation.

For acute flares, systemic corticosteroids should be used selectively. In patients who are not receiving H1-antihistamines or are receiving only a single licensed H1-antihistamine dose, the panel suggests against adding a short corticosteroid course; instead, clinicians should initiate or optimize SGAH therapy and provide a clear action plan and urgent referral to a CU specialist. In patients with an acute flare who have a low to moderate chance of improving with H1-antihistamines alone, such as those already refractory to updosed SGAH, the panel suggests adding a short course of systemic corticosteroids, for example fewer than 7 days, rather than continuing updosed H1-antihistamines alone. Any systemic corticosteroid course should have a defined stop date, and rapid referral to a urticaria specialist for implementation of safer strategies with more effective long-term disease control.

First-line advanced systemic therapy for antihistamine-refractory CU

For patients whose disease remains uncontrolled despite H1-antihistamine therapy, the JTF panel recommends adding omalizumab. The panel also suggests adding dupilumab or remibrutinib for H1-antihistamine-refractory disease. These therapies provide targeted options with different mechanisms and practical considerations. Omalizumab's greater magnitude of benefits and harms in children and adults and in CSU and CIndU, certainty of evidence, biosimilar availability (and lower cost), longstanding track record of use, and practical issues led to it being the only first-line therapy receiving a strong recommendation; many patients with CU that are SGAH-refractory will prefer starting with omalizumab. Choice among the first-line advanced treatments should incorporate expected benefits, speed and durability of response, effects on hives, itch, and angioedema, safety, comorbidities, route and frequency of administration, pregnancy or lactation considerations, monitoring requirements, access, and patient preferences.

The panel suggests adding one of these first-line advanced systemic treatments - omalizumab, dupilumab, or remibrutinib - rather than adding an oral calcineurin inhibitor such as cyclosporine or tacrolimus as the first step for H1-antihistamine-refractory CU. This sequencing reflects the balance of benefits, harms, monitoring burden, and acceptability. Clinicians should not delay effective advanced therapy solely because a patient has not endured prolonged or poorly tolerated high-dose SGAH therapy, particularly when disease remains uncontrolled and patient-important outcomes are substantially affected.

Management after partial, inadequate, or intolerant response to first-line advanced systemic therapy

If a patient has a partial response to omalizumab, the panel suggests increasing the dose and/or frequency rather than continuing standard-dose omalizumab unchanged. This should be individualized and considered with attention to response, safety, access, and cost. If a patient is intolerant, has suboptimal response, or cannot use an H1-antihistamine and a first-line advanced systemic therapy, the panel suggests switching among first-line advanced systemic therapies rather than adding another first-line advanced therapy. Combination of first-line advanced therapies should therefore not be the routine next step.

For patients with suboptimal response or refractory disease after H1-antihistamines and a first-line advanced systemic therapy, the panel suggests adding a calcineurin inhibitor rather than not adding one. In practice this most commonly refers to cyclosporine, although some patients may prefer tacrolimus. Use should be individualized and typically specialist-led, with attention to blood pressure, kidney function, drug interactions, pregnancy considerations, infection risk, and the need for laboratory monitoring. Calcineurin inhibitors may also serve as a longer bridge or later-line control strategy when first-line advanced therapy has not achieved adequate control.

Refractory CU

For patients who remain intolerant, suboptimally responsive, or refractory after H1-antihistamines and first- and second-line advanced systemic therapies, the panel suggests adding hydroxychloroquine (low certainty) or mycophenolate (very low certainty) in selected cases. These conditional recommendations should be individualized and account for delayed onset, monitoring burden, reproductive safety, ocular or laboratory monitoring needs, comorbid conditions, cost, access, and patient preferences.

The panel suggests against adding colchicine, dapsone, sulfasalazine, azathioprine, or methotrexate for most patients with refractory CU. These recommendations reflect uncertain or small benefits, potential adverse effects, monitoring burden, and/or less favorable benefit-harm profiles. Exceptions may arise when a patient has a separate comorbid condition for which one of these drugs is otherwise indicated, but such use should not be interpreted as routine CU management. Patients with such refractory disease, after verification the underlying diagnosis is CU (and other elements of the Good Practice Statement), should be referred for randomized clinical trials.

Implementation and shared decision-making

Across all recommendations, clinicians should discuss the strength of recommendation, certainty of evidence, expected benefits and harms, feasibility, cost, and patient preferences. Strong recommendations indicate that all or almost all well-informed patients would choose the recommended course. Conditional recommendations indicate that most patients would choose the suggested course, but many would not; therefore, shared decision-making is especially important. Patients should be monitored using validated activity, control, angioedema, and quality-of-life measures when feasible, and therapy should be escalated when disease remains uncontrolled and de-escalated to the lowest effective regimen after sustained control. The recommendations are not a substitute for individualized care, and qualifying remarks, values and preferences, and implementation considerations should accompany the recommendations whenever they are quoted, adapted, or translated. The underlying evidence syntheses should be cited.

Table 1 presents an overview of the recommendations.

Table 1. Overview of the 2026 JTF CU recommendations.

Clinical state	Preferred / recommended action	Generally not preferred	Key implementation point
Before therapy change	Confirm diagnosis; assess mimics; educate; written action plan; address aggravating factors; optimize adherence; review safety; plan step-down.	Routine broad allergy/lab testing in typical CU.	Use testing only when history/exam suggests specific trigger or alternative diagnosis.
Treatment-naive symptomatic CU	Oral H1-antihistamine; 2nd-generation over 1st-generation; less-sedating SGAH when feasible.	Routine topical corticosteroids as CU add-on/replacement.	Consider occupation, driving, school/work, pregnancy/lactation, age, comorbidities, cost, access.
Uncontrolled on licensed SGAH	Up-dose same SGAH up to 4x daily dose.	Mixing antihistamines; H2RA; antileukotriene; high-dose	Benefits may diminish beyond 2x; prepare for advanced therapy if uncontrolled.

		vitamin D solely for CU; NB-UVB instead of optimizing SGAH.	
Systemic steroids / flares	No maintenance steroids. Selected short course (<7 days) only for antihistamine-refractory acute flares.	Steroids for patients not yet optimized on SGAH; repeated bursts as de facto long-term care.	Defined stop date; urgent specialist referral and durable long-term plan.
First-line advanced	Omalizumab (strong); dupilumab or remibrutinib (conditional).	Calcineurin inhibitor before first-line advanced systemic therapy.	Use shared decision-making around speed/durability, safety, route, access, monitoring, comorbidities.
After first-line advanced (second-line advanced)	Increase omalizumab dose/frequency for partial response; switch among first-line advanced therapies for intolerance or suboptimal response; consider adding calcineurin inhibitor.	Routine combination of first-line advanced therapies.	Calcineurin inhibitor use is typically specialist-led with monitoring.
Refractory (third-line advanced)	Hydroxychloroquine or mycophenolate in selected patients.	Colchicine, dapsone, sulfasalazine, azathioprine, methotrexate for most patients.	Consider exceptions for separate comorbid indications and specialist-led individualized care.

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Introduction

Aims of the AAAAI/ACAAI Joint Task Force guidelines for Chronic Urticaria (Hives, Itch, and/or Swelling)

The purpose of these guidelines is to provide evidence-based recommendations about optimal management of chronic urticaria (CU) in children and adults. This is a living document, which means it will be updated periodically as new relevant information for the diagnosis and management of CU becomes available.

The target audience includes CU specialists (allergists/immunologists and dermatologists), and physicians in family medicine, pediatricians, internal medicine, and emergency medicine, physician assistants, nurses, pharmacists, patients, and other decision-makers. This document may also serve as the basis for adoption or adaptation by local, regional, national or international guideline panels and policy makers.

Health Problem and Burden of Urticaria

Urticaria is a common inflammatory condition that burdens patients, families and caregivers, health systems, and societies[16]. Urticaria presents with itchy wheals (hives), angioedema (swelling beneath the skin or mucosa), or both hives and angioedema. Hives are classically evanescent (transient, often lasting for hours, and usually resolving within 24 hours) and migratory erythematous papules or plaques with central pallor that usually resolve without post-inflammatory hyperpigmentation (post-inflammatory melanosis propensity varies and is not only determined by self-reported tendency to sunburn or tan after sun exposure, commonly classified as Fitzpatrick skin phototype[17, 18]), but never painful ecchymoses (purpura; bruising). The experience of itch may vary as some patients may describe their symptoms as stinging, burning, or pinching. Partially treated urticaria can present as itchy patches. Angioedema is rapid-onset, resolves within days, and is mast-cell mediated (formerly histaminergic angioedema)[19]. Although itch with minimal hives or swelling can be a presentation of urticaria, chronic isolated itch (pruritus) without a primary lesion rarely represents urticaria or allergy. Based on the duration of symptoms, urticaria is typically classified as acute (up to 6 weeks) or chronic (more than 6 weeks).

Acute urticaria (AU) may be due to allergic or non-allergic causes. Allergic causes include immediate IgE-mediated reactions to food, drugs, venom, or environmental allergens (e.g. contact urticaria to animal dander or saliva, or pollen), typically lasting for only a day, or, delayed urticarial reactions to drugs[20] (e.g. medications, radiocontrast dye), typically occurring over multiple consecutive days such as a week. Non-allergic causes may be infection (including asymptomatic) or vaccination, stress, hormones, non-IgE mast cell degranulators[21] (e.g. non-steroidal anti-inflammatory drugs [NSAID-induced urticaria/angioedema, abbreviated as NIUA], opioids or other mas-related G protein-coupled receptor-X2 [MRGPRX2] agonists). It may be idiopathic when no trigger is identified. The 6-week cutoff separating acute and CU is arbitrary[14, 22, 23] and reflects the decreasing likelihood of identifying a single trigger over time and increasing probability of CU as the underlying cause (most cases resolve within this timeframe). Separate AAAAI/ACAAI Joint Task Force guidelines address conditions that cause AU[20, 24-27] and anaphylaxis[28-30].

With regards to CU, an analysis of US administrative data suggests the overall prevalence of CU to be 0.80% in women and 0.32% in men[31]. It affects more adults than children.

CU primarily refers to two subtypes, chronic spontaneous urticaria (CSU; formerly chronic idiopathic urticaria [CIU]) or chronic inducible urticaria (CIndU). CU needs to be differentiated from other conditions that mimic this disorder (see below for differential diagnoses)[32-35]. While CU is generally thought to be self-limited, with almost all eventually experiencing symptom remission, the duration of CU can vary widely from patient to patient (e.g. often ranging from 1 to 10 years with a mean duration of 5 years)[36]. CSU may have a later average age of onset than CIndU (30 to 50 years vs. 20 to 35 years), and adult females are more likely than males to develop CU; sex-specific differences are less consistent in children[35, 37, 38]. Patients may experience symptom remission[39] and have a recurrence months or years later, with significant variability[36]. For example, a non-systematic review reported the proportion of patients achieving symptom remission within year 1 ranged from 21% to 47% and, at 5 years ranged from 34% and 45%. Cumulative weighted average estimates for the proportion of patients' symptoms remitting at years 1, 5 and 20 were 17%, 45% and 73%, respectively[36]. Routine clinical prediction and classification at the individual-patient level for duration of active urticaria and symptom remission remains uncertain.

Non-classical, but that may be as common as 1 to 2 out of 3 patients in specialized urticaria centers, are manifestations of CU beyond the skin. The CURE global registry (2521 patients) and specialized urticaria care centers (155 patients) reported that patients frequently expressed non-skin symptoms such as joint pain or swelling, gastrointestinal symptoms, flushing, malaise (general recurrent discomfort), or fever[40-42]. Such extracutaneous manifestations can be diagnostically challenging. For example, patients with CU and associated mild abdominal pain should not be confused with anaphylaxis[29, 30]. Further, while patients with arthralgias and myalgias should be investigated, patients rarely have an undiagnosed active inflammatory arthritis or underlying rheumatologic disease[32-35, 43]. Symptomatic dermographism, the most common form of CIndU, may present with severe itch and linear wheals or be co-morbid with CSU[41]. Altogether, clinicians should remain attentive to competing alternative diagnoses[32-35, 43].

Diagnosis of chronic urticaria

Diagnosis requires a detailed history, focusing on characterizing hives (typical vs atypical), itch, and swelling (bradykinin- vs mast cell-mediated) (**Figure 2**), physical exam, and, in atypical presentations suggestive of alternative causes, potentially select diagnostic tests to evaluate differential diagnoses (**Table 2**)[44, 45]. For patients who present with recurrent wheals without angioedema, particularly if the condition has an atypical presentation and/or wheals usually lasting >24 hours, the main conditions among the differential diagnoses include urticarial vasculitis and auto-inflammatory disorders[45]. Other common mimickers of urticarial papules and plaques that are not true hives include: papular urticaria (eg. insect bites), urticarial bullous pemphigoid, Sweet's syndrome, Well's syndrome, erythema multiforme, urticarial vasculitis, and autoinflammatory syndromes.

With regional variation, about 60% of patients with CSU have wheals only, about 35% have wheals and angioedema, and about 5% have angioedema alone (**Appendix**)[35, 41, 46]. About 1 in 3 cases of recurrent isolated angioedema represent chronic mast cell-mediated angioedema[47]. For those who present with recurrent angioedema without wheals, the main conditions among the differential diagnoses include non-mast cell-mediated angioedema which may or may not represent bradykinin-mediated angioedema, such as drug-induced angioedema (e.g. angiotensin-converting enzyme inhibitor [ACE-Inh]-induced), hereditary angioedema (HAE), and acquired angioedema due to C1-inhibitor deficiency[19]. Owing to potentially severe and rapidly progressive generalized cutaneous urticarial eruptions or severe local angioedema (e.g. globus sensation often first articulated as dyspnea, or eyelid swelling), cases of AU or CU may be first diagnosed as anaphylaxis before being revised to urticaria.

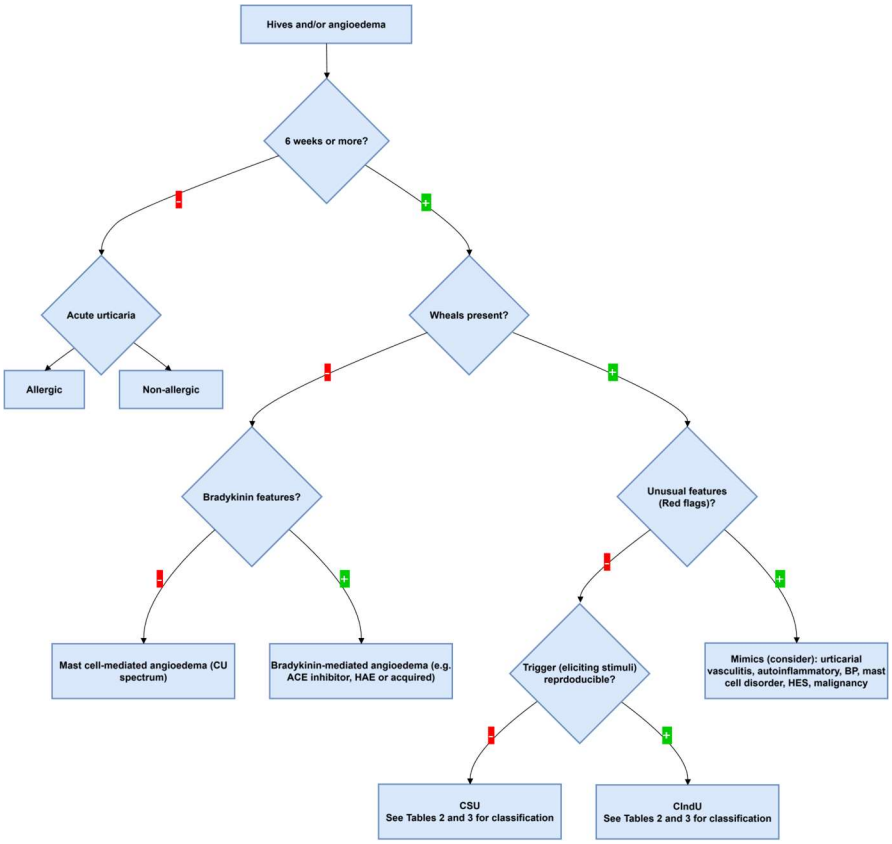


Figure 2. A diagnostic algorithm for CU (for patients presenting with wheals and/or angioedema for >6 weeks)*. With regional variation, about 60% of patients with CSU have wheals only, about 35% have wheals and angioedema, and about 5% have angioedema alone. About 1 in 3 cases of recurrent isolated angioedema represent chronic mast cell-mediated angioedema and some experts prefer to consider this condition a separate entity from CSU. Red negative (-) signs denote "no", and green positive (+) signs denote "yes". Rectangular boxes denote diagnoses. Diamonds denote decision points.

Differential diagnosis

Table 2. Common differential diagnoses for chronic urticaria

Presentation	Ddx	Examples	Clues
Hives + itch, or hive-like lesions	Infestation and infection	Bed bugs or other insect/arthropod bites	Household members affected; Travel; Papular urticaria; Lesion distribution "breakfast lunch dinner"
		Scabies	Polymorphous rash (eg. papules, excoriation, dermatitic lesions, lichenification); Genital involvement
		Helminth infection	Household members affected; Endemic or travel
	Infiltration	Lymphoma (cutaneous [MF, Sézary] or systemic) Schnitzler syndrome Cutaneous hypereosinophilic syndromes (HES) Myeloproliferative neoplasms (MPNs) Mast cell activation syndrome (MCAS) Well's syndrome (eosinophilic cellulitis) Cholestasis	- CU alone is rarely the only or dominant presentation. - Schnitzler syndrome: IgM monoclonal gammopathy, fever, arthralgia, neutrophilic Bx, responsive to IL-1 inhibitors (e.g., anakinra or canakinumab) - MPNs (e.g. polycythemia [rubra] vera, essential thrombocythemia): aquagenic pruritus, erythromelalgia, thrombosis history[48, 49]
	(Skin) Inflammation	Urticarial vasculitis (syndrome[s]) Dermatitis (AD, ACD, ICD, LSC, PN) Mastocytosis (e.g. cutaneous [UP], systemic)	- UV: Lesions>24 hrs, low C3, C4; LCV on Bx, constitutional symptoms. - Dermatitis: xerosis, scale, papules, plaques, excoriations

		Autoinflammatory conditions Bullous disorders (e.g. Urticarial bullous pemphigoid) Inflammatory skin conditions Pruritic urticarial papules and plaques of pregnancy (PUPPP; also called polymorphic eruption of pregnancy)	- Adult-onset Still's disease: e.g. Yamaguchi criteria[50] (leukocytosis, non-itchy rash during fever, arthralgia) - Sweet syndrome (fixed lesions and histology: dense neutrophilic infiltrate without vasculitis; malignancy) - Vacuoles E1 X-linked autoinflammatory somatic syndrome [VEXAS][51]: UBA1 mutation, male over age 50 years with recurrent cutaneous vasculitis, ocular inflammation, chondritis (ears/nose), elevated CRP/ESR, and cytopenias - CAPS: early onset (birth) fever, constitutional symptoms, family history, leukocytosis, elevated ESR, CRP, NLRP3 mutation, and responsive to IL-1 inhibitors - Bullous pemphigoid: older age
	Allergic and pseudoallergic reactions	Exercise-induced anaphylaxis (e.g. versus cholinergic)	Multiorgan involvement. May or may not also be food-dependent.
		NSAID-induced urticaria/angioedema (NIUA) or exacerbated skin disease (NECD; drug reactions)	NSAID exposure. Differentiate from NSAID-exacerbated respiratory disease[43] Drug reactions: urticaria is rarely only manifestation, including for serum sickness and related reactions.
		Alpha-gal syndrome (AGS)	Delayed urticaria, and likely other organ system involvement as an IgE-mediated food allergy.
Angioedema only	Bradykinin mediated angioedema	ACEi-induced, HAE, acquired angioedema due to C1-inhibitor deficiency. DPP4 inhibitors may not increase angioedema risk[52]	ACEi exposure HAE: Family history but may be spontaneous. Erythema marginatum is non-pruritic and not evanescent. AAE: Malignancy or autoimmune disease
		Gleich syndrome (episodic angioedema and eosinophilia)	Rare; Angioedema >3 days, low C3, C4, elevated IgM, eosinophils >2000, splenomegaly, weight gain, rare urticaria.
	Edema rather than angioedema	Hypoalbuminemia, Heart failure, Venous insufficiency, Superior vena cava syndrome, Rhabdomyolysis	Nephrotic syndrome, liver disease, protein-losing enteropathy; cardiac disease; varicosities, hemosiderin deposits; malignancy; recent trauma
(Atypical) cold urticaria	Inherited conditions	CAPS (FCAS, MWS, NOMID) PLAID	Child onset. Family history of immunodeficiency[53]; hives to evaporative cooling; negative to standard cold provocation testing (e.g. TempTest, ice test)
	Secondary acquired diseases	Cryoglobulin, cold agglutinin, or cryofibrinogen	Chronic Hepatitis B or C Lymphoma
Isolated Erythema (flushing)	Flushing syndromes	Drug-induced, Rosacea, Carcinoid, Pheochromocytoma, Hormonal (e.g. perimenopausal), Primary idiopathic flushing, Frey syndrome	Sweating with episodes (wet flushing) or not (dry). Pruritic or not? CU rarely presents with flushing alone.
Itch without a primary lesion	Skin-, metabolic, neurologic, or other systemic conditions	Xerosis, Complications of diabetes (e.g. neuropathic itch), Nerve impingement syndromes (e.g. brachioradial pruritus, notalgia paresthetica), Psychogenic itch, Delusional parasitosis, Other conditions (e.g. renal or liver impairment, cholestasis, or infections such as HIV)	Older adults. CU rarely presents with isolated pruritus alone.

*Partially treated hives can appear as erythema. See section on special populations for considerations in pregnancy. AAE, acquired angioedema; ACD, allergic contact dermatitis; ACEi, angiotensin-converting enzyme inhibitor; AD, atopic dermatitis; AGS, alpha-gal syndrome; BP, bullous pemphigoid; Bx, biopsy; C1-INH, C1 inhibitor; C3, complement component 3; C4, complement component 4; CAPS, cryopyrin-associated periodic syndromes; CRP, C-reactive protein; CU, chronic urticaria; Ddx, differential diagnosis; DPP4, dipeptidyl peptidase-4; ESR, erythrocyte sedimentation rate; FCAS, familial cold autoinflammatory

syndrome; HAE, hereditary angioedema; HBV, hepatitis B virus; HCV, hepatitis C virus; HES, hypereosinophilic syndrome; HIV, human immunodeficiency virus; HUV, hypocomplementemic urticarial vasculitis; HUVS, hypocomplementemic urticarial vasculitis syndrome; ICD, irritant contact dermatitis; IgE, immunoglobulin E; IgM, immunoglobulin M; IL-1, interleukin-1; LCV, leukocytoclastic vasculitis; LSC, lichen simplex chronicus; MCAS, mast cell activation syndrome; MF, mycosis fungoides; MPN, myeloproliferative neoplasm; MWS, Muckle-Wells syndrome; NECD, NSAID-exacerbated cutaneous disease; NIUA, NSAID-induced urticaria/angioedema; NLRP3, NOD-like receptor family pyrin domain containing 3; NOMID, neonatal-onset multisystem inflammatory disease; NSAID, nonsteroidal anti-inflammatory drug; PLAID, PLCG2-associated antibody deficiency and immune dysregulation; PN, prurigo nodularis; PUPPP, pruritic urticarial papules and plaques of pregnancy; UBA1, ubiquitin-like modifier activating enzyme 1; UP, urticaria pigmentosa; UV, urticarial vasculitis; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome.

Other conditions may present similarly to CU. A careful differential diagnosis is warranted, especially when clinical "red flags" are present[45]. These red flags include wheals lasting over 24 hours, purpura or ecchymoses (rather than simple post-inflammatory hyperpigmentation), dominant systemic symptoms such as near-constant fever and arthralgia rather than the milder forms seen in patients with CU[40-42]. Each condition considered in the differential diagnosis may have distinct histological, serological, or clinical features that differ from CU.

Classification

Clinicians classify CU in several ways (**Table 3**, **Table 4**) and commonly evaluate for wheals, angioedema, or both during diagnosis (**Figure 2**). The other main classification is between CSU, which has no identifiable eliciting factors, and CIndU (**Table 4**), which may by triggered by physical factors (e.g., dermographism [simple or asymptomatic, versus symptomatic; also called dermatographism; formerly urticaria facticia], cold urticaria[54, 55], heat urticaria, delayed pressure urticaria, solar urticaria, vibratory urticaria) or non-physical factors (e.g., aquagenic urticaria, contact urticaria, cholinergic urticaria). Dermographism may be symptomatic or not (also called simple dermographism). Dermographism, followed by cold urticaria are, on a population level, the most common inducible urticarias[35]. About 7% to 30% patients may experience both spontaneous and inducible lesions[56]. Dermographism classically presents with linear wheals. Cholinergic urticaria lesions, elicited in response to sweating, are typically pinpoint and intensely itchy. Delayed pressure urticaria may be a misnomer and present with delayed angioedema without wheals. **Figure 3** presents common provocation tests for diagnosis and possible prognosis of CIndU.

Table 3. Common classification approaches for chronic urticaria

Common classifications	Comment
Inducible urticaria or not	About 7% to 30% patients may experience both spontaneous and inducible lesions
With or without swelling (angioedema)	With regional variation, about 60% of patients with CSU have wheals only, about 35% have wheals and angioedema, and about 5% have angioedema alone (**Appendix**)[35, 46]. About 1 in 3 cases of recurrent isolated angioedema represent chronic mast cell-mediated angioedema[47].
Worsened by NSAIDs or not	Also referred to in drug allergy literature as pseudoallergy, type II NSAID pseudoallergy[57], or NSAID-exacerbated cutaneous disease (NECD)[20].
With vs without risk of anaphylaxis	Most CU has little to no appreciable risk for anaphylaxis, with the primary exception being cold urticaria, followed by less common cases of cholinergic (e.g. exercise-induced anaphylaxis) or solar-induced cases. A systematic review reported that about 1 in 5 (22%) of patients with cold urticaria may be at risk for anaphylaxis[58]. Patients at risk of anaphylaxis should be counseled and offered epinephrine emergency medications.
Associated with autoimmunity or not	Autoimmunity may refer to comorbid diseases (addressed in separate section), or an underlying association (addressed in next row) to an autoantigen and CU disease course or response to therapy.

Endotypes[59-62]	Common to refer to type I (autoallergic with IgE antibodies to endogenous antigens), or type IIb (autoimmune, with mast cell- and basohil-activating IgG autoantibodies) and in relation to autologous serum skin test (ASST). Current endotype classifications, however, are often overlapping and do not explain all cases of CU[59, 62-64]. Further, defining type I disease using IL-24 has not consistently been replicated. Their conceptualization is being reconsidered and their optimal operationalization in routine clinical practice remains unclear.

Table 4. Main classifications and approximate prevalence of chronic urticaria

Classification	Approximate mean prevalence (%)*
CSU	**60% of CU have CSU alone**
Wheals alone	60% of CSU
Wheals and angioedema	35%
Angioedema alone	5%
CIndU*	**25% of CU have CIndU alone**
Symptomatic dermographism	45% of CIndU
Delayed pressure	7%
Cold	20%
Cholinergic	10%
Heat	2%
Solar	5%
Aquagenic	1%
Vibratory	1%
Mixed or Multiple (multiple inducible factors)	10%
Both, also called mixed, CSU + CIndU	**15% of CU have both CSU and CIndU#**

*Regional variation occurs due to varying inducible factors (e.g. temperature). CIndU may also be typical or atypical (e.g. negative on classical provocation testing and may be localized forms or cofactor [e.g. airflow, temperature, humidity] dependent). Meta-analyses of 11 studies[65-75] are presented in the Appendix. Some experts do not consider asymptomatic (also called simple) dermographism to be a CIndU.

#Subtype distribution of either CIndU or CSU seems similar among those with or without the other concomitant form of CU. Forms of CU can evolve from one to the other.

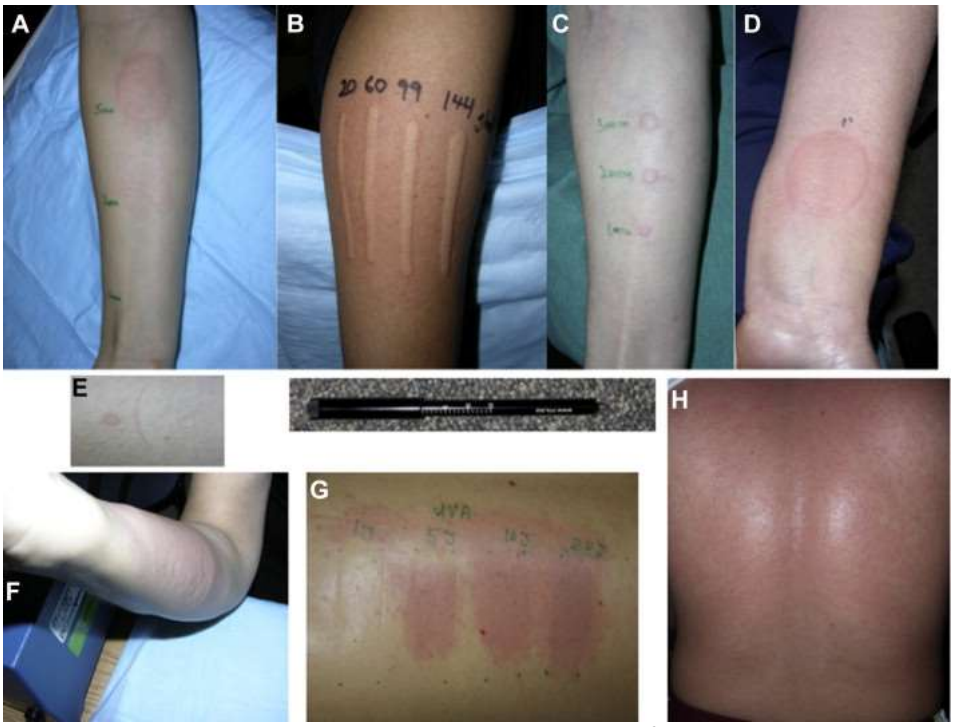


Figure 3, Physical urticaria images. Adapted with permission from Komarow et al[73]. **A**, Cold induced: 1, 3, and 5 min cold contact. **B,** Dermatographism: linear scratch by using dermographometer at 20, 60, 99 and 144 g/m^2. **C,** Delayed pressure; (at 6

hours) using 100 g/m^2 pressure for 1, 2, and 3 min. **D,** Local heat, 55°C contact for 5 s. **E,** Evaporative cooling: on left, with right side airflow blocked. **F,** Vibratory: vortex stimulation for 4 min. **G,** Solar: from UV-A at 1, 5, 10, and 20 J. **H,** Cholinergic: after exercise.

While NSAIDs are recognized exacerbating factors for CU activity, other common triggers include infections (e.g. viral and bacterial), vaccination, stress, sleep deprivation, hormone changes (e.g. puberty, menses, pregnancy, menopause, hormone replacement, hormone-based chemotherapy)[76], opioids, and alcohol (ethanol)[21].

Measures to Assess CSU Severity, Control and Quality of Life

An important component of CU management is assessment of disease severity, control and disease burden[34, 77-79]. Many patient-reported outcome measures (PROMs) have been developed and validated to assess CSU, angioedema and CIndU for this purpose[77, 80, 81]. These instruments have been widely used in clinical trials as primary and secondary endpoint measures and during routine clinical care as indices of severity and control that can be repeated longitudinally to determine efficacy of treatment regimens over time[77].

Severity and activity

Table 5 summarizes common validated PROMs currently used for management of CSU, CIndU and angioedema. The Urticaria Activity Score over 7 days (UAS7) is the most commonly used measure in clinical trials and routine practice to assess CSU activity. The UAS7 asks patients to report the two main manifestations of CSU daily for 7 days: the number of hives/wheals (called hive severity score, HSS) and the severity of itch (called itch severity score, ISS). Every day, each of the two UAS7 components are rated on a scale ranging from 0 to 3, with higher values indicating greater activity, and the maximum daily score being 6 and maximum weekly score being their sum, or 42. A UAS7 of 0 indicates no hives nor itch. Patients needing to complete the UAS7 prospectively for the 7 days prior to clinician visits may find it burdensome and therefore more difficult to use in routine clinical practice. A UAS7≤6 is considered well controlled, a UAS7 between 7 and 15 indicates mild activity, between 16 and 27 as moderate activity, and 28 to 42 as severe activity. The minimally important difference (MID), based on the integration of anchor- and distribution-based results from a 16-week phase 2 RCT evaluating add-on omalizumab vs placebo for CSU, for the UAS7 is between 9.5 and 10.5[82]. Urticaria severity and activity, whether acute or chronic, spontaneous or inducible, or angioedema classically is more intense at night. Nevertheless, studies show that reporting UAS7 twice a day and once a day are comparable[83]. A limitation of UAS7 is that it addresses only hives and itch.

Control

The Urticaria Control Test (UCT) is often used in routine clinical care[84]. The 4-item questionnaire queries about physical symptoms of urticaria (itch, hives, swelling), impact on QoL, treatment effectiveness, and symptom control over the past 4 weeks, each scored from 0 (most impairment) to 4 (no impairment)[84]. The four component scores sum to 16, defined as completely controlled (score of 16), scores of 12 to 15 are well-controlled, and scores 0 to 11 are uncontrolled. The MID for this measure is 3[84]. Recently, the UCT has been validated for a recall period of 7 days with an MID of 2[79]. While formal health status measurement comparisons of UAS7 and UCT are lacking, many insurers require evaluation of UAS7 even though the UCT may be the more feasible measure for both CSU and CIndU (those with combined disease) in routine clinical practice given its simple questions, longer recall period, and single cutoff point for discrimination. An analogous angioedema control test (AECT) is available[85].

Urticaria-related quality of life

The Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) is a 23-item questionnaire that queries the impact of pruritus, swelling, daily life activities, sleep disturbance, physical appearance, and limitations on daily activities over the last two weeks[77, 86]. Each item is based on a 1 (not at all) to 5 (very much) scale, calculated as the sum of all completed items out of the maximum possible sum of all completed items, then multiplied by 100. Similar to a percentage, the maximum score is therefore 100. The MID for this instrument is 15[77, 86]. The Dermatology Life Quality Index (DLQI), a common health-related quality of life measure for multiple diseases with prominent skin symptoms (e.g. atopic dermatitis[32]) and CU-Q2oL have been used in clinical trials as secondary or exploratory endpoints with equal frequency and often concomitantly[77]. Studies show strong internal consistency between these two instruments with Cronbach's alpha coefficients >0.8.

Digital technologies

Communication technologies (e.g. mobile phone apps) to chronicle urticaria signs, symptoms, and triggers are increasingly available. Such tracking may facilitate clinicians to further personalize individual treatment plans. Current mobile apps for CU self-evaluation include TARGET My Hives, UrCare, UrticariApp, and SymTrac HIVES and CRUSE. Despite a previous study indicating the lack of global availability of such tracking apps[87], a more recent study of the CRUSE application suggested more widespread availability and the possibility of artificial intelligence (AI) technology in supporting disease management. Likewise, the CRUSE application is able to connect to the global CURE database which could enable more robust data collection and data sharing[88].

Table 5. Patient Reported Outcome Measures (PROM) for chronic urticaria and angioedema[78, 79]

PROM	Format (recall period)	Domains	Domain Scoring	Overall range (details)	Activity Strata	MID
Disease activity						
UAS7 (Urticaria Activity Score over 7 days)	2 items Last 7 days	Itch severity score over 7 days (ISS7) and hive severity score over 7 days (HSS7)	0-3	0-42 (sum; higher worse)	0, complete control 1-6, well controlled 7-15, mild 16-27, moderate 28-42, severe	9.5 to 10.5
AAS7 (Angioedema Activity Score over 7 days; 28 and 84-day measures available)	5 items Last 7 days	Physical discomfort, ability to perform daily activities, physical appearance, global assessment	0-3	0-105 (sum; higher worse)	NR	8
Disease control						
UCT (Urticaria Control Test)	4 items Last 4 weeks	Physical symptoms, QoL impact, treatment response, symptom control	0-4	0-16 (sum; higher better)	16, complete control 12-15, well-controlled <12, uncontrolled	3
UCT7	4 items Last 7 days	Physical symptoms, QoL impact, treatment response, symptom control	0-4	0-16 (sum; higher better)	16, complete control 12-15, well-controlled <12, uncontrolled	2
AECT (Angioedema Control Test)	4 items Last 4 weeks	Frequency, QoL impact, unpredictability of AE attacks, treatment control	0-4	0-16 (sum; higher better)	10-16, controlled 0-9, poorly controlled	NR
QOL impairment						
CU-Q2oL (Chronic Urticaria Quality of Life Questionnaire)	23 items Last 2 weeks	Pruritus, swelling, daily life activities, sleep, appearance and limitations	1-5	0-100 (sum scaled out of 100; higher worse)	NR	15

AE-QoL (Angioedema Quality of Life Questionnaire)	17 items Last 4 weeks	Functioning, fatigue/mood, fear/shame, meals	1-5	0-100 (sum scaled out of 100; higher worse)	NR	6
DLQI (Dermatology Life Quality Index)	10 items Last 7 days	Symptoms/feelings, daily activities, leisure, work, school, personal relationships, treatment side effects	0-3	0-30 (sum; higher worse)	0, no impact 1-5, little impact 6-10, moderate impact 11-20, very high impact 21-30, extremely high impact	4

NR, Not reported. CIndU specific instruments exist, e.g. coldUAS for cold urticaria[89].

Pathophysiology and Mechanisms of CU

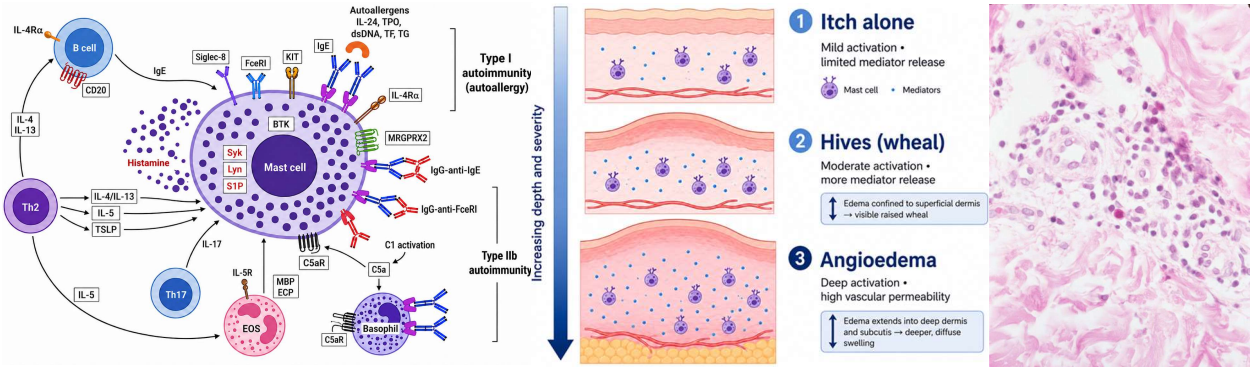


Figure 4. *Left*, immunopathophysiologic mechanisms in chronic urticaria. *Middle*, cellular and fluid localization in chronic urticaria's itch, hives (wheals), and angioedema (swelling). *Right,* histopathology of typical hive in chronic urticaria. Images adapted with permission[56, 62, 90].

A central feature of the immune pathophysiology of CU is the activation of two cells bearing the high affinity IgE receptor (FcεRI), namely mast cells and basophils[62]. When activated, these cells release histamine, prostaglandins, leukotrienes, cytokines and proteases as well as a number of other mediators that collectively lead to itch (via H1 receptors and protease activated receptors), vasodilatation and vascular leak which induce pruritic erythematous wheals, the cardinal features of CU[35, 91].

Recent evidence[92] suggests functional alterations in basophils from patients with CSU, including reduced histamine release upon IgE stimulation, lower FcεRI expression, and a state of basopenia that correlates with disease severity and resistance to antihistamines. Basophils have been further classified into responder and non-responder phenotypes based on their in vitro histamine release, with non-responders often displaying higher SHIP-2 expression. This evidence, together with altered basophil phenotype and circulation dynamics[92, 93], supports their relevance in CSU pathophysiology. Despite prior controversy regarding their role[92], accumulating data confirm that basophils, like mast cells, exhibit distinct functional properties in CSU and may influence both disease activity and therapeutic response. Basophil depletion alone with benralizumab, however, suggests that they may be sufficient but not necessary in mediating CU[94].

Although no theory of pathogenesis of CSU has been widely accepted, there is evidence for an autoimmune mechanism in some patients with CSU. Two classifications have been proposed to reflect distinct pathophysiological mechanisms[59]: the autoallergic (type I) endotype, and the autoimmune (type IIb) endotype (**Figure 4**). Both mast cells and basophils can be activated by a type I autoimmune mechanism, also commonly referred to as "autoallergy", which is mediated by IgE directed against

autoallergens[35] such as IL-24. Mast cells and basophils can also be activated by type IIb autoimmunity thought to emerge from IgG antibodies directed against either the cell-surface FcεRI or IgE bound to FcεRI. Functionally, both antibodies could lead to FcεRI cross-linking and trigger downstream signaling and degranulation. The autoallergic endotype was associated with autoreactive IgE (e.g., to TPO or IL-24), high total IgE levels, and possible association with a rapid response to anti-IgE therapy. In contrast, the autoimmune endotype was associated with IgG autoantibodies against other self-proteins like TPO, FcεRI or IgE, lower IgE levels and basopenia, and a possible association with slower response to omalizumab. There is now evidence, however, that type I and type IIb autoantibodies often co-express in the same patient as well as other antibody isotypes (IgA, IgM) to the same antigen (e.g. FcεRI) with as of yet unclear implications[95]. Thus, though there was some initial interest in conceptualizing these mechanisms into a possible endotype framework, the failure to replicate and validate aspects of it, non-unique classification of the different proposed autoantibody profiles, and imperfect biomarker prediction are leading to reconsideration of the endotype concept and its utility as strong predictors for optimal clinical action[59, 62, 95-98].

In addition to the classical FcεRI-mediated pathway, other mechanisms may contribute to mast cell and basophil activation in CSU. The presence of thrombin and other by-products of the extrinsic clotting pathway in the serum of some patients with CSU and that their presence correlates with disease severity suggests that these factors may play a role in some patients with CSU. Thrombin, for example, is known to be able to activate mast cells and basophils[99], suggesting a potential FcεRI-independent route of activation through alternative receptors or histamine-releasing factors.

More recently, Bruton's tyrosine kinase (BTK) has been shown to be a critical kinase downstream of FcεRI signaling in both human mast cells and basophils[100]. BTK was originally recognized as the critical kinase for B-cell receptor (BCR) signaling leading to the maturation of B cells. Emerging evidence demonstrates that BTK inhibition may be beneficial in CSU by limiting FcεRI-mediated activation of mast cells and basophils, but it is currently uncertain whether BTK inhibition limits the development of auto-reactive B cells and hence auto-antibody production[100].

The histopathology of typical CSU skin lesions is non-diagnostic and is similar to that seen in intracutaneous allergen-induced late phase reactions[101]. Nevertheless, biopsies may occasionally be performed to rule out other diseases (e.g. urticarial vasculitis, bullous pemphigoid, tumid Lupus, Sweet syndrome [acute febrile neutrophilic dermatosis], auto-inflammatory syndromes, as described in **differential diagnosis Table 2**). CU biopsies have a superficial and, sometimes deep, perivascular and interstitial infiltrate of lymphocytes, eosinophils and basophils with typically normal-appearing epithelium[93]. Neutrophils are usually few or absent, but a smaller subset of CU patients will have a modest degree of neutrophilia but with no neutrophilic debris or fibrinoid necrosis of vessel walls as might be seen in (leukocytoclastic) vasculitis[101]. Both Type 2 cytokines (e.g. IL-4 and IL-5) and Type 1 cytokines (e.g. interferon-γ) are noted in CU lesions[90, 101, 102]. Of note, little difference is found in the characteristics of skin biopsies of patients with and without serologic evidence for autoimmune urticaria[101, 103]. Thymic stromal lymphopoietin (TSLP), IL-25, IL-33, IL-24, and IL-31 are increased in CU lesions compared to healthy controls[90, 102]. IL-4, IL-13, and IL-31 have been implicated in histamine-independent itch mechanisms[104]. Increased expression of IL-3 and tumor necrosis factor (TNF)-α in endothelial cells has been detected in the skin biopsies of both lesional and non-lesional skin in CU[105] compared to healthy controls without allergy or CU undergoing cosmetic procedures.

In summary, there are multiple theories for the pathogenesis of CU and it is speculated that different pathways lead to mast cell and basophil activation and mediator release in different patients which

would explain why some treatments (e.g. anti-IgE therapies such as omalizumab) are effective for some patients with CU and not others. While type 2 immunity is a central feature, a subset of patients will also exhibit autoimmunity as part of their CU process or as separate autoimmune disease. The pathophysiology of CIndU involves external physical or non-physical triggers that directly or indirectly activate mast cells, often through distinct pathways (e.g., mechanical, thermal, or cholinergic stimulation), leading to mediator release and wheal formation; however, overlap with CSU mechanisms may exist.

The immunology of CU resolution is less well-defined and likely reflects at least a reversal of chronic mast cell hyperresponsiveness. The concept of CU remission is emerging and is currently a clinical definition[39].

CU Comorbidities

A number of different diseases have been reported to occur more commonly in patients with CU[106]. Relationships range from autoimmunity[107], and possible autoimmune diseases such as hypo- or hyperthyroidism, to atopic diseases or psychiatric diseases[108]. The evidence for an increased risk of such diseases among patients with CU, however, is limited by almost all being small and/or single arm prevalence studies from highly-select referral populations at high risk of bias without robust comparators or control for potential confounding. Therefore, whether the incidence and prevalence of such diseases are importantly increased among patients with CU is highly uncertain[106, 109, 110].

Approximately 20-30% of patients with CU have NSAID-exacerbated cutaneous disease (NECD) compared to 1% of the general population having analogous NSAID-induced urticaria/angioedema (NIUA)[21]. NECD entails acute exacerbation of urticaria (itchy wheals and/or angioedema) after taking aspirin or another NSAID[111]. This commonly occurs after exposure to agents that inhibit cyclooxygenase (COX)-1, via release of cysteinyl leukotrienes[112], leading to a flare of CU that may be serious. Similar to patients with aspirin exacerbated respiratory disease[43], preferentially and weakly selective COX-1 inhibitors may also cause a flare of CU at higher doses, and highly selective COX-2 inhibitors (e.g. celexocib) can be tolerated without untoward reaction (**Table 6**)[20]. COX-1 inhibitors are more likely to be tolerated in patients with NECD when CU is well-controlled[113] or in remission (i.e. many patients may tolerate NSAIDs with overlapping antihistamines). Attempts to induce tolerance via desensitization protocols have been unsuccessful[114]. In general, patients with NECD, especially those with currently uncontrolled disease with ongoing NSAID use, should be advised to avoid aspirin and NSAIDs. When aspirin or NSAIDs are clearly indicated without an equally effective alternative, such as for cardioprotection, thromboprophylaxis, dysmenorrhea, or analgesia, direct challenge can be carried out (for aspirin, the provoking dose for reaction in patients with NECD is frequently above 81 mg)[20].

Table 6. NSAIDs and related drugs that inhibit COX with varying isoenzyme selectivity

COX-1 vs COX-2 preferential inhibition	Example medications
NSAIDs that preferentially inhibit COX-1 and cross-reactivity among NSAIDs (including aspirin)	Diclofenac Etodolac Fenoprofen Floctafenine Flurbiprofen Ibuprofen Indomethacin Ketoprofen Ketorolac Meclofenamate

	Mefenamic acid Naproxen Oxaprozin Piroxicam Sulindac Tiaprofenic acid Metamizole (dipyrone)*
Nonopioid analgesics and nonacetylated salicylates that are poor inhibitors of COX-1 and only with higher concentrations of drug; cross-reactions among NSAIDs with higher doses	Acetaminophen (paracetamol) Diflunisal Salsalate Bismuth subsalicylate, bismuth salicylate
NSAIDs that preferentially inhibit COX-2 but also inhibit COX-1 at higher doses (i.e. cross-reactions among NSAIDs with higher doses)	Meloxicam Nabumetone Nimesulide
Highly selective COX-2 inhibitors that do not inhibit COX-1; cross-reactions with other NSAIDs are rare (eg, at high doses)	Celecoxib Etoricoxib Parecoxib Lumiracoxib

From Management of Chronic Spontaneous Urticaria Made Practical: What Every Clinician Should Know[21]
*Metamizole (also called dipyrone) is a pyrazolone analgesic, spasmolytic, and antipyretic drug commonly used in Latin America and parts of Europe and Asia. Although its mechanism of action is incompletely understood, metamizole and its metabolite, 4-methyl-amino-antipyrine, at least act on COX-1 and COX-2 (selectivity unclear) and inhibit prostaglandin synthesis, and therefore may also trigger hypersensitivity reactions similar to other NSAID

Complications of recurrent itch and excoriation include infection (bacterial, viral, fungal), lichen simplex chronicus, and prurigo nodularis, among others[115-117].

Patient and Caregiver Experience (Navigating Costs and Care)

Patients with CU have a protracted journey that is associated with significant disease burden. Due to lack of disease awareness and the often intermittent nature of symptoms, there may be delays in seeking healthcare[118]. When patients seek care, they often see multiple physicians in various settings including primary care physician offices, urgent care centers, or emergency rooms (ERs). National UK and US cross-sectional surveys estimate 1% of all ER visits are for urticaria (acute or chronic)[31, 119], that 25% of patients with CU visit the ER at least once for uncontrolled disease, and that 12% are hospitalized[31, 119].

Unfortunately, patients with CU are often treated symptomatically and are not provided with a long-term treatment plan to control their hives, itch, and/or swelling[120, 121]. Ultimately, they may end up seeing multiple clinicians before a correct diagnosis is made and an effective treatment plan is implemented. This process can be very frustrating for the patient, leading to increased anxiety and a sense of hopelessness if their hives remain uncontrolled and disruptive to their daily lives. It is important for the patient to find an allergist/immunologist or dermatologist with special interest and expertise in caring for patients with CU (herein referred to as urticaria specialists or experts). Since hives are often interpreted as a sign of allergy – and therefore an external stimulus – patients often struggle with trying to identify a cause (e.g. an allergen triggering their hives)[121]. Hives, however, can also be due to non-allergic causes.

Data from the Urticaria Voices survey, a global initiative amplifying patient perspectives, highlight critical barriers in diagnosis, access to treatment, and cost navigation that directly impact quality of care and outcomes[120, 122]. Using a 10-point scale (10 having the greatest negative impact), all patients with CSU (n=582), regardless of whether they were controlled or inadequately controlled, reported their disease significantly impacted their mental and emotional well-being, social life and intimate relationships as well as their activities of daily living, and financial life (mean scores ranged from 4.7 to 6 for each domain). Even among those patients who reported adequate control, they had only marginal to

moderate improvements in these quality-of-life parameters. The economic and societal burden extends beyond direct costs. Patients experience lost productivity, absenteeism, and mental health impacts - underscoring the need for integrated care models that address both medical and socioeconomic dimensions.

Treatment adherence is also frequently disrupted by cost-related barriers. According to the Urticaria Voices study, access to advanced therapies is frequently impeded by inconsistent insurance coverage, complex prior authorization processes, high out-of-pocket expenses and obscure cost-saving resources (e.g., copay cards, patient assistance programs). Patients report delaying or forgoing treatment entirely due to affordability, resulting in preventable morbidity and reduced quality of life.

In general, CU has a significant impact on the patient's well-being and quality of life necessitating the need to educate patients and physicians on the proper assessment and management of this condition. We anticipate these guidelines will be helpful for improving the patient journey.

Special populations affected by CU

Special populations affected by CU include those at extremes of age, and patients who are pregnant or breastfeeding[38, 123, 124].

Infants and children

A systematic review of studies globally reported a point prevalence in children of 1.43% with similar prevalence in males and females younger than 15 years[125]. Children with CU may experience angioedema less frequently than adults with CU[37, 126, 127]. Although data on the natural history of pediatric CU are still scarce, previous studies reported the median age of CU onset between 5 and 9 years[128, 129]. The resolution rate of CU in children is slow, with 10 per 100 patients (10%) per year achieving complete remission of symptoms[128]. The resolution rate is reported to be even slower in inducible forms[130]. There is also validation data on the use of patient-reported outcome measures such as UAS7 and UCT in children, similar to tools used in adults[131, 132]. Mimickers (differential diagnosis)[133] to consider for infancy include: viral exanthems, drug eruptions, atopic dermatitis with urticarial lesions, papular urticaria, urticarial vasculitis, and autoinflammatory syndromes such as cryopyrin-associated periodic syndromes (**Table 2**).

Regarding treating CU in children, the effectiveness of second generation H1-antihistamines (SGAH) may be higher in children[37, 133-136] and therefore the need for advanced therapies (e.g. omalizumab) lower[37]. Educational training sessions on urticaria management are effective in enhancing physicians' adherence with current recommendations[137, 138]. Difficult cases may require other therapeutic interventions, the risk-benefit ratio being carefully analyzed as data addressing adults is often extrapolated to children[139]. There are limited data available on the efficacy and safety of omalizumab in children, albeit it is approved for food allergy at age 1 year or older[140], as well as on the use of cyclosporine[141]. It is important to note that children may have a slower response to omalizumab[142].

Patients over age 65 years

In patients aged ≥65 years, data regarding CU are scarce, though recent observational studies suggest suggest 3-5% of all CU occurs in adults ≥ 65 years of age and that it is underdiagnosed[123, 143]. Compared with younger adults, older adults tend to have a shorter disease duration but higher relapse rates[144]. CSU may be more often complicated by comorbid diseases (reported in up to 70% of cases)[143], polypharmacy, and organ dysfunction in this age group[145]. Comorbidities included autoimmunity , malignancy, and

atopy[146], as well as metabolic and cardiovascular conditions such as hypertension and diabetes, which may influence disease control and treatment tolerability[144].

Polypharmacy is common, with more than 40% of older adult patients using five or more medications, and drug-induced or drug-exacerbated urticaria being frequently reported[144]. Treatment response to omalizumab may be modestly reduced in older adults (approximately 60 - 65% responders compared with 75-80% in younger patients)[144]. Side effects of sedating H1-antihistamines, such as somnolence, impaired cognition, anticholinergic adverse effects[147], and increased fall risk, are also more pronounced in this population [143]. Differential diagnoses such as urticarial vasculitis, cryoglobulinemia, urticarial phase of bullous pemphigoid, and Schnitzler syndrome (an IL-1-driven neutrophilic urticaria with IgM monoclonal gammopathy) are important[123].

Conception, pregnancy and lactation

While CU and most medications are not thought to interfere biologically with conception, the multidimensional negative impact on patient and family quality of life can impair sexual function and fertility[148]. There is still a paucity of literature regarding the management of CU in pregnant and lactating women[145]. Common interventions for CU, however, have been well studied across multiple patient populations and have demonstrated safety in pregnancy and lactation (e.g. most antihistamines) or very reassuring data without any signs of increased risk of maternal or fetal harm (e.g. omalizumab)[149-152]. All H1-antihistamines are excreted in breast milk in low concentrations, and given the concern for neonatal sedation, SGAH at standard doses are preferred and generally thought to be safe in pregnancy. Off-target effects of less-selective H1-antihistamines (e.g. first generation H1-antihistamines [FGAH]) on cholinergic acetylcholine receptors may decrease secretions and breastmilk supply or excretion. Each recommendation and associated implementation guide further addresses considerations in pregnancy, lactation and breastfeeding. CU must be distinguished from other urticarial dermatoses and causes of itch in pregnancy[14].

Health disparities - ethnicity, gender and sex disparities, Indigenous Health, and suboptimal construct of race

CU remains underdiagnosed, with many patients experiencing significant delays in receiving a diagnosis[121]. These delays may be further compounded in individuals with skin of color, where classic signs like erythema may be overlooked, and lesions may blend with surrounding skin or appear as violaceous, grey, or brown hues. The reasons for these diagnostic challenges may stem from limited representation of darker skin tones in medical education and training[153, 154]. Notwithstanding the limitations of Fitzpatrick scales to describe skin color, among medical students, urticaria was the second most commonly misidentified dermatologic condition in skin of color, with correct identification in 57.5% of cases with darker skin tones (e.g. Fitzpatrick IV-VI) compared to 82.2% with lighter skin tones (e.g. Fitzpatrick I-III)[153, 154]. Furthermore, only 4.5% of images in preclinical anatomy textbooks and 9.6% of urticaria images in online resources feature darker skin[154-156]. This lack of representation may also lead to underdiagnosis by humans and machine learning models[157-159]. Erythema in skin of color need not be red[32, 160] (**Figure 5**).

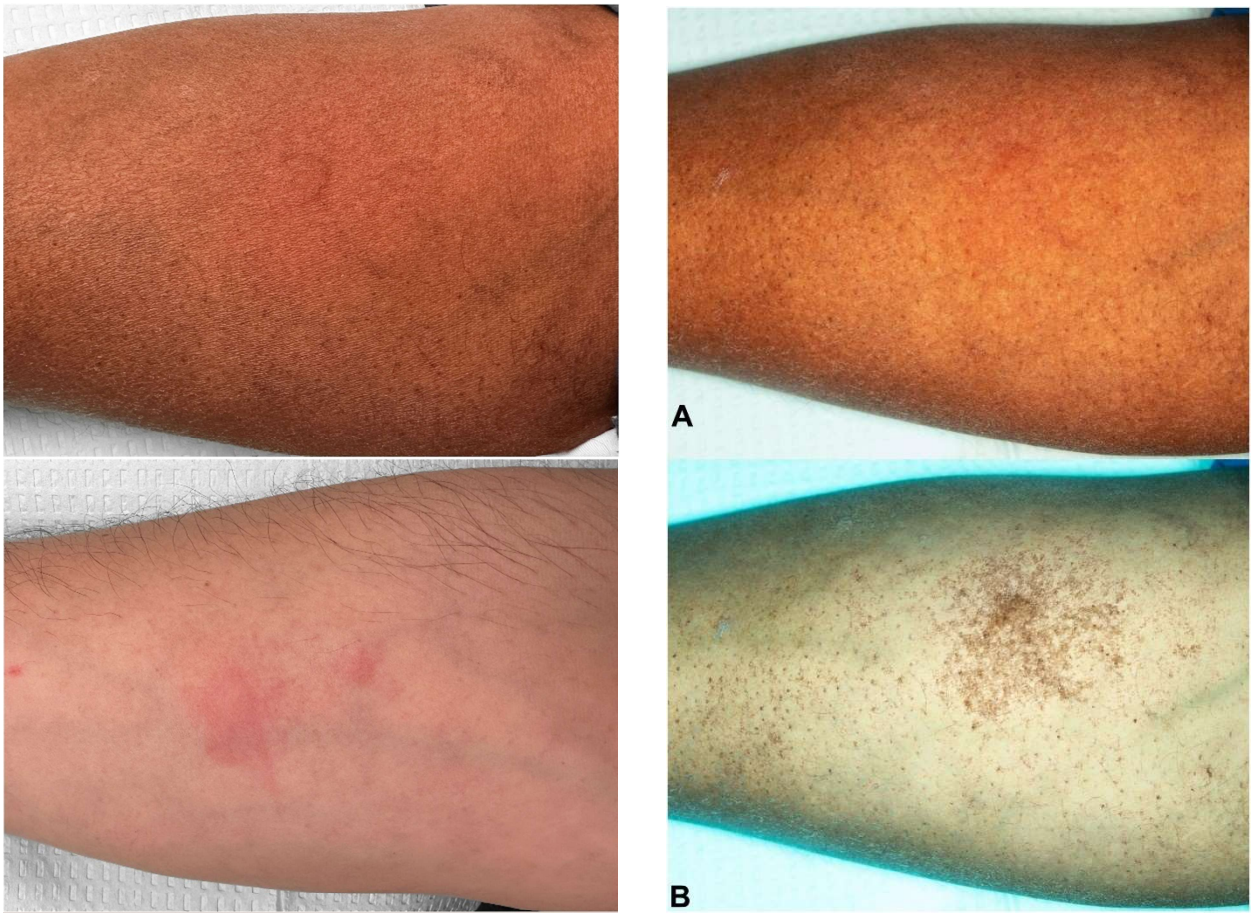


Figure 5. Adapted from Hanlon et al.[161] *Top Left,* wheal induced on the forearm by histamine prick (6 mg/mL histamine base; Jubilant Hollister-Stier LLC, Spokane, Wash) on volunteer identifying as Black photographed using standard clinic lighting and typical equipment, with overhead incandescent examination room light and an Apple iPhone 11. Wheal and erythema on the darker skin is more challenging to detect both visually and in the resulting image compared to *Bottom Left*, wheal similarly induced on volunteer identifying as White. *Right,* same image is shown **(A)** in its original raw state and **(B)** after color processing. **(A)** The wheal induced on the forearm of the volunteer identifying as Black is photographed using cross-polarized lighting where surface texture, glare, and specular highlights were blocked by the polarizer and only deeper color data are captured with a Nikon DSLR and flash system (Tokyo, Japan) that was modified with polarizers. **(B)** When the same image (wheal 6 mm and flare 22 mm) is processed using Lightroom (Adobe Inc., San Jose, CA) for color luminance contrast, the overlap of melanin is reduced, and distribution of erythema (22 mm) is more clearly visualized.

Epidemiologic data on disease prevalence for CU are limited, especially in the United States[162]. While current evidence does not clearly establish whether CSU outcomes in routine clinical practice differ by race or ethnicity, disparities in diagnosis and treatment access suggest a potentially unequal burden. One U.S. study found higher rates of omalizumab use for CSU among identifying as White compared to patients not identifying as White, although the reasons for the race-associated finding are unclear[163]. Global disparities in healthcare infrastructure (e.g. urban vs rural populations) and long-standing historical and structural impacts experienced by Indigenous Peoples limit access to optimal care[164], leading to preventable uncontrolled disease, complications[165], and inequities[166] in accessing advanced therapies such as omalizumab and other immunomodulators[167]. Co-morbidities such as autoimmune diseases, depression, and anxiety which have a higher prevalence in patients with CU and historically racialized groups, may further complicate care in under-resourced settings.

Reiterating the AAAAI/ACAAI JTFPP guidelines addressing atopic dermatitis[32], race, ethnicity, and ancestry are terms that are often confused and used incorrectly in medicine and research[168]. CU clinical trials often fail to stratify data by race, ethnicity, or socioeconomic status, masking disparities and making it difficult to know the impact of interventions more broadly. A systematic review of 23 randomized clinical trials in H1-antihistamine refractory CSU involving 2480 participants from 22 countries, found that individuals who identified as members of historically racialized groups, who were from regions other than North America/Europe, or were from low- to lower/upper-middle-income countries were underrepresented[169]. Furthermore, less than half of the studies included the patient's perspective among reported outcomes[169, 170].

Disparities in CU outcomes may also reflect the pharmacoeconomics of advanced therapeutics (e.g. omalizumab and emerging targeted agents such as remibrutinib). Payers may use utilization-limiting tools, such as prior authorization, step therapy, and higher patient cost sharing, in an attempt to minimize the use of high-cost specialty drugs. These requirements are common and often not based on the best-available evidence in both commercial and government drug insurance policies and can translate into treatment delays, patients abandoning the recommended course of treatment, mandating patients to receive treatment in a geographic region different from what would be most convenient for them (e.g. their treating clinician)[171, 172], and worse patient outcomes (both delay in benefits, and increase in harms) [173-175]. They also shift excessive, and often unpaid, administrative work onto clinicians and associated staff[176]. Such strategies aimed at mitigating cost in the short term can actually be net cost-increasing for payers because they prolong periods of uncontrolled disease and are associated with higher health care resource utilization and total health care costs, such as preventable disease exacerbations, including preventable hospitalizations and longer inpatient stays, compared with controlled disease[177-180]. Altogether, disparities may disproportionately affect underinsured or publicly insured populations, and the practices that serve them, and thereby amplify geographic and racialized disparities in access.

Achieving pharmacoequity, defined as equitable access to quality medications regardless of race or ethnicity, income, or geography, is essential for reducing disparities[171, 172]. Historic medical injustices contribute to skepticism about clinical research participation and acceptance of novel therapies, particularly in historically racialized communities. For broader uptake of both clinical trials and approved treatments, inclusive recruitment practices and community-engaged research approaches are essential[173-175]. Addressing CU disparities requires efforts at all levels of decision-making to improve recognition of varied presentations, reduce diagnostic delays, support inclusive research and treatment strategies, and ensure access to optimal care for all patient populations.

Methods – How these guidelines were created

The AAAAI/ACAAI Joint Task Force (JTF) on Practice Parameters (JTFPP) and the Evidence in Allergy Group at McMaster University developed these guidelines. The JTFPP partnered with the Evidence in Allergy Group for their methodological support in the development and dissemination of clinical practice recommendations to provide patients, clinicians, and policy makers with up-to-date, evidence-based, and user-friendly guidance.

Standards, methods, and processes for living and trustworthy guidance

The guideline panel produced the recommendations following standards for trustworthy guideline development using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach[10-12, 181-188], principles laid out by Guidelines International Network-McMaster[189], RIGHT[190], AGREE II[191], and Institute of Medicine[1, 192], and in compliance with the AAAAI/ACAAI JTFPP policies. We fulfilled criteria required to report robust use of GRADE[10]. The **Appendix** provides additional details.

Selection and support of the panel (Organization, Panel Composition, Planning and Coordination)

The JTFPP conceived the project, obtained approvals from the parent organizations, composed the guideline workgroup of clinical experts, methodologist, and Chairs, and provided overall oversight, including document review, feedback, and approval of the guideline. The guideline panel, striving for equity, diversity, and inclusiveness (e.g., age, gender, race and ethnicity, geography), included 24 individuals, of whom 14 were CU experts (allergy-immunology or dermatology specialists, many of whom were clinician-scientists), 7 were front-line clinicians (family practice, pediatrics, internal medicine, emergency medicine, nursing, physician assistant, pharmacy), and 3 individuals were patients with CU and/or caregivers. The Methods Chair (methodological and content expertise, DC) and Clinical Chairs (content expertise, SS, JAB) guided the panel discussions. A resource person with methods expertise (GG) assisted the Methods Chair (DKC), and observers (XJC, AWLC, DGR, LC, PO) from the Evidence in Allergy Group attended the panel meetings but did not directly participate in discussions. A group of additional healthcare workers (e.g., nurses, pharmacists, pharmacology & toxicology specialists, rheumatology specialists, hematology and oncology specialists, endocrine specialists, infectious disease specialists), patient and caregiver partners, and patient advocacy group representatives provided counsel to the guideline panel, including prioritizing outcomes, subgroup analyses, defining thresholds of important effects, and providing data interpretation. The Evidence in Allergy Group's researchers conducted systematic reviews of evidence and coordinated the guideline development process, including use of the GRADE approach, determining methods, screening and supporting patient and clinician partners, preparing agendas and meeting materials, facilitating panel discussions, and holding focus groups with patient and family partners.

Guideline Funding and Management of Conflicts of Interest

Development of these guidelines was wholly funded by the JTFPP via the AAAAI and ACAAI, non-profit medical specialty societies that represent allergy-immunology specialists. Most members of the guideline panel were members of the AAAAI and/or ACAAI. The JTFPP supported panel appointments, but the panel exclusively developed the recommendations.

Patient and caregiver partners were offered an honorarium by the Evidence in Allergy Group for their time and participation; otherwise, panel members did not receive payment. Some researchers who contributed to the systematic evidence reviews received grant support through the McMaster Evidence in Allergy Group and JTFPP. Other researchers participated to fulfill requirements of an academic degree or program.

Conflicts of interest of all participants were managed according to JTFPP policies[2] (https://www.allergyparameters.org/our-process) based on recommendations of the Institute of Medicine (now National Academy of Medicine)[192] and the Guidelines International Network[193]. Before appointment to the panel, individuals disclosed financial and non-financial interests. The panel updated disclosures before the panel meetings. The Co-Chairs and JTFPP reviewed the disclosures and judged which interests were conflicts and should be managed. The **Appendix** provides the completed "Disclosure of Interest" forms of all panel members. The **Appendix** also summarizes decisions about which interests were judged to be conflicts. At the time of appointment, a majority of the guideline panel, including the co-chairs, had no conflicts of interest as defined and judged by the JTFPP (i.e., no current material interest in any commercial entity with a product that could be affected by the guidelines). Some panelists disclosed new interests or relationships during the development process, but for any individual recommendation, the majority was conflict-free.

When panel members had potential conflicts of interest pertaining to specific recommendations, the management process included recusal from decision-making for those recommendations. While they were encouraged to contribute to discussions regarding scientific evidence summaries, practical issues, and implementation considerations, panel members with a current direct financial interest in a commercial entity with any product that could be affected by the guidelines and with material intellectual (non-financial) conflicts were recused from making judgments about relevant recommendations.

None of the Evidence in Allergy Group-affiliated researchers who contributed to the systematic evidence reviews or who supported the guideline-development process had any current material interest in a commercial entity with any product that could be affected by the guidelines.

Guideline perspective, outcomes, and values and preferences

The target audience for this guidance consists primarily of clinicians, but secondarily of patients, their caregivers, and healthcare decision-makers. The panel primarily considered an individual patient perspective but also took account of contextual factors (such as resources, feasibility, acceptability, equity) to accommodate adoption and adaptation for other contexts. During all discussions, which occurred via email and virtual meetings, the Methods Chair actively reminded the panel that guidelines should focus their main considerations for patient values and preferences representative of general patients with CU.

Panel members, including four patient partners who either had CU or were caregivers for individuals with the condition, considered values and preferences immediately in advance of developing each recommendation. The multistakeholder guideline panel considered a list of patient-important CU outcomes a priori, based on established methods[194], and input from panel members, patient and caregiver partners, frontline clinicians and partner CU advocacy organizations. At the outset of the guideline development process, they rated the importance of each outcome and whether they agreed with a hierarchy ranging from "critically important" to "not very important." Similarly, they set thresholds

for trivial or unimportant effect sizes, and those of small but important, moderate, and large effect sizes for benefits and harms. The Methods Chair reminded the guideline panel to make their recommendations based on the perspective of patients rather than their own values and preferences. A major source of such information was a linked systematic review addressing patient values and preferences for the treatment of CU[9]. In areas where data were lacking, other sources of information included conversations and focus groups with patient and caregiver partners, and clinicians' experience in shared decision-making with patients and families.

Sources of evidence

To create recommendations, the panel relied on evidence synthesized in systematic reviews and (network) meta-analyses[195] led by the Evidence in Allergy Group. These included:

1. Systematic review and network meta-analysis (NMA) of H1-antihistamines and adjuncts, including dose-response, for chronic urticaria[4]
2. Systematic review and meta-analysis of add-on antileukotrienes versus antihistamines alone for chronic urticaria[5] (open-access)
3. Systematic review and meta-analysis of topical corticosteroids versus no topical corticosteroids for chronic urticaria[6] (open-access)
4. Systematic review and meta-analysis of systemic corticosteroids (e.g. prednisone) for flares (exacerbations) of urticaria[7] (open-access)
5. Systematic review and network meta-analysis (NMA) of advanced therapies (biologics [monoclonal antibodies], immunomodulators [e.g. remibrutinib], and immunosuppressants [e.g. cyclosporine, azathioprine, methotrexate], ultraviolet light therapy [phototherapy]) for chronic urticaria[8] (open-access)
6. Systematic review of values and preferences of patients regarding treatment of chronic urticaria[9] (open-access from October 2026 onwards)

While the investigators responsible for the meta-analyses rated the certainty of the evidence, the guideline panel reassessed these ratings independently. Each recommendation's certainty reflects the balance of benefits to harms and therefore reflects the lowest certainty among the prioritized patient-important outcomes.

Additional recent publications by guideline authors that may add additional context include:

7. Patient-reported outcomes and measures[78]
8. Etiology/pathogenesis and pathophysiology[22, 62]
9. BTK signalling[100]
10. Biomarkers and endotypes[59]
11. How to use oral H1 antihistamines in Canada[196]

Evidence Review and Development of Recommendations

For each guideline question, the Evidence in Allergy Group prepared a GRADE Summary of Findings of the systematically reviewed scientific evidence and values and preferences. Panel members also identified additional potentially relevant studies.

Under the direction of the Evidence in Allergy Group, researchers followed the general methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (handbook.cochrane.org) and GRADE guidance for conducting systematic reviews of intervention effects and values and preferences and summarized findings within Summary of Findings and Evidence-to-Decision frameworks[12, 197]. The certainty in the body of evidence (also known as quality of the evidence or confidence in estimates) was assessed for each outcome of interest following the GRADE approach focusing on the following domains: risk of bias, imprecision, inconsistency, indirectness of the evidence, risk of publication bias, presence of large effects and dose-effect relationship[12 11, 181-186]. For network meta-analyses[195, 198] we additionally considered intransitivity[199] and incoherence[195]. Details of the GRADE approach, including definition of terms, are summarized elsewhere[12, 195, 198]. The certainty was categorized into 4 levels ranging from very low, low, moderate, and high with a target of certainty of non-zero effects. The systematic reviews and meta-analyses fulfilled explicit requirements for robust use of GRADE and to report its proper use[10].

From January 2023, and ongoing literature review to November 19, 2025, the panel developed recommendations during 27 online and in-person meetings and through online communication, and 3 formal panel recommendation setting meetings. For each recommendation, the panel reached consensus on the following: the certainty in the evidence, the balance of benefits and harms, and the values and preferences associated with the decision. The panel aimed to create a recommendation based on consensus but elected, at the beginning of the first panel meeting, to call a vote if they could not reach consensus. Before discussions started, the panel determined that a simple majority would provide the direction of the recommendation and that 80% would be required to make a strong recommendation. All members of the panel reviewed and approved the final guidelines.

Document Review

All members of the panel reviewed draft recommendations, revised, and then made them available online from ***XX**, 2026 to **XX**, 2026* for external review by stakeholders, including allied organizations, other medical professionals, patients, and the public. **XX** individuals or organizations submitted comments in addition to 8 peer-reviewers appointed by the AAAAI and ACAAI based on their medical content and methodological expertise. In response to pertinent comments, the panel accordingly revised the document, but no changes were made to the recommendations. On ***XX**, 2026*, the AAAAI/ACAAI JTFPP approved that the defined guideline-development process was followed and approved publication of the guidelines.

Understanding the recommendations

The strength of a recommendation is expressed as either strong ("the guideline panel recommends..."), or conditional ("the guideline panel suggests…") and has the following interpretation (**Table 7**):

Table 7. Interpretation of strong and conditional recommendations.

Implications for:	Strong recommendation	Conditional recommendation
Patients	All or almost all individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.

Clinicians	All or almost all individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients; clinicians must help each patient arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policy-making will require substantial debate and involvement of various stakeholders. Performance measures should assess if decision-making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty of the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

The **Infographic** summarizes the recommendations.

How to use these guidelines

JTFPP guidelines are primarily intended to help clinicians work with patients to make decisions about diagnostic and treatment alternatives. Other purposes are to inform policy, education, and advocacy, and to state future research needs. Patients may also find these guidelines informative, in particular to facilitate discussions with clinicians. These guidelines are not intended to serve as a mandate/standard of care. Clinicians must make decisions based on the clinical presentation of each individual patient, ideally through a shared process that considers the patient's values and preferences. Decisions may be constrained by specific clinical settings and local resources, including but not limited to institutional policies, time limitations, and availability of treatments. As science advances and new evidence becomes available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. The AAAAI, ACAAI, JTFPP, and Evidence in Allergy Group do not warrant or guarantee any products described in these guidelines.

Statements about the underlying values and preferences, as well as qualifying remarks accompanying each recommendation, are integral parts and serve to facilitate a more accurate interpretation. They should never be omitted when recommendations from these guidelines are quoted or translated. Implementation of the guidelines will be facilitated by the related interactive forthcoming decision aids. The use of these guidelines is also facilitated by the explicit description of the Evidence-to-Decision frameworks and Summary of Findings tables provided or cited in references accompanying each section.

JTF AAAAI/ACAAI Chronic Urticaria Management Recommendations

The **Infographic** summarizes the recommendations. **Figure 6** presents a potential flow diagram.

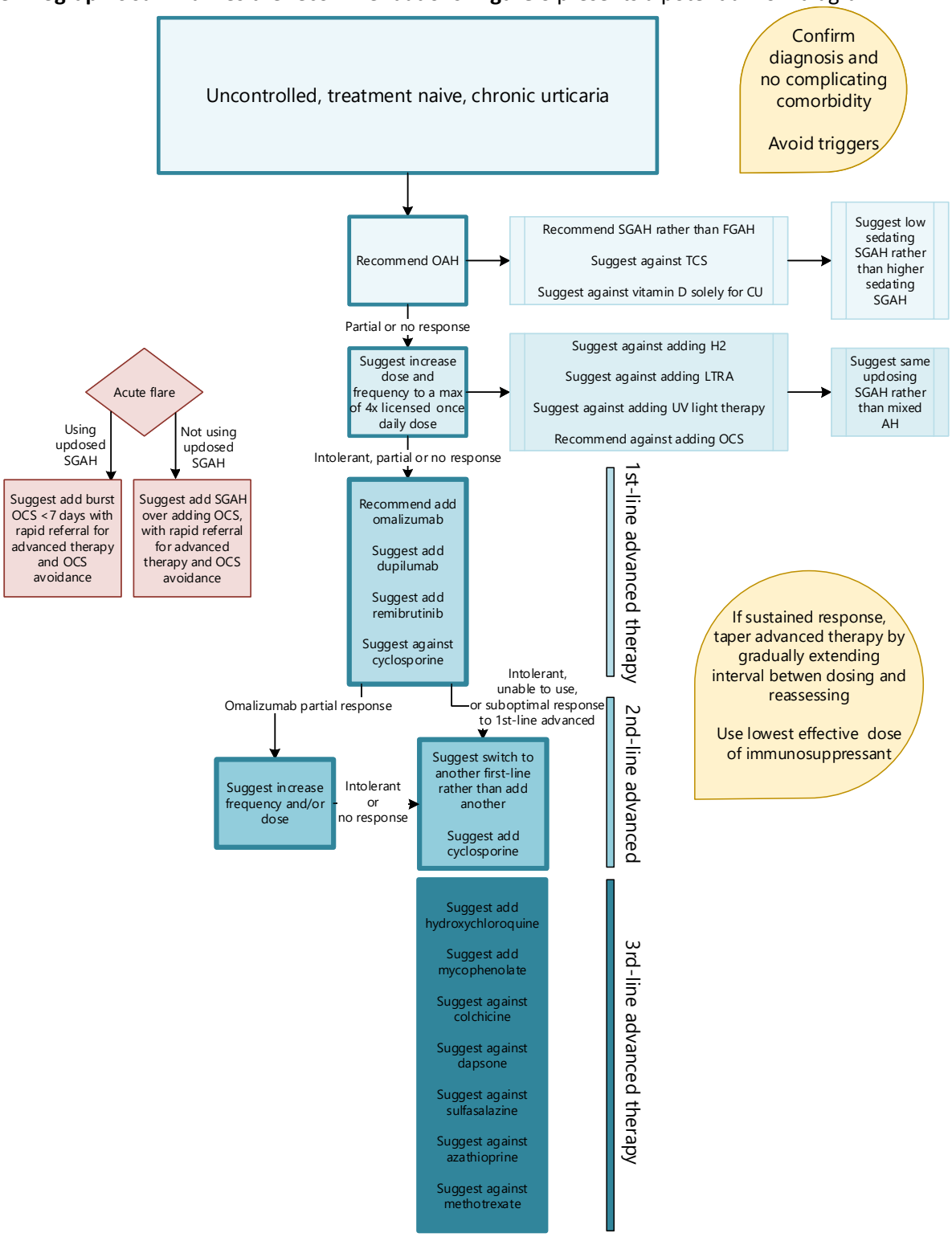


Figure 6. Flow diagram overview of 2026 JTF CU guideline recommendations

AH, antihistamine; CU, chronic urticaria; FGAH, first-generation H1-antihistamine; H2, H2-receptor antagonist; LTRA, leukotriene receptor antagonist; OAH, oral H1-antihistamine; OCS, oral corticosteroid; SGAH, second-generation H1-antihistamine; TCS, topical corticosteroid; UV, ultraviolet.

Good practice statement: Management principles for chronic urticaria

For all patients with chronic urticaria, clinicians should, before initiating, or changing therapy, first:

1. **Confirm the diagnosis and assess for complicating/alternative diagnoses** using a focused history and examination (including lesion duration and morphology, presence/absence of angioedema, and systemic symptoms) for relevant mimics or complications (e.g. urticarial vasculitis; recurrent angioedema without urticaria suggesting bradykinin-mediated angioedema or ACE-inhibitor angioedema; anaphylaxis).
2. **Provide structured education and an action plan** covering expected course, how to monitor control (e.g. UCT), and what to do during flares (including when to step-up therapy), and when and when not seeking emergency room care is required.
3. **Identify and address factors that worsen disease** (aggravating factors or triggers) and counsel on management strategies that consider potential quality-of-life trade-offs.
4. **Ensure optimal medication use** and adherence before revising management plans, including correct dosing and appropriate escalation. Once well-controlled, plan de-escalation to the lowest effective regimen, typically stepping down when symptom-free, depending on the agent, for several weeks or months (e.g. antihistamines over weeks, biologics over months)[39].
5. **Review expected adverse reactions** and safety considerations of current and proposed therapies.
6. **After a thorough history and physical examination, no additional diagnostic investigations may be appropriate.** For example, counsel that routine allergy testing (skin prick testing and/or allergen-specific IgE tests) generally does not identify the cause of chronic urticaria or guide symptom control and should be reserved for the very rare situation where the history strongly suggests a specific IgE-mediated trigger (e.g., suspected food [e.g. alpha-gal syndrome] or drug hypersensitivity). Further, extensive lab testing, including CBC and inflammatory markers, is not required for patients with CU and an otherwise unremarkable history and physical, which, like any medical consultation, includes a standard review of systems[200, 201].

Rationale

Aligning with GRADE guidance for Good Practice Statements[188, 202-204], this statement addresses common, high-yield, but easy-to-overlook steps that reduce misdiagnosis, improve control, self-efficacy, and assessment, reduce preventable exacerbations, and minimize the risk of harm. These actions are supported by linked indirect evidence (e.g. distinct management pathways for bradykinin-mediated angioedema rather than chronic urticaria) and foundational clinical principles, and the JTF panel inferred that formal evidence syntheses for each principle would be an inefficient use of guideline resources.

Emerging evidence suggests several laboratory biomarkers may correlate with disease endotypes and treatment response in CSU (e.g. low basophils/eosinophils and elevated CRP/D-dimer may indicate poor response to H1-antihistamines; low total IgE and elevated anti-TPO may suggest poor response to omalizumab, and, conversely, a good response to cyclosporine).[59, 64, 205] Validated, reproducible biomarkers and thresholds that reliably guide routine treatment selection, however, are not yet firmly

established. The JTF is systematically synthesizing the evidence for biomarkers to predict treatment response and will address this clinical question in a future living guideline update.

STEP 1. TREATMENT NAÏVE CHRONIC URTICARIA

Patients with new CU are those newly diagnosed and not yet treated. They may undergo their initial assessment across multiple clinical settings, including primary care in clinic or hospital-based services (e.g., family medicine, internal medicine, pediatrics), as well as in emergency departments during acute flares.

Who this information is most relevant to: patients with new presentations of the disease and clinicians involved in their initial evaluation and treatment, including primary care clinicians, emergency physicians and relevant specialists.

ANTIHISTAMINES

CU is an immune-mediated disease, including being mast cell-mediated, and most patients will require pharmacological therapy to manage symptoms. While avoidance of identifiable triggers (factors that cause exacerbation) may be sufficient for some individuals with mild or intermittent symptoms, such as in those with solely inducible urticaria, H1-antihistamines are commonly used in the management of CU.

Antihistamines, acting as inverse agonists, are classified by whether they inhibit H1 or H2 receptors. H1-antihistamines are further divided into first- and second-generation agents, which differ in sedative effects, dose, administration frequency, and cost. H2 receptor antagonists (H2RAs, e.g. famotidine, brand name Pepcid AC) are primarily used for gastric acid suppression and may be used off-label as an adjunct in combination with H1-antihistamines for CU. In this document, we refer to antihistamines as H1-antihistamines, and H2-receptor antagonists as H2RAs, to emphasize that H1-antihistamines are primarily used to treat urticaria. Throughout this document, when referring to H1-antihistamines, we are referring to oral and systemic H1-antihistamines, not topical H1-antihistamines. H1-antihistamine use may vary according to dose and frequency, and is influenced by patient characteristics (e.g., age and comorbidities), potential drug interactions, and care setting. **Table 8** provides examples of over-the-counter (available without a prescription) and prescription treatments for CU.

Medication (generic name)	Drug type	Example dose form(s)	Example packages	Strengths commonly available	Direct price	Retail price
Diphenhydramine	FGAH (recommended against)	Tablet, capsule, liquid	24 tablets	25 mg; 50 mg; 12.5 mg/5 mL	$7.99-13.4	$4.22 per 25 mg-tablet
Doxepin	FGAH (recommended against)	Tablet	90 tablets	10 mg or 25 mg	$10.15 – 12.13	$54.90 – 66.60
Hydroxyzine	FGAH (recommended against)	Tablet	90 tablets	10, 25, or 50 mg	$6.76 – 9.50	$45.90 – 70.20
Cetirizine	SGAH	Tablet	90 tablets, 3 x 120mL	10 mg, 1mg/mL bottle	$6.35 – 11.35	$44.10 – 54.00
Desloratadine	SGAH	Tablet	90 (redi)tablets	2.5 or 5 mg	$18.61 – 290.49	$317.70 – 519.00
Fexofenadine	SGAH	Tablet	90 tablets	60 or 180 mg	$17.14 – 19.26	$45.00 – 45.90
Levocetirizine	SGAH	Tablet	90 tablets, 3 x 148mL	5 mg, 2.5 mg/5mL bottle	$7.88 – 41.74	$232.20 – 278.19
Loratadine	SGAH	Tablet	90 tablets, 3 x 120mL	10 mg, 5 mg/5mL bottle	$7.06 – 23.94	$27.00 – 1021.50
Omalizumab	Biologics	PFS, pen	1 syringe/pen per box	75, 150, and 300 mg	$1475 per month	$1,525.61 per 150mg
Dupilumab	Biologics	PFS, pen	Carton	200 mg; 300 mg	$4,193.03 per carton	$3100.84-5132.09 per carton
Remibrutinib	BTK inhibitor	Tablet	60 tablets	25 mg	$4,424.01 per bottle	$4,521 per bottle
Hydroxychloroquine	Immunomodulator	Tablet	90 tablets	100-400 mg	$10.87–68.22	$219.6–783
Azathioprine	Immunosuppressant	Tablet	90 tablets	50, 75, 100 mg	$19.53–348.88	$135–2216.70
Cyclosporine	Immunosuppressant	Capsule	30 capsules	25-100 mg	$93.54–358.57	$107–399
Tacrolimus	Immunosuppressant	Capsule	30 capsules	0.5–5 mg	$8.62–19.87	$57–678
Dapsone	Antibiotic	Tablet	90 tablets	25-100 mg	$39.50–80.87	$225–252
Methotrexate	Immunosuppressant	Tablet, injection*	90 tablets, 2 x 2 mL	2.5 mg, 10 mg, 25 mg/mL	$13.11, $4.20	$259.20, $41.54
Mycophenolate	Immunosuppressant	Capsule, liquid	90 capsules	500 mg	$18.97	$526.50
Sulfasalazine	Immunomodulator	Tablet	90 tablets	500 mg	$22.82	$56.70
Colchicine	Immunomodulator	Tablet, capsule	90 tablets	0.6 mg	$9.55	$528.30
Famotidine	H2RA	Tablet	90 tablets	10, 20, or 40 mg	$6.40–11.03	$24.3–113.4
Montelukast	Leukotriene receptor antagonist	Tablet	90 (chewable) tablets	4, 5 or 10 mg	$7.38 – 32.50	$341.37 – 551.70
Zileuton ER	5-lipooxygenase inhibitor	Tablet	90 tablets	600 mg	$166.72	$2909.70

Prednisone	Oral corticosteroid	Tablet	90 tablets	1-50 mg	$7.19–14.69	$53.1–165.6

Table 8. Some medications used for chronic urticaria. Prices in US dollars from GoodRx, CostPlusDrugs, and manufacturer websites as of December 2025. See the JTF Atopic Dermatitis guideline for a listing of topical anti-inflammatory treatments including topical corticosteroids[32]. *Forms available include drawing from a vial using a syringe, pre-filled, or autoinjector.

The **Appendix** provides practical information about considering and implementing each treatment.

Question 1. Should patients with chronic urticaria use H1-antihistamines vs supportive care alone?

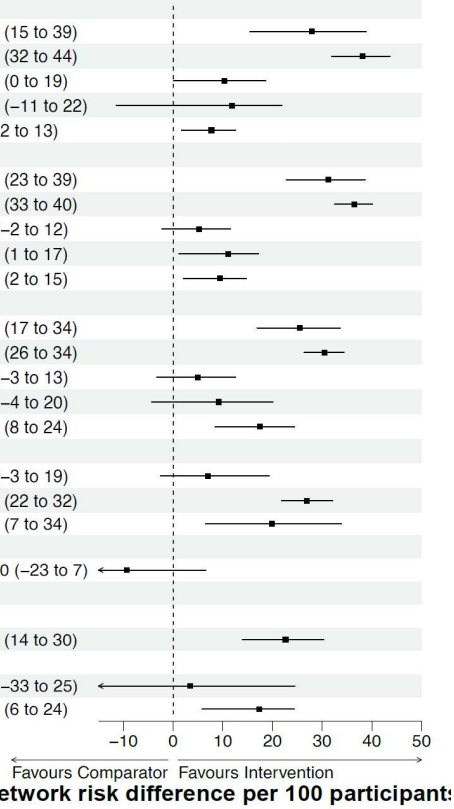
Recommendation 1. In patients with treatment-naïve and symptomatic chronic urticaria, the JTF panel recommends using oral H1-antihistamines rather than supportive care alone (strong recommendation, high certainty evidence).

Benefits and harms: The linked systematic review and NMA evaluating all H1-antihistamine treatments, including dose and frequency[4], included 211 RCTs with 22,187 children and adults. The median baseline urticaria activity (measured with UAS7, score range 0 to 42, higher scores indicate greater activity) was 28 (range of study means 12 to 40). The median treatment duration was 4 weeks (range 0.6 to 12 weeks). Details on the characteristics of the included studies are in the online supplement of the linked systematic review[4]. There was no strong evidence of tachyphylaxis.

The evidence (**Figure 7**) showed that when compared to placebo (37% spontaneous improvement rate), 1st generation H1-antihistamines (FGAH; 65% improving) and SGAH (75% improving) resulted in a large improvement in urticaria activity (risk difference [RD] of FGAH vs placebo, 28%, 95% confidence interval [CI] 15% to 39%; and SGAH vs placebo, RD 38%, 95%CI 32% to 44%, respectively; both high certainty). Low-certainty evidence suggests that FGAH may improve sleep disturbance (RD 7, 95%CI -3 to 19), whereas high-certainty evidence showed that SGAH result in a large improvement (RD 27, 95%CI 22 to 32). Similarly, SGAH resulted in a large improvement in quality of life (RD 23, 95%CI 14 to 30). No FGAH RCTs, however, addressed this outcome. Second generation agents, for example cetirizine, also may decrease angioedema activity (measured with 0 to 3 scale; higher scores indicate worse activity) when compared to placebo (mean difference [MD] -0.63, 95%CI -1.29 to 0.03).

FGAH (e.g. chlorpheniramine, cinnarizine, clemastine, dexchlorpheniramine, diphenhydramine, and hydroxyzine) had similar sedating effects and were among the most sedating agents. High-certainty evidence showed a large increase in the risk of sedation (RD 21, 95%CI 9 to 39). Intermediate sedating agents (e.g. cetirizine, levocetirizine, and rupatadine) had similar sedating effects, showing an increased risk of sedation (RD 5.1, 95%CI 2.5 to 8.8). The least sedating agents (e.g. bilastine, loratadine, desloratadine, and fexofenadine) also had similar effects, showing little to no difference when compared to placebo (RD 0.1; 95%CI -1.2 to 2.2). **Figure 7** presents the summary of findings of the NMA addressing H1-antihistamines and their adjuncts.

Intervention and Comparator	Participants meeting MID (%) Intervention	Comparator	Certainty of Estimate	Network risk difference per 100 participants (95%CrI)
Improvement in urticaria activity (UAS7, 0–42)				
First Gen H1 vs Placebo	65	37	High	28 (15 to 39)
Second Gen H1 vs Placebo	75	37	High	38 (32 to 44)
Second Gen H1 vs First Gen H1	75	65	Low	10 (0 to 19)
Second Gen H1 + H2 vs Second Gen H1	87	75	Very Low	12 (−11 to 22)
Second Gen H1 + LTRA vs Second Gen H1	83	75	Moderate	8 (2 to 13)
Improvement in itch severity (NRS, 0–3)				
First Gen H1 vs Placebo	72	41	High	31 (23 to 39)
Second Gen H1 vs Placebo	77	41	High	36 (33 to 40)
Second Gen H1 vs First Gen H1	77	72	Low	5 (−2 to 12)
Second Gen H1 + H2 vs Second Gen H1	88	77	Low	11 (1 to 17)
Second Gen H1 + LTRA vs Second Gen H1	87	77	Moderate	10 (2 to 15)
Improvement in wheal severity (NRS, 0–3)				
First Gen H1 vs Placebo	59	33	High	26 (17 to 34)
Second Gen H1 vs Placebo	64	33	High	31 (26 to 34)
Second Gen H1 vs First Gen H1	64	59	Low	5 (−3 to 13)
Second Gen H1 + H2 vs Second Gen H1	73	64	Low	9 (−4 to 20)
Second Gen H1 + LTRA vs Second Gen H1	81	64	Moderate	17 (8 to 24)
Improvement in sleep disturbance (NRS, 0–3)				
First Gen H1 vs Placebo	24	17	Low	7 (−3 to 19)
Second Gen H1 vs Placebo	44	17	High	27 (22 to 32)
Second Gen H1 vs First Gen H1	44	24	Low	20 (7 to 34)
Second Gen H1 + H2 vs Second Gen H1			Very Low	
Second Gen H1 + LTRA vs Second Gen H1	34	44	Very Low	−10 (−23 to 7)
Improvement in urticaria-related quality-of-life (DLQI, 0–30)				
First Gen H1 vs Placebo			Very Low	
Second Gen H1 vs Placebo	70	47	High	23 (14 to 30)
Second Gen H1 vs First Gen H1			Very Low	
Second Gen H1 + H2 vs Second Gen H1	73	70	Very Low	3 (−33 to 25)
Second Gen H1 + LTRA vs Second Gen H1	87	70	Moderate	17 (6 to 24)



Antihistamine	Participants with sedation (%) Intervention	Placebo	Certainty of Estimate	Network risk difference per 100 participants
First-Generation H1 Antihistamine				
Chlorpheniramine	18	3.3	High	14.7 (2.9 to 38.7)
Cinnarizine	22.2	3.3	Moderate	18.9 (1.6 to 58.1)
Clemastine	12.2	3.3	High	8.9 (3.7 to 17.3)
Cyproheptadine	38	3.3	High	34.7 (19.6 to 52.6)
Dexchlorpheniramine	62.8	3.3	High	59.5 (14.0 to 89.9)
Diphenhydramine	10.8	3.3	Moderate	7.5 (−1.4 to 39.7)
Hydroxyzine	21.3	3.3	High	18.0 (10.4 to 28.3)
Second-Generation H1 Antihistamine				
Acrivastine	4.4	3.3	Moderate	1.1 (−0.8 to 4.6)
Bepotastine	1.8	3.3	High	−1.5 (−2.5 to 1.0)
Bilastine	3.6	3.3	Moderate	0.3 (−1.8 to 5.5)
Cetirizine	8.4	3.3	High	5.1 (2.5 to 8.8)
Cetirizine + Ranitidine	6.3	3.3	Moderate	3.0 (−2.1 to 24.3)
Desloratadine	3.9	3.3	Moderate	0.6 (−1.4 to 4.8)
Ebastine	3.7	3.3	Moderate	0.4 (−1.5 to 4.5)
Fexofenadine	[illegible]	[illegible]	[illegible]	[illegible]
Levocetirizine	9.8	3.3	Moderate	6.5 (2.1 to 13.7)
Loratadine	3.4	3.3	High	0.1 (−1.2 to 2.2)
Rupatadine	6.5	3.3	Moderate	3.2 (0.3 to 8.1)
Other				
Doxepin	24.2	3.3	High	20.9 (8.9 to 39.1)
Ketotifen	13.8	3.3	High	10.5 (4.8 to 19.2)

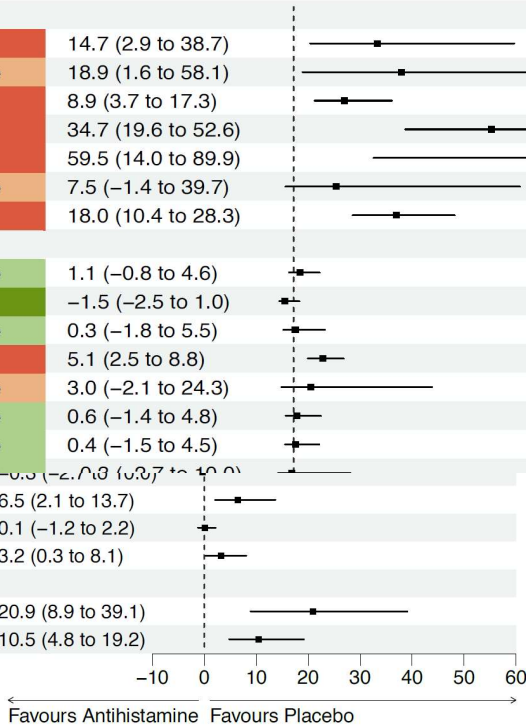


Figure 7. Summary of findings of the systematic review and NMA addressing H1-antihistamines and their adjuncts for CU.

Values and Preferences: The systematic review informing values and preferences for CU treatments[9] showed that, across treatment options, patients are likely to place high value on rapid and sustained relief of hives, itch, and swelling over mild and short-term adverse effects or burdens. However, patients may prioritize safety as the risk or severity of adverse effects increase. For H1-antihistamine use, many patients may place importance on avoiding serious adverse events and minimizing frequent bothersome side effects such as sedation, which can persist into the next day for FGAH, and dry mouth. When treatments are similarly effective, moderate-certainty evidence suggests that patients prefer oral, convenient, low-burden therapies, even if daily dosing is required, and probably favor treatment over watchful waiting despite the possibility of spontaneous symptom resolution. Patients and other panelists raised frequent patient concerns of long-term H1-antihistamine use and the possible association of chronic FGAH use and increased risk of dementia[206], and no clear association with SGAH use[207]. The dementia evidence may be strongest in older adults (e.g. aged 65 or greater)[206, 208-211]. The panel inferred patients would prefer to avoid this uncertain risk. Similarly, patients voiced concerns about possible weight gain with H1-antihistamines, such as that clearly evidenced with cyproheptadine (common off-label) use as an appetite stimulant, and may prefer avoiding this uncertain association (e.g. by limiting H1-antihistamine use or using agents without such an association). Overall, the panel inferred that there is probably no important uncertainty or variability in patient values and preferences.

Contextual factors: H1-antihistamines are widely available and generally low-cost, particularly 1st and several 2nd generation agents, many of which are available as generics and over the counter in some settings. **Table 8** summarizes the costs of different H1-antihistamines. Using H1-antihistamines unlikely importantly increases resource use compared with not using them and may reduce downstream costs by improving symptom control and decreasing healthcare visits. H1-antihistamines are generally easily accessible, equitable, feasible, and acceptable across healthcare settings. Cost of agents may vary by region and insurance coverage which could potentially affect equitable access. The panel noted, however, that acceptability may be lower for agents with higher risk of sedation and anticholinergic effects[147].

Summary of rationale: This recommendation places high value on the high certainty in the evidence of the relative effects of the options. The panel inferred that all or almost all well-informed patients will value the large patient-important benefits and safety of using H1-antihistamines over placebo. The recommendation also clarifies first-line therapy in almost all scenarios as oral antihistamines, with, as the next recommendation shows, is preferred as SGAH, rather than other interventions (e.g. topical corticosteroids).

Implementation considerations: As shown in the next recommendation, the JTF panel implies that all or almost all patients should use an H1-antihistamine, and that H1-antihistamine should be a SGAH. The supplement summarizes practical issues in a 1–2-page handout about how to use H1-antihistamines.

Question 2. Should patients with chronic urticaria use 1st generation H1-antihistamines vs 2nd generation H1-antihistamines?

Recommendation 2. In patients with treatment-naïve and symptomatic chronic urticaria, the JTF panel recommends using 2nd generation H1-antihistamines rather than 1st generation H1-antihistamines (strong recommendation, low certainty evidence).

Benefits and harms: **Figure 7** summarizes the findings from the linked systematic review and NMA addressing H1-antihistamines[4]. Compared to FGAH, SGAH may improve urticaria activity (RD 10, 95%CI 0 to 19); and may result in a large improvement in sleep disturbance (RD 20, 95%CI 7 to 34). Whereas direct RCT high certainty data supported improvements to urticaria-related QoL with SGAH versus placebo, no RCTs addressed either FGAH vs placebo or SGAH, and therefore the benefits of FGAH to QoL remain uncertain.

Comparing H1-antihistamines, as described in Recommendation 1, FGAH (e.g. chlorpheniramine, cinnarizine, clemastine, dexchlorpheniramine, diphenhydramine, and hydroxyzine) are among the most sedating agents, whereas some SGAH (e.g. bilastine, loratadine, desloratadine and fexofenadine) are among the least sedating. In addition, the panel noted the risk for abuse and misuse of FGAH[212, 213], uncertain association with long-term FGAH and cognitive impairment among adolescents and adults,[214] dementia risk with cumulative exposure seen mostly in older adults[206, 208-211], as well the potential increased risk of seizures when used in young children.[215] Improved urticaria control, and less sedation and less off-target pharmacologic effects may reduce the risk of the weight gain and cognitive impairment that is more strongly associated with FGAH over SGAH. [216]

Values and Preferences: Consistent with those described above, the systematic review of values and preferences for CU treatment[9] and direct patient partner input favored SGAH over FGAH due to rapid and sustained[217] symptom control, less sedation, and other adverse effects. Patient partners noted that patients will likely choose the least sedative H1-antihistamine to avoid limitations in daily functioning (e.g., work and school performance, or as a strong requirement to avoid any sedating medications such as work involving [heavy] machinery, driving, military, police, or pilots); that more effective urticaria control is preferable to suboptimal control with sedation for sleep and associated cognitive impairment. Overall, the panel inferred that there is probably no important variability in patient values and preferences.

Contextual factors: Both FGAH and SGAH are generally and similarly inexpensive, widely available (**Table 8**), and share similar contextual factors as described above. The improved efficacy, safety, and practical considerations further supported SGAH over FGAH. Improved urticaria control may also lead to less overall H1-antihistamine use (time and financial resources) with SGAH over FGAH.

Summary of rationale: Faced with low certainty for improved effectiveness with SGAH over FGAH and high certainty for improved safety, the panel inferred patients place a high value on avoiding patient-important harms that could interfere with daily functioning, including sedation, potential cognitive impairment, weight gain, and potential increased risk of seizure (young children) and, therefore that all or almost all well-informed patients would choose SGAH over FGAH (strong recommendation).

Implementation considerations: The supplement summarizes practical issues in a 1–2-page handout about how to use H1-antihistamines.

Question 3. Should patients with chronic urticaria using 2nd generation H1-antihistamines use specific agents, or any?

Recommendation 3. In patients with treatment-naïve and symptomatic chronic urticaria, the JTF panel suggests the use of less sedating 2nd generation H1-antihistamines rather than more sedating 2nd generation H1-antihistamines (conditional recommendation, low certainty evidence).

Conditions to consider:

- When choosing a SGAH to recommend, consider the existing SGAH a patient is already on and agents, if any, they have tried at time of consultation. If tolerated without adverse reaction (e.g. sedation), then they may prefer to remain on that H1-antihistamine over switching. A number of patients, however, that are suboptimally controlled and/or have experienced adverse effects may prefer switching.
- In favor of higher-sedating H1-antihistamines: Patients who might benefit from off-target effects of higher-sedating H1-antihistamines, e.g. some patients with comorbid vasomotor rhinitis may prefer the anticholinergic action of cetirizine to reduce anterior and posterior nasal drip.
- In favor of less-sedating H1-antihistamines: Patients prioritizing the least sedation risk possible.
- Data in pregnancy and lactation are less robust for some agents (e.g., bilastine and rupatadine) over others (e.g. cetirizine, loratadine)

Benefits and harms: The linked systematic review and NMA evaluating all H1-antihistamine treatments found high certainty for similar effectiveness among SGAH for improving urticaria outcomes, low-certainty evidence for more sedating (cetirizine, levocetirizine, rupatadine; risk 8.4%) versus least sedating (bilastine, loratadine, desloratadine, fexofenadine; 3.4% risk vs 3.3% risk with placebo), and high-certainty for no increase in serious harms (**Figure 7**).

Values and Preferences: The systematic review of patient values and preferences and direct patient and caregiver input showed that most patients prioritize rapid and sustained symptom control over minor burden or harms. The evidence also suggests that across SGAH, patients likely do not express strong preferences for one agent over another when effectiveness, accessibility, and costs are similar. However, when potential harms increase, particularly sedation, patients may prefer treatments perceived as less sedating, especially when daily functioning, work, or safety-sensitive activities are affected[9]. The panel therefore inferred that there is possibly important variability in patient values and preferences when choosing among SGAH.

Contextual factors: SGAH are widely used, and choosing less sedating over more sedating agents generally does not involve substantially higher direct costs (**Table 8**). Use of less sedating compared to more sedating SGAH is likely acceptable to most patients. In most clinical settings, selecting one SGAH over another is feasible, although formulary restrictions, insurance requirements, and local availability may influence which agents can be used in practice.

Summary of rationale: Given the similar effectiveness, this recommendation places high value on the low certainty evidence of minimizing harm (e.g. sedation) when achieving urticaria control. The low certainty for an important difference in harm and variability in patient values and preferences and contextual factors drove the conditional recommendation.

Implementation considerations: Clinicians should adjust the prescription and refills to each patient's disease activity. The supplement summarizes practical issues in a 1-2 page handout about how to use H1-antihistamines.

Mechanism of action of H1-antihistamines

H1-antihistamines act as inverse agonists at histamine H1 receptors, stabilizing the inactive receptor conformation to block histamine-mediated symptoms[217, 218].

Question 4. Should patients with chronic urticaria add topical corticosteroids vs not?

Recommendation 4. In patients with chronic urticaria, the JTF panel suggests against using topical corticosteroids (glucocorticoids) as add-on or replacement to oral H1-antihistamines (conditional recommendation, low certainty evidence).

Conditions to consider:

- The generalized, evanescent and migratory nature generally favor against adding topical corticosteroids over other more systemic-acting drugs such as oral SGAH.
- For topical corticosteroids – if very localized (small BSA involvement) on non-sensitive area (e.g. not face/folds), could consider alone or as an adjunct (e.g. very mild overall disease activity, very localized CindU [e.g. DPU]).
- In patients with comorbid eczematous dermatitis, using such as atopic dermatitis[32], topical anti-inflammatory medications[219] alone or in combination with oral SGAH may be favorable.
- In patients with comorbid angioedema, the evidence more strongly favors oral H1-antihistamines over topical corticosteroids.

Benefits and harms: The systematic review and meta-analysis addressing topical corticosteroids (glucocorticoids) for urticaria[6] found 19 RCTs that included 379 patients, primarily adults, and low certainty evidence for reduced urticaria activity (ratio of means, 0.47 [95%CI 0.38 to 0.59]) versus placebo and high certainty for safety for up to the studied 6 week duration of treatment. Topical agents typically comprised moderate or high-potency topical corticosteroids [32, 219]; the few studies addressing low-potency topical corticosteroids showed a similar treatment effect. The data demonstrated very serious indirectness as most studies addressed wheal size rather than urticaria activity, and mostly addressed skin prick-induced wheal rather than patients with CU, which led to rating the certainty of evidence down to low. The direct topical corticosteroids data for urticaria did not address angioedema, sleep disturbance, urticaria-related QoL, or exacerbations.

Values and Preferences: Consistent with those described above, the systematic review of values and preferences for CU treatment[9] together with direct patient partner input, showed that patients valued rapid and sustained symptom control, less sedation and other adverse effects, and the use of oral or topical treatments. While topical treatments may be at first more intuitive and perceived to be less invasive to self-administer, the panel inferred that they would only be practical to use when urticaria was highly localized. Instead, SGAH and associated clear action plans are more likely to achieve disease control in the more common scenario where urticaria (hives and/or itch) is generalized or scattered across a cumulative large body surface area; this also avoids concerns of widespread topical corticosteroids use, both in terms of harms after chronic use and the unpleasant feel of widespread cream or ointment application. Further, patient preference for relief of itch, which is highly uncertain if topical corticosteroids relieve, led to favoring against its addition to routine urticaria management plans.

Overall, the panel inferred that there is probably no important variability in patient values and preferences.

Contextual factors: Most topical corticosteroids are available by prescription and some low-potency[32, 219] topical corticosteroids are available over-the-counter (e.g. hydrocortisone 0.5% to 1%). See the associated atopic dermatitis guideline for example costs[32]. When wheals are localized, they are generally accessible, acceptable, feasible, and equitable. When wheals are generalized, however, acceptability and feasibility decrease.

Summary of rationale: The panel inferred that most well-informed patients would place a low value on the uncertain benefits and certain safety of adding topical corticosteroids, and instead, place a great value on the greater certainty and magnitude of benefits with oral SGAH. The low certainty evidence for topical corticosteroids' benefits to urticaria control drove the conditional recommendations.

Implementation considerations: The supplement summarizes practical issues in a 1-2 page handout about how to use topical corticosteroids. The above recommendations do not apply to wet wrap therapy that is sometimes used in atopic dermatitis. Avoid high-potency (classes 1 and 2) topical corticosteroids for prolonged periods of time (>4 weeks) and limit its use on sensitive areas (face, folds, groin) as instances of atrophy, telangiectasia, and striae may be more likely to occur in these areas. Continuous and prolonged use of low-potency topical corticosteroids on sensitive areas can also cause these effects.

Mechanism of action of topical corticosteroids

TCS exert their effect primarily by binding to glucocorticoid receptors (GR) that are expressed in most skin cell types, both structural cells and bone-marrow derived cells, and underscore their widespread benefits as well as their risk profile[220].

Corticosteroids stabilize mast cells and inhibit their degranulation. This inhibition is thought to be mediated by multiple mechanisms including: reduction in mast cells number (mastopenia), suppression of phosphatidylinositol (PI)3-kinase activation, uncoupling IgE receptors from calcium flux, downregulation of P2X7 receptors on mast cells[221-223].

TCS benefits in CU are also mediated by their rapid inhibition of vasodilators, particularly prostaglandins that mediate their rapid vasoconstrictive effects[224]. They also strengthen endothelial cell-cell contact and in so doing limit vascular permeability and the edema and induration that arises from this[225]. By inhibiting NF-κB signaling they limit inflammation induced endothelial barrier disruption[226]. Collectively, these mechanisms may explain how TCS leads to reduction in erythema and induration in CU lesions.

STEP 2. H1-ANTIHISTAMINE REFRACTORY CHRONIC URTICARIA

Recommendation 2 makes a strong recommendation to use SGAH rather than FGAH. Therefore, when referring to H1-antihistamines throughout the following sections, unless otherwise specified, the JTF panel is referring to SGAH.

UPDOSING SECOND GENERATION H1-ANTIHISTAMINES

Question 5. Should patients with refractory chronic urticaria to 1x licensed SGAH dose, increase dose and frequency to maximum 4x daily dose vs not?

Recommendation 5. In patients with chronic urticaria refractory to 1x licensed H1-antihistamine dose, the JTF panel suggests increasing the dose and/or frequency to maximum of 4x the licensed once daily dose rather than not updosing (conditional recommendation, low certainty evidence).

Conditions to consider:

- For updosing – Patients who have not yet tried any other SGAH and who prefer rapid acting and easily accessible and titratable medication.
- Against updosing – Intolerable sedating or other adverse reactions to separately trying 2 or more different SGAH, or factors such as children or older patients, frailty, or comorbidity that might increase harms and burdens with high dose SGAH, or individuals that place a higher value on long-acting effective therapies (e.g. biologics) over its burdens and adverse effects.

Benefits and harms: The systematic review, dose-response, and network meta-analysis of H1-antihistamines for CU[4] included 211 unique RCTs representing 22,187 participants randomly assigned to placebo or one of 55 unique H1-antihistamines or its combinations.

The dose-response curve (**Figure 8**) showed that when compared to placebo (37% spontaneous improvement rate), a single dose of SGAH improved urticaria activity in 73% of individuals and incremental benefits thereafter (2x dose improving in 81%, 4x dose in 89%), traded off by an increase in sedation (2x dose causing sedation in 12 more per 1000 participants [95%CI 7 more to 18 more] or RR vs placebo 1.36 [95%CI 1.21 to 1.54], 4x dose causing sedation in 32 more per 1000 participants [95%CI 9 more to 68 more] or RR vs placebo 1.99 [95%CI 1.28 to 3.08]). As described in recommendation 3, SGAH are stratified into, on average, more or less sedating, and recognizing there may be inter-individual response and preference. SGAH with intermediate overall sedation includes cetirizine, levocetirizine, and rupatadine, and therefore, have greater sedation potential if used for updosing. SGAH with least sedation includes bilastine, loratadine, desloratadine and fexofenadine.

Values and Preferences: Similar to the previous recommendations addressing H1-antihistamines, the systematic review of values and preferences for CU treatment[9] and direct patient partner input favored 2x to 4x dose SGAH due over their associated minor, on average, harms, but that there may be important variability in how patients might prioritize that tradeoff. When harms become more severe or frequent, patient priorities may shift to safety over maximal efficacy.

Contextual factors: H1-antihistamines are generally accessible, feasible to use, low cost (**Table 8**), and equitable. Updosing H1-antihistamines may also be resource-savings compared to advancing therapy to biologics or immunomodulatory small molecules. Thus, the contextual factors generally favored updosing.

Summary of rationale: The panel inferred that most well-informed patients with CU refractory to 1x dose (one licensed SGAH dose) would place a high value on the uncertain benefits and certain practicality and harms of updosing SGAH up to to 4x its total daily dose over not updosing. The low certainty evidence for the precise tradeoffs between benefits and harms, as well as the values and preferences and contextual factor considerations, drove the conditional recommendations.

Implementation considerations: Most patients will find it easier to use a double dose twice a day rather than a single dose four times per day, though the timing of symptoms may also influence personalized dosing. Patients should understand the flexibility in tailoring dosing to their disease activity. Not all

patients should have to persist through significant harms or burdens of 4x daily dosing (4x the licensed once daily dose): the linked dose-response network meta-analysis showed diminishing benefits and uncertain evidence beyond 2x dosing. Further, the inclusion criteria for RCTs of advanced therapies only required patients to be refractory to a single dose of H1-antihistamine. Therefore, clinicians should offer to prepare patients refractory to 1x, and especially after 2x, dose H1-antihistamine for advanced therapy. This includes considerations laid out in the good practice statement (correct diagnosis, correct medication use, no complications or complicating comorbidity [e.g. completing a skin biopsy or biopsies]), potential advanced therapy prognostic markers (e.g. ordering bloodwork), and considering initiating advanced therapy. The supplement summarizes practical issues in a 1-2 page handout about how to use H1-antihistamines.

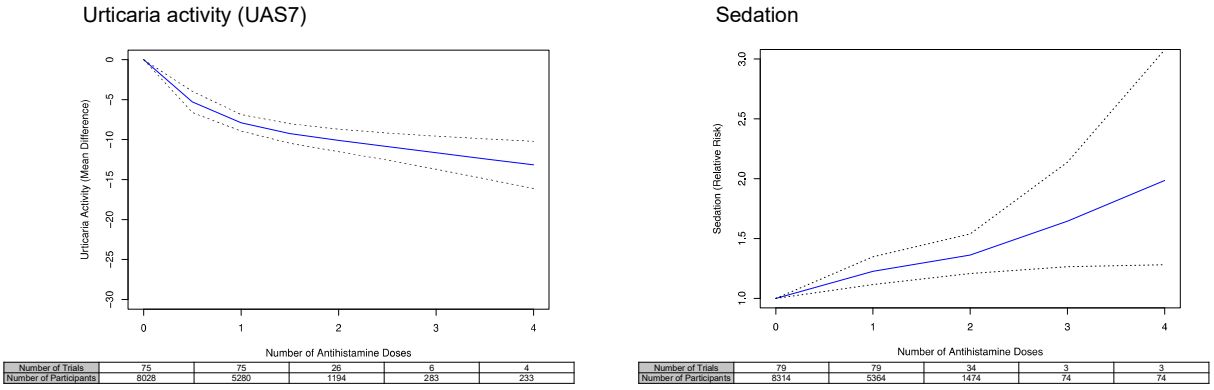


Figure 8. Dose-response curve of benefits and harms of increasing (updosing) oral antihistamines from systematic review and meta-analyses addressing H1-antihistamines and their adjuncts for CU.

Question 6. Should patients with chronic urticaria who are updosing H1-antihistamines use the same single SGAH vs use a combination of different H1-antihistamines (mixed antihistamines)?

Recommendation 6. In patients with chronic urticaria who are updosing 2nd generation H1-antihistamines, the JTF panel suggests using the same 2nd generation H1-antihistamine rather than mixing H1-antihistamines (e.g., 2nd generation H1-antihistamine and 1st generation H1-antihistamine, or two different 2nd generation H1-antihistamines) (conditional recommendation, low certainty evidence).

Conditions to consider:

- Updosing with the same or two different SGAHs – Generally it is simpler to use the same H1-antihistamine for updosing. Rare scenarios to mix are where a slightly more sedating H1-antihistamine might be preferred over those that cause least sedation, such as due to insurance coverage and cost considerations.
- Updosing by mixing SGAH and FGAH - Adding FGAH to SGAH is unfavorable in all or almost all patients due to increased risk of adverse effects including sedation and cognitive impairment, with lower efficacy compared to using SGAH (Recommendation 2).

Benefits and harms: As described in the above recommendation, SGAH are stratified into, on average, more or less sedating, and recognizing there may be inter-individual response and preference. SGAH

with intermediate overall sedation include cetirizine, levocetirizine, and rupatadine, and therefore, have greater sedation potential if used for updosing. SGAH with least sedation include bilastine, loratadine, desloratadine and fexofenadine. FGAH have the greatest sedation potential (RD 21, 95%CI 9 to 39, and increasing with increased dose), are less effective, shorter and slower acting compared to SGAH.

Values and Preferences: Consistent with those for the above recommendations, the systematic review of patient values and preferences[9] and direct patient and caregiver input prioritization of rapid, sustained, effective, and safe therapy, particularly when potential harms increase as they do in updosing, the panel therefore inferred that there is likely little to no variability in patient values and preferences when choosing to updose SGAH with greatest benefits and minimizing sedation potential.

Contextual factors: The primary contextual factor considerations proved consistent with those regarding choosing among SGAH (Recommendation 3). When insured, prescription H1-antihistamines may be the least costly, whereas when patients do not have medication/drug insurance and have to be bear the cost directly, some OTC H1-antihistamines may be the most cost-effective (e.g. purchasing in bulk loratadine or cetirizine). For these reasons, when updosing patients with moderate-severe CU who are refractory to a single dose SGAH it is preferable in most to updose with the same SGAH, one with the least sedation potential. However, in a small minority of patients it may be optimal to use a combination of a more sedating (e.g. cetirizine) and a less sedating (e.g. bilastine, fexofenadine) SGAH to minimize costs and for maximal drug effectiveness

Summary of rationale: The panel inferred that most well-informed patients with CU refractory to 1x dose H1-antihistamine and that are updosing would place a high value on the uncertain benefits and certain practicality and harms of updosing with the same SGAH over mixing H1-antihistamines for updosing. The low certainty evidence for improved safety, as well as the contextual factor considerations, drove the conditional recommendations.

Implementation considerations: The supplement summarizes practical issues in a 1-2 page handout about how to use H1-antihistamines.

Mechanism of action of updosing H1-antihistamines

Pharmacodynamic data[227] show that at 4 hours post-administration, standard doses of antihistamines such as desloratadine, fexofenadine, and levocetirizine result in receptor occupancy rates of 71%, 95%, and 99%, respectively[227]. It is plausible, albeit not strongly and unequivocally borne out by the RCT evidence, that higher doses or frequencies of SGAH increase their pharmacologic action, and therefore improve urticaria outcomes even further.

Question 7. Should patients with chronic urticaria refractory to H1-antihistamine add an H2RA vs continue with 1-4x licensed dose H1-antihistamine?

Recommendation 7. In patients with chronic urticaria refractory to 1x licensed dose H1-antihistamine, the JTF panel suggests updosing H1-antihistamines rather than adding an H2RA (conditional recommendation, very low certainty evidence).

Conditions to consider:

- While H2RAs, such as the most widely available one, famotidine, have small benefits to urticaria activity, they are generally safe, and could be considered for short term adjunctive use as a bridge to advanced therapy.

Benefits and harms: The linked systematic review and NMA evaluating all antihistamine treatments, including adding H2RAs[4] to H1-antihistamines, analyzed 211 RCTs with 22,187 children and adults and showed (**Figure 7**) showed very low certainty for small, likely patient unimportant, improvement in urticaria activity (MD -3.83 [95%CI -10.41 to 2.77]; 87 vs 75% experiencing important improvement for an NNT of 9) and similarly low or very low certainty estimates for the either itch or wheal subcomponent, and urticaria-related QoL. No data addressed either angioedema or sleep disturbance. Compared to using H1-antihistamines alone, adding a H2RA to H1-antihistamine did not increase harms (sedation, overall adverse events, adverse events leading to discontinuation, serious adverse events).

Values and Preferences: The systematic review of values and preferences for CU treatment[9] and direct patient partner input showed patients prefer rapid and sustained symptom control, avoiding sedation and other adverse effects, and oral treatments. H2RAs, being largely over-the-counter oral medications and familiar to patients, may therefore be attractive to some, but the majority are likely to favor the higher certainty and large magnitude of benefits with H1-antihistamines with or without updosing. For some patients who are hesitant to advance to the next step in therapy, such as omalizumab, dupilumab, or remibrutinib, they may prefer a short (e.g. 1 to 2 weeks) trial of H2RAs while starting preparations for advanced therapy. Overall, the panel inferred that there may be important variability in patient values and preferences.

Contextual factors: Using either H1-antihistamines alone or in combination with H2RAs should have no major impact to acceptability, accessibility, feasibility, or equity. The panel inferred the primary factor was the opportunity cost of time, energy, and perhaps the modest financial cost with adding H2RAs to SGAH, rather than focusing on either updosing SGAH or moving forward to advance therapies.

Summary of rationale: The panel inferred that most well-informed patients with CU refractory to 1x dose H1-antihistamine would place a high value on the more certain benefits, harms and burdens of continuing with SGAH, their updosing, or advanced therapies (e.g. omalizumab, dupilumab, remibrutinib) over adding an H2RA to SGAH. The (very) low certainty evidence for added benefits, as well as the potential variable values and preferences and contextual factor considerations, drove the conditional recommendation.

Implementation considerations: The primary H2RA used and recommended is the over-the-counter available and safe medication, famotidine. Other H2RAs may not be as safe (e.g. cimetidine and its multiple adverse reactions and drug interaction downsides) and should not be used. H2RAs are used as short term therapy and should not be used for months without monitoring as chronic use may increase the risk of hip fracture and osteoporosis and respiratory and GI infections[228]. The supplement summarizes practical issues in a 1–2-page handout about how to use H1-antihistamines, including H2RAs.

Mechanism of action of H2RAs

H2RAs, including famotidine and cimetidine, function as competitive antagonists at histamine H2 receptors on the basolateral surface of gastric parietal cells, thereby inhibiting gastric acid secretion pathways[229].

Combination therapy of H1 antihistamines and H2 antihistamines may be effective due to inhibition of the shared CYP3A4 metabolic pathways, with increased plasma concentrations rather than true pharmacologic synergy[230].

ANTILEUKOTRIENES (RECEPTOR ANTAGONISTS AND LIPO-OXYGENASE INHIBITORS)

Question 8. Should patients with chronic urticaria refractory to H1-antihistamines add an antileukotriene vs continue with 1-4x licensed dose of H1-antihistamine?

Recommendation 8. In patients with chronic urticaria refractory to 1x H1-antihistamine, the JTF panel suggests updosing H1-antihistamines rather than adding an antileukotriene (conditional recommendation, moderate certainty evidence).

Conditions to consider:

- For most patients, the modest, potentially patient unimportant, benefits and uncertain rare neuropsychiatric effects of adding an antileukotriene such as montelukast to SGAH will be outweighed by the more certain benefits and safety of updosing SGAH or pursuing advanced therapies.
- While the available RCT data do not directly address angioedema, they do support efficacy of antileukotrienes for acute (exacerbations of) urticaria, and, non-randomized studies suggest that antileukotrienes may be particularly effective in reducing mast cell-mediated angioedema activity. Therefore, select patients might favor adding antileukotrienes to improve control of severe angioedema over its uncertain and rare neuropsychiatric effects.
- Consistent with its re-emphasized boxed warning, patients with psychiatric comorbidities such as severe anxiety/depression disorder, suicide, psychosis, may be at risk for increased harm, and therefore net harm, from antileukotrienes.

Benefits and harms: The linked systematic review and NMA evaluating all H1-antihistamine treatments, including adding antileukotrienes[4] to H1-antihistamines, analyzed 211 RCTs with 22,187 children and adults and included estimates from a dedicated systematic review and meta-analysis of add-on antileukotrienes to SGAH for CU (34 RCTs) and acute urticaria (4 RCTs)[5] with follow-up mostly for 2 to 12 weeks. **Figure 7** summarizes the findings showing add-on montelukast's high certainty for small, possibly patient unimportant, improvement in urticaria activity (MD -5.17 [95%CI -6.53 to -3.8]; 87 vs 75% [RR 1.16] experiencing important improvement for an NNT of 9) and similar certainty estimates for either itch or wheal subcomponent. Add-on montelukast to SGAH may also improve urticaria-related quality of life (low certainty, MD -4.40 [95%CI -8.15 to -0.65]; 94% vs 79% experiencing improvement). Angioedema activity estimates, addressed in only 1 RCT, were highly uncertain (very low certainty, MD -0.80 [95%CI -1.45 to -0.15] on a numeric rating scale ranging from 0 to 3; 77% vs 40% [RR 1.93] improving for an NNT of 3). Sleep disturbance estimates were also uncertain. With moderate certainty, add-on LTRAs likely did not increase overall adverse events, but there is very low certainty, driven primarily from non-randomized data, for a rare, possibly patient unimportant, increase in neuropsychiatric events (8.4% with add-on antileukotriene vs 7.8% without [RD 0.6% increase, 95%CI 0.3% to 1.0% more]).

Values and Preferences: The systematic review informing values and preferences for CU treatments[9] showed that, across treatment options, patients are likely to place high value on rapid and sustained

relief of hives, itch, and swelling over mild and short-term adverse effects or burdens. However, patients may prioritize safety as the risk or severity of adverse effects increase. When treatments are similarly effective, moderate-certainty evidence suggests that patients prefer oral, convenient, low-burden therapies, even if daily dosing is required.

For add-on antileukotriene use, some patients may place importance on avoiding an uncertain and rare increase in neuropsychiatric effects, whether they are an increase in nightmares, mood change, anxiety/depression exacerbation, or more serious adverse events such as suicidality. Conversely, some patients may place greater value on the uncertain benefits to urticaria activity if they have partial disease control with SGAH alone and prefer to avoid using advanced therapies. Another scenario may be patients who place a relatively high value on the uncertain benefits to angioedema over other outcomes, including rare uncertain harms. Overall, the panel inferred that there is possibly important variability in patient values and preferences.

Contextual factors: Add-on leukotrienes are available as generic medicines and are low cost (**Table 8**). Discussing its boxed warning and treatment alternatives, however, may consume more time resources. Antileukotrienes other than montelukast may require laboratory monitoring (e.g. zafirlukast or zileuton and liver enzyme/function monitoring). While accessible, feasible, and equitable, it may not be acceptable for some.

Summary of rationale: The panel inferred that most well-informed patients with CU would place a high value on the more certain benefits, harms and burdens of continuing with SGAH, their updosing, or advanced therapies (e.g. omalizumab, dupilumab, remibrutinib) over adding an antileukotriene to SGAH. The potential variable values and preferences and contextual factor considerations drove the conditional recommendation.

Implementation considerations: Shared-decision making, as with any conditional recommendation, is crucial to personalize recommendations to individual patient circumstances, values and preferences. The availability of antileukotriene(s) varies by region. The most common is montelukast, a leukotriene receptor antagonist, dosing varies by age. In the U.S., zileuton, a 5-LO inhibitor is also available. The available RCT evidence for antileukotrienes for urticaria mainly addresses montelukast (33 out of 34 RCTs; 1 RCT addressed zafirlukast) and no other antileukotriene (e.g. pranlukast). Antileukotrienes are used in combination with SGAH, not alone. When considering antileukotrienes, specifically consider neuropsychiatric history and risk, and counsel patients regarding signs, symptoms, and when to discontinue. As with other therapies that may compete with escalating to advanced therapies, address the good practice statement and consider investigations to predict response to advanced therapy. The supplement summarizes practical issues in a 1–2-page handout about how to use antileukotrienes.

Mechanism of action of antileukotrienes

Leukotrienes are lipid mediators and metabolites of arachidonic acid.[231] Allergic inflammation is commonly associated with increased levels of leukotriene C_4 (LTC_4). In chronic urticaria, LTC_4 is one of the mediators produced primarily by activated mast cells contributing to vasodilatation, itch, and activation of inflammatory cells (including mast cells). The class of antileukotriene medications have two different mechanisms of action: inhibition of 5-lipoxygenase (5-LO), an enzyme that is upstream of leukotriene synthesis such that production of LTC_4 plus other leukotrienes, is reduced or blockade of the $CysLT_1$ receptor, which is the primary receptor for LTC_4.

VITAMIN D

Question 9. Should patients with chronic urticaria add vitamin D supplementation vs not?

Recommendation 9. In patients with chronic urticaria refractory to 1x H1-antihistamine who are not already on vitamin D, the JTF panel suggests against adding high dose vitamin D supplementation (e.g. 4000 per day to 60,000 IU every 1-2 weeks) for the sole purpose of improving chronic urticaria rather than not adding supplementation (conditional recommendation, very low certainty evidence).

Conditions to consider:

- Some patients, especially in northern latitudes, may already be on vitamin D supplementation as either a stand-alone supplement or as part of a multivitamin.
- The 2021 United States Preventive Services Task Force, and many other organizations, recommend against screening for vitamin D deficiency in adults[232].

Benefits and harms: The systematic review and network meta-analysis (NMA) of advanced therapies (biologics [monoclonal antibodies], immunomodulators [e.g. remibrutinib], and immunosuppressants [e.g. cyclosporine, azathioprine, methotrexate], ultraviolet light therapy [phototherapy]) for CU[8], including supplements such as vitamin D, analyzed 11,135 participants and 83 RCTs. The median baseline urticaria activity (measured with UAS7, score range 0 to 42, higher scores indicate worse disease) was 30 (range of study means 14 to 39). Among these, three placebo-controlled RCTs addressed supplemental vitamin D for CU among adults, ranged from 6 to 12 weeks in duration, and studied very high dose vitamin D supplementation[8] (50,000 to 60,000 IU weekly, or every two weeks; some guidelines suggest the upper safe limit of vitamin D supplementation may be 10,000 IU per day, but are uncertain[232]). A blinded RCT published in 2014 compared 4000 IU per day versus 600 IU per day among adults with CU added to cetirizine (a more sedating SGAH, up to 4x dose), ranitidine (an H2RA, 150 mg twice per day), and montelukast (an antileukotriene, 10 mg once daily)[8, 233]. Improvements were reported within 4 to 8 weeks after adding supplementation.

The evidence (**Figure 9**) for add-on vitamin D supplementation proved very uncertain for a small, likely patient unimportant change in urticaria activity (very low certainty, MD -4.74 [95%CI -8.14 to -1.33]). The RCTs did not robustly address any other prioritized outcomes, including angioedema activity and adverse events.

Classic vitamin D toxicity occurs mainly with prolonged, uncontrolled use of very high doses and is characterized by hypercalciuria, hypercalcemia, and long-term complications such as renal and soft-tissue calcifications[232, 234-237]. Reported AEs are due to prescription errors, overuse of OTC supplements, and inappropriate use of megadoses for presumed extra-skeletal benefits. In contrast, vitamin D supplementation at guideline-recommended doses is generally safe. Current evidence supports a cautious, physiologic, and well-monitored approach to vitamin D supplementation, avoiding unnecessarily high target serum 25(OH)D levels and favoring conservative dosing strategies in clearly deficient populations.

Values and Preferences: The systematic review of values and preferences for CU treatment[9] and direct patient partner input found preference for rapid and sustained symptom control, less sedation and other

adverse effects, and oral and topical treatments. While over-the-counter supplemental oral vitamin D at doses of 4000 IU per day are less invasive compared to injections, their speed of action is uncertain (may take 4 to 8 weeks). Very high doses (e.g. 50,000 to 60,000 IU per week or every 2 weeks) may be administered as prescription medications by mouth or injection. While most patients might prefer therapies with more certain speed of action, others may prefer to use over the counter (natural) health supplements over prescription medicines. Thus, the panel inferred that there is possibly important variability in patient values and preferences regarding whether to add supplemental vitamin D or not.

Contextual factors: Supplemental vitamin D at 4000 IU per day is available, accessible, feasible, low resource (financial, time) costly, and equitable. It is likely acceptable for many. In contrast, very high dose prescription supplemental vitamin D (e.g. 50,000 to 60,000 IU per week or every two weeks) may be available and feasible but more resource costly, harder to access, and possibly less equitable.

Summary of rationale: The panel inferred that most well-informed patients would place a high value on the more certain benefits, including speed of action, harms and burdens of continuing with SGAH, their updosing, or advanced therapies (e.g. omalizumab, dupilumab, remibrutinib) over adding supplemental vitamin D, especially at very high doses and for those that are not already on supplements. The potential very low certainty for benefits, variable values and preferences, and contextual factor considerations drove the conditional recommendation.

Implementation considerations: Many patients have indications for vitamin D supplementation for reasons other than urticaria. The recommendation applies to changing or adding supplementation for the sole purpose of improving urticaria control. The safety of high dose supplemental vitamin D is uncertain and, if used, requires ongoing monitoring and time-limits. The supplement summarizes practical issues in a 1-2 page handout about how to use supplemental vitamin D.

	Urticaria Activity (Itch and Wheal Severity) UAS7 (0–42)	Percentage of Angioedema-Free Weeks	Urticaria QoL CU-Q$_2$OL (0–100)	Any Adverse Event§
	MD (95%CrI)	MD (95%CrI)	MD (95%CrI)	RD (95%CrI)
Baseline	29.70	72.62%	43.60	56%
Immunomodulators and Immunosuppressants				
Azathioprine	-8.07 (-16.14 to -0.01)			18% more (18% fewer to 37% more)
Colchicine			-2.39 (-13.19 to 8.40)	
Cyclosporine	-10.18 (-14.92 to -5.43)		-8.25 (-18.11 to 1.61)	21% more (3% more to 33% more)
Dapsone	-3.91 (-9.15 to 1.32)		-9.24 (-23.28 to 4.80)	32% more (7% fewer to 43% more)
Hydroxychloroquine	-5.98 (-12.01 to 0.04)		-12.14 (-25.00 to 0.71)	
Methotrexate			-4.03 (-15.92 to 7.85)	1% more (21% fewer to 21% more)
Mycophenolate*	-15.01 (-25.29 to -4.74)			36% fewer (48% fewer to 16% fewer)
Sulfasalazine*	-10.65 (-20.92 to -0.37)			20% fewer (32% fewer to 7% fewer)
Biologics				
Barzolvolimab	-7.18 (-11.29 to -3.07)			8% more (8% fewer to 22% more)
Benralizumab	-2.84 (-10.31 to 4.62)	-2.46% (-25.21% to 20.28%)	-0.28 (-11.20 to 10.64)	2% fewer (20% fewer to 15% more)
Canakinumab	0.02 (-10.40 to 10.43)		-2.78 (-22.21 to 16.65)	
Dupilumab	-6.01 (-10.57 to -1.46)		-9.73 (-21.51 to 2.05)	0% more (11% fewer to 10% more)
Ligelizumab	-6.68 (-9.60 to -3.76)	17.49% (13.06% to 21.91%)	-14.14 (-19.23 to -9.04)	4% more (3% fewer to 10% more)
Omalizumab (Low Dose)†	-5.25 (-7.83 to -2.68)	5.08% (-5.75% to 15.91%)	-8.23 (-12.84 to -3.62)	4% more (1% fewer to 8% more)
Omalizumab (Standard Dose)‡	-8.37 (-10.28 to -6.46)	8.75% (1.93% to 15.56%)	-12.68 (-15.85 to -9.52)	4% more (1% fewer to 8% more)
Quilizumab	-4.48 (-14.82 to 5.86)			
Tezepelumab	-2.00 (-8.29 to 4.28)	1.39% (-17.43% to 20.21%)	-4.69 (-14.32 to 4.94)	13% more (3% fewer to 25% more)
BTK Inhibitors				
Fenebrutinib	-5.75 (-12.06 to 0.57)			3% more (17% fewer to 20% more)
Remibrutinib	-7.65 (-11.75 to -3.54)	15.00% (3.16% to 26.84%)	-11.65 (-18.24 to -5.05)	3% more (6% fewer to 11% more)
Rilzabrutinib	-2.89 (-10.36 to 4.58)			12% more (6% fewer to 26% more)
Other Interventions				
Autologous Serum Therapy (Intramuscular)	-5.16 (-8.22 to -2.10)		-5.08 (-12.66 to 2.49)	
Autologous Serum Therapy (Subcutaneous)	-8.06 (-13.53 to -2.60)		-7.85 (-18.46 to 2.75)	
Autologous Whole Blood Therapy	-4.00 (-7.99 to -0.02)		-6.83 (-14.32 to 0.67)	
Narrowband UVB	-5.26 (-10.58 to 0.07)		-1.95 (-16.55 to 12.64)	
Vitamin D	-4.74 (-8.14 to -1.33)			

High or moderate certainty evidence	Low or very low certainty evidence
Among the most effective	May be among the most effective
Among the intermediate effective	May be among the intermediate effective
Possibly better than placebo	May be better than placebo
Not different from placebo	May not be different from placebo
Among the most harmful	May be among the most harmful

Figure 9. Summary of findings from systematic review and network meta-analysis (NMA) of advanced therapies (biologics [monoclonal antibodies], immunomodulators [e.g. remibrutinib], and immunosuppressants [e.g. cyclosporine, azathioprine, methotrexate], ultraviolet light therapy [phototherapy]) for chronic urticaria[8]. The GRADE approach informed certainty of evidence ratings. Interventions were categorized based on nonzero effect, with effectiveness categories representing magnitude of treatment effect and certainty ratings reflecting trustworthiness of evidence. Detailed categorizations of all 42 interventions are available in Online Repository. *Results for mycophenolate and sulfasalazine come from separate frequentist meta-analysis †Low-dose omalizumab refers to doses below 300 mg or administration less frequently than every 4 weeks (eg, 150 mg every 4 weeks, 75 mg single dose). ‡Standard-dose omalizumab is defined as 300 mg administered every 4 weeks. §Online Repository provides subset of commonly reported adverse events.

Mechanism of action of supplemental vitamin D

The role of vitamin D has been explored in relation to more than 100 outcomes in a wide range of diseases, including musculoskeletal, oncologic, cardiovascular, autoimmune, infectious, and metabolic disorders, as well as allergic/immunologic conditions – such as food allergy, rhinosinusitis, asthma, atopic dermatitis, and CU[238, 239]. Vitamin D has been hypothesized to have immunomodulatory and anti-inflammatory effects, including inhibition of histamine release via stabilization of mast cells and suppression of proinflammatory Th1 and Th17 immune responses [239, 240]. Vitamin D also has been reported to inhibit B-lymphocyte function leading to reduced IgE production, and can influence proliferation, survival, differentiation, and function of mast cells[239, 241]. Patients with CU have been reported to have low 25-OH Vitamin D levels compared to healthy controls. Although this does not prove causation, in a number of reports this finding has been interpreted as implying Vitamin D deficiency is associated with CU disease activity[239].

UV LIGHT THERAPY (PHOTOTHERAPY)

Question 10. Should patients with chronic urticaria add UV light therapy vs not?

Recommendation 10. In patients with chronic urticaria refractory to 1x H1-antihistamine, the JTF panel suggests updosing H1-antihistamines rather than adding narrow-band UV light therapy (conditional recommendation, very low certainty evidence).

Conditions to consider:

- Patients who prefer a different adverse effect profile, or to avoid immunosuppressant medications and their required monitoring (no blood monitoring in this instance), and who desire more rapid symptom relief may prefer NB-UVB over other treatments. For example, patients who are pregnant or planning to become pregnant may prefer NB-UVB.
- NB-UVB can be difficult to access, and hence, patients who must travel large distances, incur costs (eg, parking, gas, time), or face long wait times may prefer other treatments over NB-UVB.
- Conversely, exceptional circumstances that clinicians and patients might consider desirable include when accessing NB-UVB for the patient is highly convenient and cost-effective.
- NB-UVB can be used in pregnancy and lactation. It is less often used in children.
- Patients with photoresponsive comorbidities, such as atopic dermatitis (eczema), psoriasis or vitiligo, may prefer to use NB-UV-B to address more than one condition, compared with other treatments with efficacy only in CU.
- Conversely, patients who also have photosensitive conditions, photodermatoses, or risk factors or a history of skin cancer may prefer to not use phototherapy.

Remark: The panel did not formally develop recommendations for other forms of phototherapy (also known as light therapy), such as UV light A band (UV-A) alone or with psoralen (PUVA), as UV-A–based therapies are associated with more harms and have even lower certainty for benefits[8, 32, 242, 243].

Benefits and harms: The systematic review and network meta-analysis (NMA) of advanced therapies (biologics [monoclonal antibodies], immunomodulators [e.g. remibrutinib], and immunosuppressants [e.g. cyclosporine, azathioprine, methotrexate], ultraviolet light therapy [phototherapy]) for CU[8], including narrow-band ultraviolet B (NB-UVB, 311–313 nm wavelength range), analyzed 11,135 participants and 83 RCTs. Among these, three RCTs addressed NB-UVB for CU among adults and ranged

from 6 to 12 weeks in duration[8] at typical in-clinic NB-UVB protocols of 2-3 sessions per week added to SGAH.

The evidence (**Figure 9**) for add-on NB-UVB proved very uncertain for a small, possibly patient unimportant improvement in urticaria activity (very low certainty, MD -5.26 [95%CI -10.58 to 0.07]) and urticaria-related QoL (very low certainty, MD -1.95 [95%CI -16.55 to 12.64] on DLQI [0 to 30 with higher being worse]). Similarly, the panel's expert evidence suggested with very low certainty that 25% to 40% of patients with CU undergoing NB-UVB therapy achieve an important improvement, and only rarely achieve complete control. The RCTs did not robustly address any other prioritized outcomes, including adverse events. NB-UVB's safety is better established for atopic dermatitis[32, 242]: A 10-year cohort study in Korea including 60,321 patients with vitiligo found no increased risk of nonmelanoma or melanoma skin cancer, stratified by number of sessions (from <50 to >500). An analysis of a Scottish cancer registry of 3,867 patients made the same conclusion. The cohort study from Korea addressing vitiligo, however, found an increased risk of actinic keratosis for patients who had undergone more than 200 sessions (HR, 2.27 [95% CI, 1.53-3.37]). A common adverse event is erythema. Clinical experts remarked that long-term UV-B exposure might induce darkening of the skin and that this may, or may not, be desirable for patients.

Values and Preferences: The systematic review of patient values and preferences[9] and direct patient and caregiver input showed that most patients prioritize rapid and sustained symptom control over minor burden or harms. With NB-UVB requiring 2-3 clinic visits weekly for several weeks, the burdens are high and the panel therefore inferred undesirable for many. Some patients, however, may prefer to avoid medications, or have multiple photo-responsive conditions, and therefore have strong preference for phototherapy. The panel therefore inferred that there is possibly important variability in patient values and preferences when considering add-on NB-UVB.

Contextual factors: NB-UVB's requirement for 2-3 visits each week to the few specialized facilities (e.g. hospital or urban clinics) with well-maintained NB-UVB units and trained staff with clear standard operating procedures imply, for almost all patients, a large trade-off in burdens and resources, both financial and time, for uncertain benefit. Patients may find transportation and having to undress and re-dress for phototherapy unacceptable. Clinical experts remarked patients often must bear a co-pay if accessing NB-UVB. While possibly available, acceptability, accessibility, feasibility, and equity are all factors that favor against NB-UVB for CU.

Summary of rationale: The panel inferred that most well-informed patients would place a high value on the more certain and larger benefits and smaller harms and burdens of continuing with SGAH, their updosing, or advanced therapies (e.g. omalizumab, dupilumab, remibrutinib) over adding NB-UVB. The potential very low certainty for NB-UVB's benefits, variable values and preferences, and contextual factor considerations drove the conditional recommendation.

Implementation considerations: The supplement summarizes practical issues in a 1-2 page handout about how to use NB-UVB light therapy (phototherapy). Although NB-UV-B is also available using home devices, they lack robust evidence addressing their efficacy and safety, and comparability with clinic-based NB-UV-B, including for treating CU.

Mechanism of action of NB-UVB

NB-UVB phototherapy is an effective treatment for various inflammatory skin conditions, primarily through its anti-inflammatory and immunosuppressive effects. It induces apoptosis in activated T-Lymphocytes and dendritic cells, reducing immune proliferation and activation in the skin. It also modulates dendritic cell function, leading to reduced antigen presentation and a shift towards immune tolerance[244]. In chronic urticaria, additional proposed disease-relevant mechanisms include increasing the threshold for mast-cell degranulation, suppressing stimulated histamine and other inflammatory mediator release, and possibly reducing dermal mast-cell burden[245].

ORAL AND SYSTEMIC CORTICOSTEROIDS (GLUCOCORTICOIDS)

Question 11. Should patients with chronic urticaria add oral corticosteroids as maintenance vs not?

Recommendation 11. In patients with H1-antihistamine refractory chronic urticaria, the JTF panel recommends against adding oral corticosteroids (glucocorticoids) as maintenance for chronic urticaria (strong recommendation, low certainty evidence).

Benefits and harms: The linked systematic review and meta-analysis of systemic corticosteroids (glucocorticoids, e.g. prednisone) for flares (exacerbations) of urticaria[7] meta-analyzed 12 RCTs addressing 944 children and adults and found similar effects in either AU (8 RCTs) or CU (4 RCTs). Most (10 of 12) RCTs added systemic steroids to H1-antihistamines. The RCTs addressing maintenance therapy for CU administered systemic corticosteroids for between 7 days and 7 weeks. Risk of bias among almost all studies led to rating down the certainty of the body of evidence for benefits.

Compared to continuing SGAH alone, adding systemic corticosteroids likely improves urticaria activity (moderate certainty, OR 2.17 [95%CI 1.43 to 3.31]; 84% improving with systemic steroids vs 70% without for a NNT of 7), may improve itch (low certainty, OR 2.44 [95%CI 0.87 to 6.83]; 93% vs 84% for a NNT of 11). The RCTs did not address other prioritized patient important urticaria outcomes including angioedema and quality of life.

In terms of harms, adding systemic corticosteroids as maintenance therapy for CU likely leads to large increases in their known toxicities (moderate certainty, OR 2.76 [95%CI 1.00 to 7.62]; 26% vs 11% experience an adverse reaction for an NNH of 7). For multiple indications, repeated cycles of short-term (<7 days) systemic corticosteroids and long-term systemic corticosteroid use cause a range of common and serious harms[246-251] including fragility fractures secondary to osteoporosis, bone avascular necrosis, heart attack/stroke, diabetes, pneumonia, weight gain and obesity, glaucoma and cataract formation, and neuropsychiatric changes, among others, and, upon discontinuation, secondary adrenal insufficiency and life-threatening adrenal crisis.

Values and Preferences: The systematic review of values and preferences for CU treatments[9] and direct patient and caregiver input showed that, across treatment options, patients are likely to place high value on rapid and sustained relief of hives, itch, and swelling, and for that, are willing to bear mild and short-term adverse effects or burdens. Patients prioritize, however, safety as the risk or severity of adverse effects increase. For systemic corticosteroids, the panel inferred that most patients prefer avoiding the well-recognized multiple frequent harms and serious adverse events associated with chronic systemic

corticosteroid use. Overall, the panel inferred that there is probably no important uncertainty or variability in patient values and preferences.

Contextual factors: Systemic corticosteroids are low-cost medicines, that, given their wide range of harms, may consequently increase resource utilization for patients, clinicians, and health systems. While feasible and accessible, they are probably not acceptable in most scenarios.

Summary of rationale: The panel inferred that all or almost all well-informed patients would place a high value on avoiding the certain frequent and potentially serious harms associated with systemic corticosteroids as a long-term strategy to control urticaria over its moderate certainty for moderate improvement in urticaria activity and uncertainty for improvement in other patient-important outcomes. The large harms associated with chronic systemic corticosteroids, and patient preference and contextual factors against their use, drove the strong recommendation.

Implementation considerations: Most systemic steroids are available as oral forms (e.g. prednisone). Alternative forms include injections that vary in duration of action (e.g. dexamethasone, triamcinolone). The supplement summarizes practical issues in a 1-2 page handout about how to use oral and systemic corticosteroids. See below about the potential rare scenario where, for a patient with a defined start date of an advanced therapy, systemic steroids might be considered through shared decision-making as a short (ideally less than 2 weeks) bridge to advanced therapy. See the advanced therapies and cyclosporine sections for long-term management strategies, including potential longer bridge therapies.

ACUTE EXACERBATIONS OF CHRONIC URTICARIA (FLARES)

As described in the Introduction, factors associated with an acute increase in urticaria activity over its basal waxing and waning disease activity include [systemic] NSAID use, stress, sleep deprivation, hormonal changes, and infection. For instance, patients, such as those with typically only mild hives in CSU, may experience marked periocular angioedema impairing vision, tongue swelling, and generalized hives prompting urgent or emergent presentation.

Question 12. In people with an acute exacerbation of chronic urticaria, should they use a short course of oral corticosteroids vs not?

Recommendation 12a. In patients with chronic urticaria who experience an acute flare and who are receiving either no H1-antihistamines or only a single licensed H1-antihistamine dose, the JTF panel suggests against adding a short course of systemic corticosteroids (glucocorticoids) (conditional recommendation, moderate certainty evidence).

Conditions to consider:

- Favoring against corticosteroids - If patient has tried little to no H1-antihistamines, use a SGAH and recommend updosing up to 4x dosing as per the recommendations above.

Note: If systemic corticosteroids are nevertheless used despite this recommendation, they should have a defined stop date and arrange urgent CU specialist follow-up. Preferred management, however, is to initiate and/or optimize SGAH, provide an action plan, and arrange urgent CU specialist follow-up.

Benefits and harms: The linked systematic review and meta-analysis of systemic corticosteroids (e.g. prednisone) for flares (exacerbations) of urticaria[7] including 12 RCTs addressing 944 children and adults

found that among patients who have not yet tried H1-antihistamines, compared to continuing SGAH alone, adding systemic corticosteroids likely improves urticaria activity (moderate certainty, OR 2.17 [95%CI 1.43 to 3.31]; 98% improving with systemic steroids vs 96% without for a NNT of 45).

In terms of harms, adding systemic corticosteroids likely leads to large increases in their known toxicities (moderate certainty, OR 2.76 [95%CI 1.00 to 7.62]; 26% vs 11% experience an adverse reaction for an NNH of 7). Common adverse events in patients with AD using systemic corticosteroids include mood change, rebound flares shortly after drug discontinuation, gastrointestinal adverse reactions (e.g. dyspepsia, gastric irritation), weight gain, insomnia, adrenal insufficiency, and growth impairment[246, 247, 251]. Less than 30 days of oral corticosteroids, for any indication, is associated with sepsis (IRR, 5.3 [95% CI, 3.80-7.41]; 5 vs 1 per 1000), venous thromboembolism (IRR, 3.33 [2.78-3.99]; 8 vs 2 per 1000), and fracture (1.87 [1.69-2.07]; 27 vs 14 per 1000).[246] For multiple indications, repeated cycles of short-term (<7 days) systemic corticosteroids cumulatively promote a range of common and serious harms[246-251].

Values and Preferences: Similar to those addressed in Recommendation 12, the systematic review of values and preferences for CU treatments[9] and direct patient and caregiver input led the panel to infer that most patients with an acute exacerbation that is likely H1-antihistamine responsive will prefer to established efficacy and safety of SGAH over the moderate and uncertain benefits and established harms associated with systemic corticosteroids. Overall, the panel inferred that there may be important uncertainty or variability in patient values and preferences.

Contextual factors: The contextual factor considerations remain similar to those summarized in Recommendation 12.

Summary of rationale: The panel inferred that most well-informed patients with an acute exacerbation of urticaria that are potentially responsive to H1-antihistamines would place a high value on the certain benefits and safety of SGAH, including updosing them, over the certain frequent and less common serious harms associated with systemic corticosteroids, and its uncertain moderate benefits. The close balance between benefits and harms, uncertainty, and variability in patient values and preferences drove the conditional recommendation.

Implementation considerations: The implementation considerations for H1-antihistamines and systemic corticosteroids are addressed earlier and in their corresponding sections in the eAppendix. If a patient has tried only the licensed once daily dose of H1-antihistamine, they should, aligning with the recommendations above, trial updosing SGAH. Part of the motivation that may lead clinicians to prescribe systemic corticosteroids even in mild cases that are likely H1-antihistamine responsive may be to reduce the potential for repeat health care utilization (e.g. repeat urgent clinic visit or ER visit). Similar to the approach to delayed prescriptions of antibiotics for acute otitis media, or other conditions, one option for clinicians seeing patients in urgent or emergent care that are likely to respond to antihistamines, is, if there is sufficient concern that the patient might not respond to antihistamines, to provide a delayed prescription for oral corticosteroids that can be filled if necessary. Further, rapid referral to urticaria specialists can also lead to definitive long-term management plans and may obviate the need for patients to fill such prescriptions. Together, these steps may facilitate achieving the overarching goal of safe and sustained urticaria control.

In terms of minimizing short- and long-term harms, Clinicians prescribing systemic corticosteroids should, before prescribing a new round, evaluate the patient to understand their lifetime cumulative corticosteroid exposure.

Recommendation 12b. In patients with chronic urticaria and an acute flare with a low to moderate chance to improve (e.g., are already H1-antihistamine refractory) with updosed H1-antihistamines alone, the JTF panel suggests adding a short (e.g. <7 days) course of systemic corticosteroids (glucocorticoids) rather than continuing updosed H1-antihistamines alone (conditional recommendation, moderate certainty evidence).

Conditions to consider:

- If used, have a defined stop date. Either way, rapid referral to a CU specialist and plan for next steps and long-term management is essential.

Benefits and harms: The linked systematic review and meta-analysis of systemic corticosteroids (glucocorticoids, e.g. prednisone) for flares (exacerbations) of urticaria[7] including 12 RCTs addressing 944 children and adults and found similar effects in either AU (8 RCTs) or CU (4 RCTs). The RCTs addressing a short course (also called pulse or burst) of systemic corticosteroids for acute exacerbations of urticaria administered systemic corticosteroids for between 3 to 7 days or as a single long-acting corticosteroid such as dexamethasone. Risk of bias among almost all studies led to rating down the certainty of the body of evidence for benefits.

Among patients who have already tried H1-antihistamines to address acute exacerbations of urticaria, compared to continuing H1-antihistamines alone, adding systemic corticosteroids likely improves urticaria activity (moderate certainty, OR 2.17 [95%CI 1.43 to 3.31]; 32% improving with systemic steroids vs 18% without for a NNT of 7), may improve itch (low certainty, OR 2.44 [95%CI 0.87 to 6.83]; 93% vs 84% for a NNT of 11). The RCTs did not address other prioritized patient important urticaria outcomes including angioedema and quality of life.

The harms remained the same for short-course steroids as summarized in Recommendation 12 above. [246, 247, 251]

Values and Preferences: The systematic review of values and preferences for CU treatments[9] and direct patient and caregiver input showed that, across treatment options, patients are likely to place high value on rapid and sustained relief of hives, itch, and swelling, and for that, are willing to bear mild and short-term adverse effects or burdens. Patients prioritize, however, safety as the risk or severity of adverse effects increase. For systemic corticosteroids, the panel inferred that most patients with an acute exacerbation that is H1-antihistamine refractory will be aware of few treatment options to rapidly address their urticaria and will commonly present for urgent or emergent care, and, at that time, may be willing to accept a moderate improvement in disease activity over the well-recognized multiple frequent harms and less common serious adverse events associated with short-course systemic corticosteroid use. Overall, the panel inferred that there may be important uncertainty or variability in patient values and preferences.

Contextual factors: Systemic corticosteroids are low-cost medicines, whose recognized harms that may increase resource utilization for patients, clinicians, and health systems may also be counterbalanced by a decrease in resource utilization with rapid, albeit potentially transient in some, control (e.g. reduced change of re-presentation to emergency room for continued flare). They are feasible and accessible, and may be acceptable in flaring patients who are H1-antihistamine-refractory.

Summary of rationale: The panel inferred that most well-informed patients with an acute exacerbation of urticaria refractory to H1-antihistamines would place a high value on its possible benefits over avoiding the certain frequent and less common serious harms associated with systemic corticosteroids. The close balance between benefits and harms, uncertainty, and variability in patient values and preferences drove the conditional recommendation.

Implementation considerations: Clinical experts reported that they often see patients undergoing repeated cycles of systemic corticosteroids rather than accessing safer and more effective long-term CU control strategies. Thus, any prescription or use of systemic corticosteroids should be time-limited and prompt rapid referral to an urticaria expert to enable optimal long-term management. The supplement summarizes practical issues in a 1-2 page handout about how to use oral and systemic corticosteroids.

Mechanism of action of systemic corticosteroids

As described in the mechanism of topical steroids section, systemic corticosteroids exert their therapeutic effects via multiple mechanisms involving both genomic and non-genomic pathways, including its effects on mast cells (stabilization, suppression of degranulation, and promotion of apoptosis), reduction of cellular infiltrates, inhibition of inflammatory mediator release, and vasoconstriction.

STEP 3. CHRONIC URTICARIA ADVANCED 1 – First-line treatments for chronic urticaria uncontrolled with a H1-antihistamine

As shown above, about 30 to 40% of individuals will be refractory to standard management with H1-antihistamines, and there is diminishing improvement beyond a single, and especially, 2x, dose. Despite insurers frequently requiring refractoriness to 4x dosing, and for variable and arbitrary intervals, to be eligible for advanced therapy almost all clinical trials of first-line advanced agents (e.g. omalizumab, dupilumab, remibrutinib) enrolled patients (i.e. they were eligible to participate) if they were refractory to only 1x dose of H1-antihistamine[8] ("standard-dose", e.g. Omalizumab phase 3 trial [Q4882g]; LIBERTY-CSU CUPID A enrolled 60% of participants refractory to 1x dose[252]). A notable exception is an omalizumab clinical trial addressing patients specifically refractory to 4x dosing and yielded findings similar to other omalizumab trials enrolling patients refractory to 1x dosing[253].

In the following "steps" or "lines" of treatment, patients do not necessarily have to exhaust all possible treatments in one "Step" or "line" of therapy to advance to the next "step" (e.g. advanced step 1, advanced step 2, etc.) or "line" (e.g. first-line, second-line, etc.). Advanced therapies are those required to maintain optimal CU control among patients refractory, intolerant, or unable to use a SGAH.

OMALIZUMAB

Question 13. Should patients with chronic urticaria refractory to H1-antihistamines add omalizumab?

Recommendation 13. In patients with chronic urticaria refractory to a H1-antihistamine, the JTF panel recommends adding, rather than not adding, omalizumab (strong recommendation, moderate certainty evidence).

Benefits and harms: The systematic review and network meta-analysis (NMA) of advanced therapies (biologics [monoclonal antibodies], immunomodulators [e.g. remibrutinib], and immunosuppressants [e.g. cyclosporine, azathioprine, methotrexate], ultraviolet light therapy [phototherapy]) for CU[8], including omalizumab (e.g. Xolair, Omlyclo biosimilar), analyzed 11,135 participants and 83 RCTs. Among these, 24 RCTs addressed omalizumab[8] added to SGAH for 4 to 52 weeks.

The evidence (**Figure 9**) for add-on standard dose omalizumab (i.e. 300 mg subcutaneously every 4 weeks) showed high certainty for a large improvement in urticaria activity (MD -8.37 [95%CI -10.28 to -6.46] on UAS7; 73% vs 43% improving) and in urticaria-related QoL (MD -12.68 [95%CI -15.86 to -9.52] on DLQI). Moderate certainty evidence showed improved angioedema free weeks (81% vs 73% of weeks) and little to no difference in overall adverse events (60% vs 56% reporting an AE, most commonly local injection site reactions). Adding low-dose omalizumab (e.g. less than 300 mg dosing, such as 150 mg, or less frequent than every 4 weeks) led to benefits intermediate between standard dose omalizumab and placebo with similar safety to standard dose omalizumab (**Figure 9**). Most patients will see a response within 2-6 weeks (i.e. after the 1st or 2nd injection). A smaller proportion of individuals may be slow responders that take between 3-6 months to respond.

Values and Preferences: The systematic review informing values and preferences for CU treatments[9] and direct patient and caregiver partner input showed that, across treatment options, patients are likely to place high value on rapid and sustained relief of hives, itch, and swelling over mild and short-term adverse effects or burdens, including effective injection therapies and the rare and uncertain association with more severe adverse effects (e.g. rare and uncertain association with anaphylaxis upon administration) when H1-antihistamines are not sufficient to achieve urticaria control. Overall, the panel inferred that there is probably no important uncertainty or variability in patient values and preferences.

Contextual factors: Omalizumab drug costs are substantial (**Table 8**). Biosimilars, available in Canada and other world regions and set to become available in the US in late 2026, possibly September, are sold at an approximate 30% to 40% lower price. Mitigating such direct costs may be a reduction in indirect costs (lost productivity, work/school absenteeism, urgent/emergent care visits). Such financial and time savings to the patient may be enhanced with most pursuing self-administration with autoinjector pens or pre-filled syringes and may be reduced if required for in-clinic (physician or injection clinic) visits for administration. Patient support programs may also facilitate cost reduction and access.

Summary of rationale: The panel inferred that most well-informed patients with moderate to severe H1-antihistamine-refractory CU would place a high value on the certain benefits and safety of adding standard-dose omalizumab over not adding it. The large benefits and little to no harms, certainty, and patient values and preferences and contextual factors favoring omalizumab drove the strong recommendation.

Implementation considerations: Omalizumab 300 mg subcutaneously every 4 weeks is superior to 150 mg subcutaneously every 4 weeks and all or almost all patients should start with 300 mg subcutaneously every 4 weeks. Dosing is approved for adults and adolescents aged 12 years or older, and dosing seems similar for children less than 12 years of age[254], with well-established safety for such age groups using omalizumab for urticaria as well as conditions other than urticaria (e.g. food allergy, asthma)[140, 255]. Patients who are overall well-controlled but have an important flare at week 3 or 4 of their 4-week dosing interval could consider switching to omalizumab subcutaneously 150 mg every 2 weeks, if they value the marginal increase in control compared to the increase in injections. While omalizumab may be

preferred first-line advanced therapy for almost all patients at this step, clinicians should consider comorbidity and possible predictive markers in decision making.

Various techniques can be used to assist individuals who have a fear of injections, such talking through the procedure, and distraction or the use of a vibrating device (e.g. Buzzy bee, if patient does not have severe vibratory inducible urticaria).

Though benefits can be seen within 1-2 weeks, treatment response may take 3-4 months. The supplement summarizes practical issues in a 1-2 page handout about how to use omalizumab (e.g. Xolair, Omyclo biosimilar).

Many patients who still require omalizumab for CU control can maintain control with longer intervals. In addition, since CSU is not a permanent disease, many patients can be tapered off therapy. When patients sustain control for 3 dose intervals, or 3 months, whichever is longer, taper omalizumab by gradually increasing the interval between injections (e.g. q4w to q5, to q6w, to q8w, q8w to stopping), decreasing dose (e.g. from 300 mg to 150 mg), or both. Interval changes are the simplest. As there is no robust evidence for optimal dose interval extension, however, regimens may vary[21, 256, 257].

Mechanism of action of omalizumab

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that binds circulating free IgE, preventing IgE from binding FcεRI and reducing free IgE levels. Reduced free IgE leads to downregulation of FcεRI expression on mast cells and basophils and can decrease the likelihood and intensity of mast-cell/basophil activation and mediator release.

DUPILUMAB

Question 14. Should patients with chronic urticaria refractory to H1-antihistamines add dupilumab?

Recommendation 14. In patients with chronic urticaria refractory to a H1-antihistamine, the JTF panel suggests adding, rather than not adding, dupilumab (conditional recommendation, low certainty evidence).

Conditions to consider:

- Favoring against – Patients with mast cell-mediated angioedema, or cold urticaria[258], as an important component to their CU. Patients who prefer a faster onset of action (dupilumab's gradual onset over approximately 6-12 weeks) and possibly larger treatment effect with other medications (e.g. omalizumab, remibrutinib). Patients with active inflammatory arthritis may prefer to avoid the rare and uncertain association with dupilumab and arthritis/arthralgias. Patients who place a greater value on the extensive data supporting safe use of omalizumab during pregnancy and lactation over the existing and reassuring, but relatively smaller body of evidence, for safety of dupilumab in pregnancy and lactation.
- Favoring for – Patients with CU who have comorbidities that also respond to dupilumab, such as atopic dermatitis (eczema), prurigo nodularis, bullous pemphigoid, eosinophilic asthma and/or chronic obstructive pulmonary disease (COPD), chronic rhinosinusitis (e.g. with nasal polyps; allergic fungal rhinosinusitis [AFRS][259]), and eosinophilic esophagitis (EoE).

Benefits and harms: The systematic review and network meta-analysis (NMA) of advanced therapies (biologics [monoclonal antibodies], immunomodulators [e.g. remibrutinib], and immunosuppressants [e.g. cyclosporine, azathioprine, methotrexate], ultraviolet light therapy [phototherapy]) for CU[8], including omalizumab (e.g. Xolair, Omlyclo biosimilar), analyzed 11,135 participants and 83 RCTs. Among these, 3 RCTs (n=397 participants; LIBERTY CUPID study A, B, and C) addressed dupilumab[8] added to SGAH for 24 weeks.

The evidence (**Figure 9**) for add-on dupilumab showed moderate certainty for an important improvement in urticaria activity (MD -6.01 [95%CI -10.57 to -1.46] on UAS7; 65% vs 43% improving), and low certainty for a possible improvement in urticaria-related QoL (MD -9.73 [95%CI -21.51 to 2.05] on DLQI). Response was typically seen between 4 and 12 weeks, increasing to a possible plateau at 6 months (the longest duration of continuous treatment in the trials). Low certainty evidence showed no important improvement in angioedema free weeks (MD 2.32 [95%CI -6.95 to 11.58]; and similar inference for incidence of angioedema). Moderate certainty evidence showed little to no difference in overall adverse events (56% vs 56% reporting an AE, most commonly injection site reactions). A small RCT addressing patients with typical cold urticaria (n=82) despite regular/daily use of a H1-antihistamine showed no important differences between dupilumab and placebo treatment groups on multiple indices of urticaria outcomes at 24 weeks, albeit the trial's about 25% dropout rate in both groups led to high risk of bias towards null effects[258].

Values and Preferences: The evidence for patient values and preferences for dupilumab was similar to that for omalizumab (recommendation 14)[9]. While sustained in effect, the panel inferred that some patients may place large preference on rapid resolution of hives (e.g. preference for resolution within 2 days to 2 weeks rather than 3 months or longer[9]) whereas dupilumab's benefits slowly increase over its studied treatment duration. The panel inferred, however, that patients with severe refractory urticaria will prioritize sustained symptom resolution and that a duration of 6-12 weeks will still be acceptable to all or almost all, and that there is probably no important uncertainty or variability in patient values and preferences.

Contextual factors: The contextual factors for dupilumab are similar to those of omalizumab (**Table 8**), except there is no current dupilumab biosimilar and therefore drug costs are higher.

Summary of rationale: The panel inferred that most well-informed patients with moderate to severe H1-antihistamine-refractory CU would place a high value on the certain benefits and safety of adding dupilumab over not adding it. The moderate benefits and little to no harms, and uncertainty including low certainty in the quality of life and angioedema, and contextual factors drove the conditional recommendation.

Implementation considerations: While dupilumab may be an option for a first-line advanced therapy (approved age 2 years or above), clinical experts remarked that most patients will likely start with omalizumab. Though the panel did not issue a formal recommendation comparing omalizumab vs dupilumab at this stage, a much greater body of evidence supports omalizumab for urticaria and its effect sizes proved larger for almost all benefit outcomes. Clinicians should consider comorbidity and possible predictive markers in decision making. Many implementation considerations for dupilumab are similar to omalizumab. The supplement summarizes practical issues in a 1-2 page handout about how to use dupilumab.

Mechanism of action of dupilumab

Dupilumab acts in CSU by blocking the IL-4 and IL-13 signaling pathways via the IL-4R alpha common chain. This acts to inhibit type 2 inflammation by reducing IgE production and decreasing FceR1 expression on mast cells and basophils, resulting in decreased activation and bioactive mediator release.

ORAL BTK INHIBITORS – REMIBRUTINIB

Question 15. Should patients with chronic urticaria refractory to H1-antihistamines add remibrutinib?

Recommendation 15. In patients with chronic urticaria refractory to a H1-antihistamine, the JTF panel suggests adding, rather than not adding, remibrutinib (conditional recommendation, low certainty evidence).

Remarks: Remibrutinib is currently indicated only for adult patients. Ongoing trials will address adolescents (NCT05677451). Remibrutinib is also being investigated to treat multiple sclerosis, Sjogren's syndrome, myasthenia gravis, peanut allergy[260] (NCT05432388), and hidradenitis suppurativa. The pharmaceutical company terminated a study addressing asthma (NCT03944707). Other BTK inhibitors, such as rilzabrutinib are being investigated for chronic urticaria, and remibrutinib and acalabrutinib, for example, are being studied to address anaphylaxis[261-263].

Conditions to consider:

- Favoring against – Adult patients who prefer avoiding a daily oral medication for sustained control, or who prefer greater certainty in safety and/or different adverse effect profiles associated with omalizumab or dupilumab. Patients who are pregnant or breastfeeding will prefer omalizumab or dupilumab (see corresponding sections for considerations).
- Favoring for – Adult patients who prefer oral medications over uncertain harms, especially long-term, or who prefer rapid acting medications, and for whom cost is not a dominant issue.

Benefits and harms: The systematic review and network meta-analysis (NMA) of advanced therapies (biologics [monoclonal antibodies], immunomodulators [e.g. remibrutinib], and immunosuppressants [e.g. cyclosporine, azathioprine, methotrexate], ultraviolet light therapy [phototherapy]) for CU[8], including omalizumab (e.g. Xolair, Omlyclo biosimilar), analyzed 11,135 participants and 83 RCTs. Among these, 3 RCTs (n=1236 adults) addressed remibrutinib[8] added to SGAH for 12 weeks. Response is typically seen in 2-4 weeks, some as soon as the first week, and the proportion responding increases to a plateau around 3-4 months.

The evidence (**Figure 9**) for add-on remibrutinib showed moderate certainty for a large improvement in urticaria activity (MD -7.65 [95%CI -11.75 to -3.54] on UAS7; 71% vs 43% improving), urticaria-related QoL (MD -11.65 [95%CI -18.24 to -5.05] on DLQI) and angioedema free weeks (88% vs 73%]). Low certainty evidence showed little to no difference in overall adverse events (56% vs 56% reporting an AE, most commonly URTIs [RD 5%, NNH 20], UTI [RD 2%, NNH 50], petechiae and bleeding [RD 2%, NNH 50]). Among the RCTs and placebo-controlled comparative short (12-24 weeks) follow-up time, no BTK inhibitor-associated cardiovascular events (e.g. atrial fibrillation, stroke) were detected and therefore the evidence for long-term safety is very uncertain at this time. The unblinded non-comparative findings to 52 weeks, while reassuring, provide overall low certainty for no important increase in harm[264, 265].

Values and Preferences: The evidence for patient values and preferences for remibrutinib was similar to that for omalizumab and dupilumab (recommendations 14 and 15)[9]. While patients considered minor bleeding events included in the minor harms previously considered, they preferred to avoid severe bleeding or serious cardiovascular events. The panel inferred that there is probably no important uncertainty or variability in patient values and preferences.

Contextual factors: The contextual factors for remibrutinib are similar to those of omalizumab (**Table 8**), except there is no current remibrutinib generic drug and therefore drug costs are higher.

Summary of rationale: The panel inferred that most well-informed patients with moderate to severe H1-antihistamine-refractory CU would place a high value on the certain benefits and low certainty for safety of adding remibrutinib over not adding it. The large benefits balanced by low certainty for an increase in harms, and contextual factors drove the conditional recommendation.

Implementation considerations: While remibrutinib may be an option for a first-line advanced therapy, clinical experts remarked most patients will likely start with omalizumab. Though the panel did not issue a formal recommendation comparing omalizumab vs remibrutinib at this stage, a much greater body of evidence supports omalizumab for urticaria and its effect sizes proved larger for almost all benefit outcomes. Rembrutinib's FDA product insert suggests avoiding live vaccines in patients on BTK inhibitors. Though not formally studied in an RCT, analogous to the growing sentiment in atopic dermatitis for oral JAK inhibitors[32], on-demand use of remibrutinib might be considered for special situations (e.g. severe flare, critical event such as a wedding) or to replace or minimize short-course oral corticosteroids. Consider comorbidity and possible predictive markers in decision making. The supplement summarizes practical issues in a 1-2 page handout about how to use remibrutinib.

Mechanism of action of BTK inhibitor (e.g. remibrutinib)

BTK inhibitors suppress mast cells and basophils FceRI pathway rapidly as well as suppress B cell autoantibody production in autoimmune disorders.

First in class for B cell malignancies, where the BTK inhibitors were first developed, was ibrutinib. Many subsequent versions.

CALCINEURIN INHIBITORS – CYCLOSPORINE (Cyclosporin, ciclosporin) and TACROLIMUS

Question 16. Should patients with chronic urticaria refractory to H1-antihistamines add cyclosporine?

Recommendation 16. In patients with chronic urticaria refractory only to a H1-antihistamine, the JTF panel suggests adding one of the first-line advanced systemic treatments (omalizumab, dupilumab, remibrutinib) rather than adding a calcineurin inhibitor (conditional recommendation, low certainty evidence).

Conditions to consider:

- Favoring against – Patients who prefer medications with greater certainty for benefits and safety, and with far less associated harms (e.g. omalizumab, dupilumab, and possibly remibrutinib). Cyclosporine is even more unfavorable in patients with comorbidities such as chronic kidney disease, hypertension, cardiovascular disease, malignancy. Patients with risk factors or

comorbidities for harms from cyclosporine (eg, cardiovascular risk factors, difficult to control hypertension, renal dysfunction), or who place a high value on avoiding possible hypertrichosis or gum hypertrophy may place a greater value on avoiding these potential harms compared with cyclosporine's probable benefits.

- Favoring for – Patients who strongly prefer low-cost oral cyclosporine over certain harms and burdens (including monitoring by both the patient and clinician), both short- and long-term, who prefer rapid acting medications.
- Cyclosporine for CU has conventionally been administered at low (1-3 mg/kg per day) doses rather than the high doses (4-5 mg/kg per day) seen in other inflammatory diseases. Whether to start at a low dose and titrate up to effect, or to start at a high dose and titrate down, depends on multiple factors, including the patient's disease severity at the time and the patient's desired rapidity of effect balanced by the increased risk of harm with higher doses. Patients should be on the lowest dose possible that achieves patient-important benefit and minimizes harms.
- Exceptional circumstances that clinicians and patients might consider desirable when rapid control of H1-antihistamine-refractory CU is required if there are delays or challenges in accessing preferred first-line therapies (e.g. omalizumab):
    - As a brief duration bridge (preferred over systemic corticosteroids) to one of the preferred systemic therapies.
    - Rare use for a severe flare or for special social circumstances (e.g., before a major life event).

Benefits and harms: The systematic review and network meta-analysis (NMA) of advanced therapies (biologics [monoclonal antibodies], immunomodulators [e.g. cyclosporine], and immunosuppressants [e.g. cyclosporine, azathioprine, methotrexate], ultraviolet light therapy [phototherapy]) for CU[8], including omalizumab (e.g. Xolair, Omlyclo biosimilar), analyzed 11,135 participants and 83 RCTs. Among these, 6 RCTs (n=329) addressed cyclosporine[8] added to SGAH for 4 to 16 weeks. Response is typically seen within days to weeks.

The evidence (**Figure 9**) for add-on cyclosporine showed low certainty for a large improvement in urticaria activity (MD -10.18 [95%CI -14.92 to -5.43] on UAS7) and a possible important improvement in urticaria-related QoL (MD -8.25 [95%CI -18.11 to 1.61] on DLQI). The studies did not address angioedema activity. Consistent with the evidence for harms of cyclosporine for AD[32] and psoriasis[266], moderate certainty evidence showed cyclosporine results in a large increase in adverse events (77% vs 56% reporting an AE, most commonly paresthesia [RD 18%, NNH 6], abdominal pain [RD 10%, NNH 10], hypertension [RD 4%, NNH 25]). Other commonly associated harms include hypertrichosis, gum injury, and kidney injury (typically reversible). Among the RCTs and short (16 weeks) follow up time, no cancers associated with long-term cyclosporine use for solid organ transplant were detected and therefore the evidence for long-term safety is very uncertain. A single RCT in adult patients receiving a renal transplant reported dose-dependent increase in cancer risk, starting at 2 years, and increasing in 7 years.

Values and Preferences: The evidence for patient values and preferences for cyclosporine was similar to that for omalizumab and dupilumab (recommendations 14 and 15)[9]. In addition, the review showed that on average, patients were willing to accept a 4.5 percentage point (pp) increase in kidney dysfunction for a 10 pp increase in CU control outcomes[9]. Furthermore, patients were willing to accept a 15.4 pp increase in kidney injury risk if treatment could lead to long-term remission.[9] Therefore, as the frequency and severity or seriousness of adverse reactions increases, patients place an increasing emphasis on safety over efficacy. The panel inferred that there is probably no important uncertainty or variability in patient values and preferences.

Contextual factors: The contextual factors for cyclosporine are similar to those of omalizumab (**Table 8**). Cyclosporine requires clinical (e.g. blood pressure, clinical exam and patient self-examination), and blood test (kidney function) monitoring which may limit acceptability, accessibility, feasibility, and equity.

Summary of rationale: The panel inferred that most well-informed patients with moderate to severe H1-antihistamine-refractory CU would place a high value on avoiding the certain severe and important harms over low certainty for large benefits with adding cyclosporine to H1-antihistamines compared to adding one of the first-line advanced systematic treatments (e.g. omalizumab). The low certainty for benefits and harms, values and preferences, and contextual factors drove the conditional recommendation.

Implementation considerations: While cyclosporine may rarely be an option for a first-line advanced therapy, clinical experts remarked most patients will likely start with omalizumab. Though the panel did not issue a formal recommendation comparing omalizumab vs cyclosporine at this stage, a much greater body of evidence supports omalizumab for urticaria and its effect sizes proved larger for almost all benefit outcomes with lower potential for harm and burden.

The longest duration to use cyclosporine that is safe is not clear, although patients are often transitioned to other maintenance therapies within 1 to 2 years. If cyclosporine is initiated, a discontinuation plan should be preset. A 3-month trial is common. In certain inflammatory skin diseases, such as atopic dermatitis, there is anecdotal evidence that sudden discontinuation of cyclosporine, rather than a gradual tapering (e.g. over 1-2 months), may lead to exaggerated rebound in some patients (temporary worsening of disease beyond the pre-treatment baseline); no robust evidence informs optimal discontinuation in inflammatory skin disease including CU, however. The efficacy and safety of cyclosporine combined with other advanced systemic treatments is uncertain, albeit there is encouraging emerging evidence, so far non-randomized, for combination omalizumab and cyclosporine[267, 268].

Multiple ideal body weight calculators are available for dosing. The eAppendix provides additional practical information and implementation considerations, including examples of blood pressure, renal function, and other monitoring, in 1-2 page handouts. While monitoring cyclosporine blood levels compared to symptom-based clinical monitoring has not borne out to definitively improve treatment efficacy and safety in, for instance, randomized trials, some experts advocate for routinely monitoring cyclosporine blood levels for, at minimum, with the intention to limit supratherapeutic exposure and therefore perhaps minimize harm. Compared to unmodified (generic or Sandimmune brand name) versions, modified (microemulsion generic drug, eg, Neoral or Gengraf brand names) ones may lead to more rapid time to effect, potentially larger treatment effects, albeit often in ranges of magnitude of uncertain patient importance, and lower risk of harm formulations of cyclosporine[32]. Use the lowest dose possible. Typically, patients with CU are more responsive (i.e. experience efficacy at lower doses) to cyclosporine than other inflammatory skin conditions, such as atopic dermatitis[32].

Tacrolimus is a calcineurin inhibitor similar to cyclosporine. There is very limited direct evidence for its use in the treatment of CU[269]. Clinicians prescribing tacrolimus for patients with CU should discuss the extrapolation and therefore lower certainty of its effects compared cyclosporine[270]. Experts reported that some patients intolerant of cyclosporine may tolerate tacrolimus and vice versa.

Mechanism of action of oral calcineurin inhibitors (e.g. cyclosporine)

Cyclosporine, binding to cyclophilin, and tacrolimus, binding FK-binding proteins, inhibit calcineurin-dependent signaling. These drug–protein complexes inhibit calcineurin activity and therefore reduce NFAT activation and transcription of IL-2 and other cytokines important for T cell activation, polarization, and function (e.g. IL-4)[271]. Calcineurin inhibitors can also inhibit histamine release from mast cells and basophils *in vitro*[272, 273].

STEP 4. CHRONIC URTICARIA ADVANCED 2 – Second-line treatments for chronic urticaria refractory, intolerant, or unable to use sa H1-antihistamine and a first-line advanced therapy

Despite optimal use of SGAH and first-line advanced systemic therapies, 20-30% of patients with severe refractory CU will remain affected with high disease activity.

Question 17. Should patients with chronic urticaria refractory to H1-antihistamines and a partial response to omalizumab, increase the dose and/or frequency of omalizumab vs continue same dose omalizumab?

UPDOSING OMALIZUMAB

Recommendation 17. In patients with chronic urticaria refractory to a H1-antihistamine and a partial response to omalizumab, the JTF panel suggests increasing the frequency and/or dose (to, in very rare cases, a maximum 600 mg every 2 weeks) rather than continuing standard dose omalizumab (conditional recommendation, very low certainty evidence).

Conditions to consider:

- Favors for – if there is a response with standard dose omalizumab (e.g. UAS7 improvement from pre-initiation assessment of 9 or more points) already or if wearing off of urticaria control just before the next scheduled dose is observed (e.g. at week 2 or week 3 of an every 4 week dosing schedule). If urticaria control is wearing off early, then an increase in dosing frequency might be first favored before increasing dose. Both approaches, increasing the dose of omalizumab or increasing the frequency of injections, will achieve comparably higher steady state drug levels. Patients with overweight or obesity may be associated with response to updosing.
- Favors against – little to no response (e.g. UAS7 < 9 points change from baseline) after at least 4, if not 6, months of standard dose omalizumab. There is limited data for conversion of non-responders to partial or complete responders in this population. Biomarkers such as a low total IgE, elevated CU index, and/or basopenia may suggest poor response[64]. Additionally, patients with chronic autoimmune urticaria might respond better to remibrutinib or dupilumab. Biomarkers, however, are imperfect predictors and so far have limitations[59] (see Pathophysiology section).

Benefits and harms: The linked systematic review and network meta-analysis (NMA) of advanced therapies[8], identified only non-randomized studies, often case series (single arm without a comparator group), addressing omalizumab updosing from 300 mg subcutaneously every 4 weeks to either more frequent doses and/or higher doses. The maximum dose used tended to be 600 mg per month

administered as 300 mg every 2 weeks, though one study reported using 450 mg or 600 mg every 2 weeks.

The evidence (**Figure 10**) for updosing omalizumab was very uncertain due to all studies being nonrandomized and uncontrolled in design, imprecise, representing a total of about 200 events in 461 patients. The lack of a control group led the panel to use external evidence, the omalizumab-non responding group, from the placebo arm of the CUPID B trial (omalizumab refractory or intolerant population) to simulate a comparator and further lowers the certainty estimate of the treatment effect of updosing. Most studies did not specify whether the population studied were solely partial responders to standard dose omalizumab, solely non-responders, or a mixture of both. The meta-analyzed studies showed very low certainty evidence for updosing omalizumab to yield UAS7≤6 and/or UCT≥12 (a well-controlled state) in 43% of those updosing versus 19% not (RR 2.28 [95%CI 1.66 to 3.14]; NNT 5, very low certainty). Similarly, the meta-analyzed studies showed very low certainty evidence for updosing omalizumab to yield a partial or greater response (e.g. UAS7<16) in 67% of those updosing versus 39% not (RR 1.72 [95%CI 1.47 to 2.02]; NNT 4, very low certainty). Though maximum reported dosing was 600 mg, these were among very few patients, and, the single report stated, "In 9 patients with interval frequency shortening during [high dose] (600 mg) omalizumab treatment, no additional clinical improvement was observed."[274] Harms, low certainty, were similar to standard dosing and are further supported by dosing more frequently or at higher doses than 300 mg every 4 weeks being safe when used for asthma, chronic sinusitis with nasal polyps, or IgE-mediated food allergy.

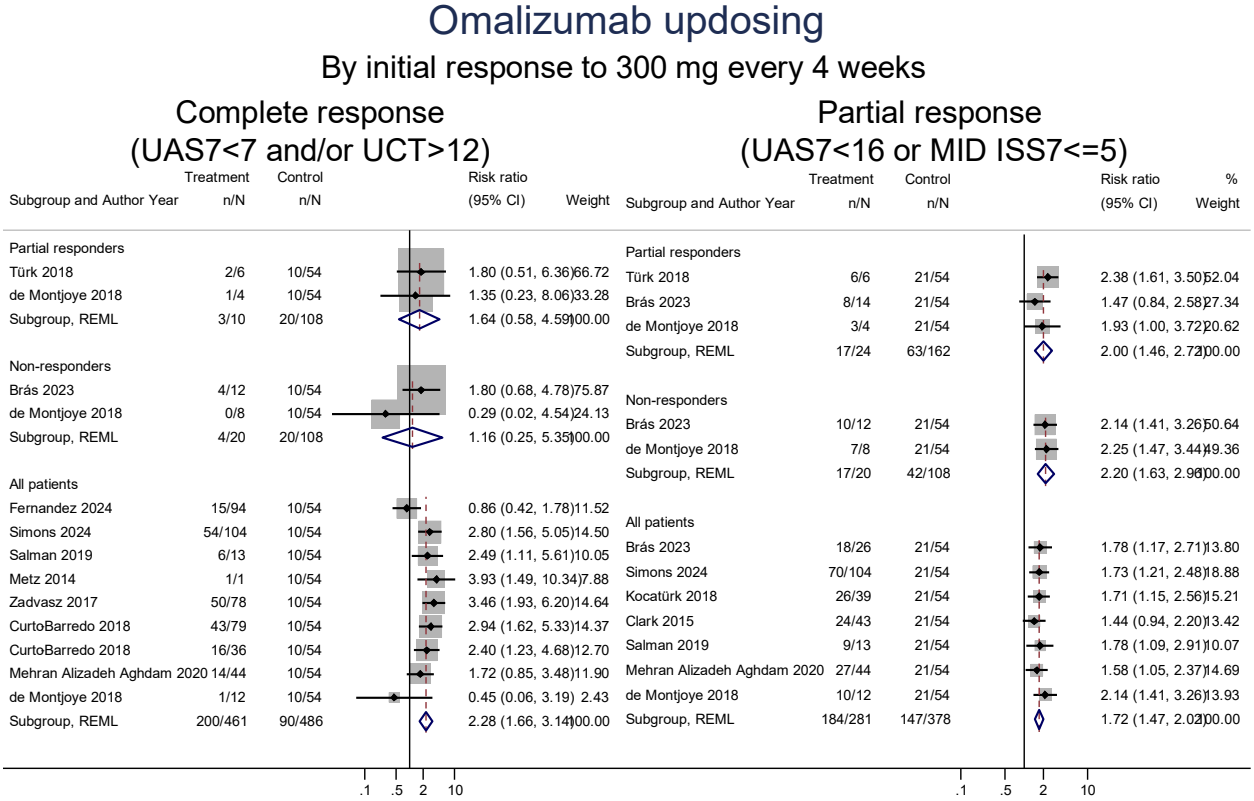


Figure 10. Meta-analysis of available studies addressing updosing of omalizumab for improved urticaria activity, ***Left*** showing well-controlled urticaria activity (UAS7≤6 and/or UCT≥12), ***Right*** showing partial response (UAS7<16 or achieving a minimally important improvement in severity scores). Outcomes are stratified by whether the population studied were partial responders to the initial omalizumab dose after 3-6 months of therapy, non-responders (little to no improvement after 3-6 months), or an aggregate overall population not-specifying in detail the response to initial omalizumab. Findings are GRADE very low certainty due to their non-randomized design, high risk of bias, and indirectness due to none of the available studies having a control arm

and the need to use external evidence, control arm responses from the CUPID B clinical trial of omalizumab refractory patients, to estimate effects.

Values and Preferences: The evidence for patient values and preferences for omalizumab updosing was similar to that for omalizumab (recommendation 14)[9]. The panel inferred that there is probably no important uncertainty or variability in patient values and preferences.

Contextual factors: The contextual factors for omalizumab updosing are similar to those of omalizumab standard dosing (**Table 8**).

Summary of rationale: The panel inferred that most well-informed patients with moderate to severe H1-antihistamine-refractory CU and a partial response to omalizumab would place a high value on the uncertain benefits over the uncertain uncommon and rare harms of updosing omalizumab over continued standard-dose omalizumab and SGAH alone. The (very) low certainty for benefits and harms, values and preferences, and contextual factors drove the conditional recommendation.

Implementation considerations: The supplement summarizes practical issues in a 1-2 page handout about how to updose omalizumab (e.g. 150 mg subcutaneously every 2 week, 300 mg subcutaneously every 2 week, 450 mg subcutaneously every 2-4 weeks, 600 mg subcutaneously every 2-4 weeks). Given the high resource implications, the 600 mg every 2 weeks regimen should be used very rarely. Throughout omalizumab updosing, the overarching Good Practice Statement principles should be followed and patient re-evaluation occur.

Question 18. Should patients with chronic urticaria who are intolerant, suboptimally responsive, or unable to use an H1-antihistamine and a first-line advanced systemic therapy (e.g. omalizumab, dupilumab, remibrutinib) add or switch to another first-line advanced therapy?

ADDING OR SWITCHING ANOTHER ADVANCED THERAPY, CYCLOSPORINE

Recommendation 18. In patients with chronic urticaria who are intolerant, suboptimally responsive, or unable to use a H1-antihistamine and a first-line advanced systemic therapy (omalizumab, dupilumab, remibrutinib), the JTF panel suggests switching (among omalizumab, dupilumab or remibrutinib), rather than adding, another first-line advanced therapy (conditional recommendation, low certainty evidence).

Conditions to consider:

- Many of the conditions to consider are similar to those presented previously for cyclosporine (Recommendations 15-16).
- Switching might be informed by comorbidity and predictive factors for treatment response, such as a growing list of biomarkers. The certainty and quantitative predictive value of biomarkers, however, remains low certainty. Therefore, while biomarker-informed switching is currently attractive, its comparative benefits, harms, burdens, and resource utilization compared to empiric switching have not been formally studied (e.g. in a large robust RCT).

Benefits and harms: The systematic review and network meta-analysis (NMA) of advanced therapies (biologics [monoclonal antibodies], immunomodulators [e.g. remibrutinib], and immunosuppressants [e.g. cyclosporine, azathioprine, methotrexate], ultraviolet light therapy [phototherapy]) for CU[8], including omalizumab (e.g. Xolair, Omlyclo biosimilar), analyzed 11,135 participants and 83 RCTs. **Figure 9** summarizes their effects. Among the studies, few directly analyzed patients specifically refractory to omalizumab, dupilumab, or remibrutinib, such as LIBERTY CUPID B (dupilumab; all omalizumab-intolerant or incomplete responders who discontinued omalizumab and switched to dupilumab) and the REMIX-1 and REMIX-2 RCTs (remibrutinib; approximately 30% exposed previously to omalizumab [intolerant or incomplete response and discontinued omalizumab during the trial]). The findings among the three LIBERTY-CSU CUPID studies, however, had widely overlapping confidence intervals and slight variation in their point estimates, and therefore, the true effects among the trials may be consistent with one another and chance alone may explain their variation. Other conventional immunosuppressants and immunomodulators addressed patients refractory to multiple medications, but often not specifically refractory to at least one of the modern advanced first-line systemic treatments. No RCT specifically addressed combined therapy with more than one first-line advanced systemic therapy. Therefore, while it is plausible that the benefits and harms of combining advanced systemic treatments are likely at least additive, the evidence is uncertain. Given the serious indirectness of the evidence, the JTF panel rated the certainty of the body of evidence as low.

Values and Preferences: Beyond those presented previously, the systematic review informing values and preferences for CU treatments[9] and direct patient and caregiver partner input emphasized in this scenario that the patient preference for simple urticaria treatment plans that maximize efficacy, minimize harm and burdens (disruption to daily activities), favored discontinuation of ineffective therapies and switching to a likely effective one. For instance, if adding dupilumab and omalizumab, that could mean the patient is receiving 4 different injections every 2 to 4 weeks, and both the review and patient input showed that, while tolerable by many, patients with CU prefer to avoid injections. Patient preference to avoid additive harms and burdens further supported switching over combination treatment with advanced first-line systemic treatments. The panel, however, recognized that there may be important uncertainty or variability in patient values and preferences. For instance, some patients may place a higher value on the most effective therapies possible, even if combined, over their potential increased harms and burdens. Also, patients partially responsive to one therapy may prefer to remain on that therapy and add another advanced first-line treatment so as not to lose any of the benefit from the partial response to the first medication.

Contextual factors: The JTF panel inferred that switching will likely be acceptable, feasible, equitable, and incur the similarly high resource costs previously reviewed for each component advanced first-line systemic treatment. In contrast, by adding another first-line advanced treatment as combined therapy, time and financial resource costs will be much higher, and may not be feasible for many due to costs or lack of insurance coverage, thereby decreasing equity.

Summary of rationale: The panel inferred that most well-informed patients with moderate to severe H1-antihistamine- and first-line advanced treatment-refractory CU would place a higher value on the more certain benefits, harms, and burdens, with switching over the uncertain benefits and harms, and certain increase in burdens with adding (combination treatment). The low certainty for the tradeoff of benefits and harms, variability in values and preferences, and contextual factors drove the conditional recommendation.

Implementation considerations: The supplement summarizes practical issues in a 1-2 page handout about how to use each advanced first-line therapy.

Question 19. Should patients with chronic urticaria who are suboptimally responsive or refractory to H1-antihistamines, and a first-line advanced systemic therapy add cyclosporine vs continue as is?

Recommendation 19. In patients with chronic urticaria who are suboptimally responsive or refractory to a H1-antihistamine and a first-line advanced systemic therapy, the JTF panel suggests adding, rather than not adding, a calcineurin inhibitor (conditional recommendation, low certainty evidence).

Conditions to consider:

- Many of the conditions to consider are similar to those presented previously for calcineurin inihbitors (Recommendation 17)
- If refractory to a first-line advanced therapy, most patients may prefer switching among the 1st line advance agents, given their efficacy, safety, certainty, practical issues, and values and preferences, rather than adding cyclosporine.
- If, however, cost, access, and the burden of polytherapy are not concerns for the patient and/or there is partial response to the first advanced therapy, they may favor adding over switching to another advanced therapy. For example, there is encouraging emerging evidence, so far non-randomized, for combination omalizumab and (low dose) cyclosporine[267, 268], but its precise efficacy and safety compared to switching or other approaches is very uncertain[269].

Benefits and harms: As reviewed in Recommendation 17, the systematic review and network meta-analysis (NMA) of advanced therapies for CU[8], showed that cyclosporine may be among the most effective therapies, often studied in treatment-refractory CU, but also is among the most certain to increase both frequent minor as well as potentially serious harms, especially with long durations and high doses such as 5 mg/kg (**Figure 9 and Recommendation 17**). There is no RCT evidence in CU addressing the hypothesized potential for cyclosporine to induce long-term immunomodulation, or the newer concept of remission[36] off-therapy (a period, possibly permanent [i.e. cure], of no disease activity).

Values and Preferences: The evidence for patient values and preferences for cyclosporine was similar to that for cyclosporine when considered as a first-line therapy (Recommendation 17)[9]. In addition, the panel, including direct input from patients and caregivers, emphasized that the values and preferences for a tradeoff between potential benefits and harms at this advanced severity and refractoriness would likely be more closely balanced and encounter important variability among patients. Recommendation 19 addresses the considerations for switching versus adding advanced therapies.

Contextual factors: The contextual factors for cyclosporine are similar to those reviewed previously for Recommendation 17 (**Table 8**), including cyclosporine's requirement for blood pressure and blood test (kidney function) monitoring which may limit acceptability, accessibility, feasibility, and equity. Recommendation 19 addresses contextual factor considerations for switching versus adding advanced therapies.

Summary of rationale: The panel inferred that most well-informed patients with moderate to severe H1-antihistamine- and first-line advanced treatment-refractory CU would place a high value on the uncertain benefits over the certain short-term harms and burdens, and uncertain rare long-term harms with

adding, rather than not adding, cyclosporine. The low certainty for the tradeoff of benefits and harms, the likely variability in values and preferences, and contextual factors drove the conditional recommendation.

Implementation considerations: Recommendation 17 and its associated supplement address implementation guidance and practical issues about how to use cyclosporine.

STEP 5. CHRONIC URTICARIA ADVANCED 3 - Third-line treatments for chronic urticaria refractory, intolerant, or unable to use to a H1-antihistamine(s) and first-and second-line advanced therapies

About 5% of patients with CU will be refractory to advanced first- and second-line therapies. The Good Practice Statement particularly applies here. Analogous to the approach of other refractory difficult-to-treat and severe disease states, patients refractory to first- and second-line advanced treatments should, for example, ensure the diagnosis is correct (e.g. Schnitzler's syndrome, urticarial vasculitis [syndrome]), no complicating conditions, that exacerbating factors have been addressed, and adherence adequate. The available published evidence addressing these severe refractory patients with CU is very limited and therefore treatment benefits uncertain as well as predictors of their response. Many therapies are conventional immunosuppressants or immunomodulators used more commonly in rheumatology or transplant medicine. For these patients, all or almost all should try available first-line advanced therapies and appropriate second-line advanced strategies before attempting the below options for refractory CU. Referral to randomized clinical trials should also be considered.

HYDROXYCHLOROQUINE (HCQ)

Question 20. Should patients with chronic urticaria who are intolerant, suboptimally responsive, or refractory to a H1-antihistamine and first- and second-line advanced systemic therapies ADD hydroxychloroquine vs continue as is?

Recommendation 20. In patients with chronic urticaria who are intolerant, suboptimally responsive, or refractory to a H1-antihistamine and first- and second-line advanced systemic therapies, the JTF panel suggests adding, rather than not adding, hydroxychloroquine (conditional recommendation, low certainty evidence).

Conditions to consider:

- Favored for - Patients in whom hydroxychloroquine (HCQ) will treat more than one condition (e.g. rheumatologic disease), or who place a higher value on HCQ's potential benefits over its slow onset of action (usually several months) and potential harms.
- Favored against – Patients who have major risk factors for retinal toxicity, beyond dose, include duration of use (e.g. daily dose 5mg/kg or less for <10 years considered low risk), renal disease, and concomitant tamoxifen, or for those who prefer a faster acting agent.

Benefits and harms: The linked systematic review and network meta-analysis of advanced therapies for CU identified 2 RCTs addressing HCQ[8]. They enrolled 76 adults with severe refractory CU. In general, HCQ takes 1-3 months to take effect.

Compared to control, low certainty evidence shows that HCQ may improve urticaria severity (MD -5.98 [95%CI -12.01 to 0.04]) and urticaria-related quality of life (MD -12.14 [95%CI -25.00 to 0.71]). No data addressed angioedema. In terms of harms, best estimates are derived from a systematic review published in 2021 addressing the harms of HCQ for a variety of indications[275]. The most reported adverse reaction included nausea (9% vs 5%, high certainty, RR 1.79 [95%CI 1.30 to 2.48])[275]. There was no increase in retinopathy or cardiac complications in early follow-up[275]. Long-term (over 10 years) HCQ use is associated with a 1-2% risk of retinopathy at recommended doses of 5 mg/kg or lower and routine screening can detect subclinical changes years before the onset of toxicity that may begin as loss of visual acuity and progress to additional loss of peripheral vision and night vision[276-278]. Very high dose HCQ may rarely, and possibly only in the context of other pro-arrhythmic factors such as active COVID-19 infection, cause fatal cardiac complications (e.g. arrythmia)[279]. Less common and uncertain associated adverse reactions include skin hyperpigmentation, photosensitivity, gastrointestinal symptoms, and myopathy, including cardiomyopathy[279, 280].

Values and Preferences: The systematic review of patient values and preferences[9] and direct patient and caregiver input led the panel to infer that most patients would place a higher value on the potential benefits of HCQ at this level of refractoriness over its slow onset of action and minor early harms or rare long-term ones. The panel felt, however, that there may be important variability in patient values and preferences when considering add-on HCQ.

Contextual factors: HCQ is accessible, feasible, acceptable, low in resource consumption (**Table 8**), and equitable. HCQ does not require routine bloodwork monitoring. Long-term HCQ use requires routine retinopathy assessment.

Summary of rationale: The panel inferred that most well-informed patients with moderate to severe H1-antihistamine- and first- and second-line advanced treatment-refractory CU would place a high value on the possible uncertain important benefits of adding, rather than not adding, HCQ over its certain minor short-term harms and uncertain rare long-term harms. The very low certainty for the tradeoff of benefits and harms, contextual factors, and the likely variability in values and preferences drove the conditional recommendation.

Implementation considerations: The American College of Rheumatology 2025 Guideline for the Treatment of Systemic Lupus Erythematosus (SLE), for example, recommends, “In people with SLE receiving HCQ therapy, we conditionally recommend a long-term average daily HCQ dose goal of ⩽5 mg/kg [actual weight] over a dose goal of >5 mg/kg to minimize retinal toxicity; use of short courses of higher dose (between 5 and 6.5 mg/kg/d) therapy may be necessary at initiation of treatment or to maintain disease control.”[276, 277, 281] A maximum of 400 mg per day is recommended[278]. If at risk for medication-induced or congenital long QT, consider baseline and follow up electrocardiogram (ECG), though there is no universal consensus about specific frequency of monitoring in at-risk patients[282]. As above, follow guidance for HCQ-associated retinopathy screening at baseline (includes soon after starting). The American Academy of Ophthalmology suggests annual screening with optical coherence tomography (OCT), along with wide-pattern fundus autofluorescence (FAF) where available, thereafter, but that it may be deferred for the first 5 years if there are no significant risk factors (e.g. beyond dose and duration of use, risk factors include renal disease, concurrent tamoxifen use, as well as initiation of HCQ therapy at older ages)[278]. The supplement summarizes practical issues in a 1-2 page handout about how to use HCQ.

Mechanism of action of hydroxychloroquine

Hydroxychloroquine is a lysosomatropic drug, and has been classified as a disease modifying anti-rheumatic drug (DMARD) and antimalarial. Its mechanism of action for efficacy in patients with antihistamine-resistant chronic urticaria is not fully understood. Hydroxychloroquine accumulates within acidic endosomes and lysosomes, increases intravesicular pH, and thereby impairs endolysosomal function, including antigen processing and major histocompatibility complex class II presentation, pattern-recognition receptors, and perhaps mast cell granules [283, 284]. The downstream immunomodulating and anti-inflammatory effects include inhibition of mast cell activation, stabilization of lysosomal membranes, decreasing production of prostaglandins and cytokines (IL-1, IL-6, TNF-alpha), and perhaps B cell activation and immunoglobulin production [283-285]. Hydroxychloroquine has also been shown to lead to mast cell storage of inactive tryptase, and reduced expression of mast cell IL-8 and GM-CSF[286].

MYCOPHENOLATE (mycophenolate mofetil, mycophenolic acid)

Question 21. Should patients with chronic urticaria who are intolerant, suboptimally responsive, or refractory to a H1-antihistamine and first- and second-line advanced systemic therapies ADD mycophenolate vs continue as is?

Recommendation 21. In patients with chronic urticaria who are intolerant, suboptimally responsive, or refractory to a H1-antihistamine and first- and second-line advanced systemic therapies, the JTF panel suggests adding, rather than not adding, mycophenolate (conditional recommendation, very low certainty evidence).

Conditions to consider:

- Patients who place a higher value on mycophenolate's uncertain potential benefits over its more certain slow onset of action (usually several weeks to months) and potential harms.
- As before, prefer calcineurin inhibitor before mycophenolate, except in situations such as intolerance or contraindications to CNI (e.g. hypertension or kidney disease that prevents CNI use), or patient preference.

Benefits and harms: The linked systematic review and network meta-analysis of advanced therapies for CU identified no RCTs, and 6 non-randomized studies addressing mycophenolate at doses of 1 to 2.5 grams per day[8]. They enrolled 181 patients with severe refractory CU. In general, mycophenolate, including its dose-escalation, takes weeks to take effect.

Compared to control, very low certainty evidence shows that mycophenolate may improve urticaria severity (MD -15.01 [95%CI -25.29 to -4.74], very low certainty). No data addressed urticaria-related quality of life or angioedema. Panel experts commented that in their uncontrolled observations, about 33% of individuals refractory to omalizumab and calcineurin inhibitors respond to therapy, and, despite the need for lab monitoring and frequent GI adverse effects, is otherwise generally well tolerated (very low certainty). It may work slower compared to calcineurin inhibitors. In terms of harms, best estimates are derived from mycophenolate's use for rheumatologic conditions [281, 287-289]. Frequent dose-related harms are gastrointestinal (anorexia, nausea, vomiting, diarrhea), genitourinary (dysuria, urgency), and cytopenias. Mycophenolate may increase the risk of severe infections (e.g. pneumonia)[290], and has a rare and uncertain association with increased malignancy including lymphoma. Mycophenolate mofetil

during pregnancy increases miscarriage during the first 3 months (first trimester), and birth defects. Further, mycophenolate mofetil decreases blood levels of the hormones in oral birth control (oral contraceptive pills).

Values and Preferences: Similar to dapsone and sulfasalazine, the systematic review of patient values and preferences[9] and direct patient and caregiver input showed that patients place a high value on improvement in urticaria symptoms and that safety is prioritized over efficacy as the frequency and severity of harms increases. The panel inferred that there may be important variability in how patients view the tradeoffs between the uncertain benefits of mycophenolate at this level of refractoriness versus its common harms or rare serious ones.

Contextual factors: Mycophenolate is accessible and feasible, but may not be acceptable for all or almost all, and, given its need for frequent ongoing monitoring, is moderate in resource consumption and may not be optimally equitable.

Summary of rationale: The panel inferred that most well-informed patients with moderate to severe H1-antihistamine- and first- and second-line advanced treatment refractory CU would place a high value on the uncertain large benefits of adding, rather than not adding, mycophenolate over the more certain common harms and uncertain rare ones. The very low certainty for the tradeoff of benefits and harms, contextual factors, and values and preferences drove the conditional recommendation.

Implementation considerations: Mycophenolate has a Risk Evaluation and Mitigation Strategy (REMS) website: https://www.mycophenolaterems.com/. Mycophenolate is available as either mofetil (CellCept) or as mycophenolic acid (Myfortic), with most data addressing mycophenolate mofetil. Mycophenolate is typically not used concomitantly with a calcineurin inhibitor. Panel experts commented that a typical medication regimen may cost about $50 USD per month (drug cost alone). The supplement summarizes practical issues in a 1-2 page handout about how to use mycophenolate.

Mechanism of action of mycophenolate

Mycophenolate mofetil is a prodrug of mycophenolic acid (MPA) that inhibits inosine-5'-monophosphate dehydrogenase, a rate-limiting enzyme in de novo guanosine nucleotide synthesis. Because activated T and B lymphocytes rely heavily on this pathway, mycophenolate preferentially suppresses lymphocyte proliferation, antibody generation, and downstream immune activation. MPA also inhibits the glycosylation and expression of adhesion molecules, and the recruitment of lymphocytes and monocytes into sites of inflammation.[291-293]

COLCHICINE

Question 22. Should patients with chronic urticaria who are intolerant, suboptimally responsive, or refractory to a H1-antihistamine and first- and second-line advanced systemic therapies ADD colchicine vs continue as is?

Recommendation 22. In patients with chronic urticaria who are intolerant, suboptimally responsive, or refractory to a H1-antihistamine and first- and second-line advanced systemic therapies, the JTF panel suggests against adding colchicine (conditional recommendation, very low certainty evidence).

Conditions to consider:

- Exception may be comorbidity requiring colchicine.
- Favoring against – Patients who prefer medications with greater certainty or magnitude of benefits (e.g. mycophenolate, azathioprine), or with a different profile of potential harms.
- Favoring for – Patients who strongly prefer low-cost colchicine and possibly small magnitude of benefits over its certain harms and burdens. While urticaria with neutrophilic infiltration seen on skin biopsy may suggest a greater response to colchicine, the evidence for neutrophilic urticaria in predicting CU treatment response to colchicine, however, is very uncertain and largely based on biologic rationale and uncontrolled observations.

Note: This recommendation does not apply to other conditions that may mimic typical chronic urticaria or for other diseases where colchicine has evidence for efficacy, such as patients with urticarial vasculitis (syndrome), autoinflammatory conditions, or Sweet's syndrome. This note reinforces the Good Practice Statement.

Benefits and harms: The linked systematic review and network meta-analysis of advanced therapies for CU identified 2 RCTs addressing colchicine[8]. They enrolled 64 adults with CU and followed them for 1 or 12 weeks.

Based on UAS7, 29 patients assigned to colchicine 1 mg daily added to H1-antihistamines reported a mean (SD) score of 14.22 (3.77) and, at 3 months, 2.58 (3.00) compared to the 22 patients assigned to the H1-antihistamine-only control group at baseline 14.90 (2.92) and, at 3 months, 5.77 (4.82) (very low certainty, MD -2.51 [95%CI -4.67, -0.35]). The study reported similar effects among component itch and wheal scores, as well as urticaria-related quality of life (very low certainty). No data addressed angioedema. Panel experts commented that their uncontrolled observations, more often (but not exclusively) in patients with biopsy evidence of neutrophilic infiltration, included approximately 20-40% of refractory patients improving after starting colchicine (very low certainty evidence).

Harms of colchicine are well established from large RCTs addressing its modern investigation and use for cardiovascular disease (e.g. primary and secondary prevention; atrial fibrillation, over 25,000 study participants), gout, pericarditis, and familial mediterranean fever (FMF)[294-297]. The most common adverse reactions are gastrointestinal effects, primarily dose-dependent diarrhea followed by abdominal pain and nausea/vomiting, in 8% versus 5% in placebo (RR 1.46 [95%CI 1.05 to 2.03], moderate certainty). In one systematic review and meta-analysis of 14,188 patients from 21 randomized controlled trials addressing cardiovascular disease[294], colchicine 0.5 mg daily did not increase gastrointestinal events (RR 0.99 [95% CI 0.88–1.12]), as opposed to a higher dose of 0.5-1 mg daily (RR 2.09 [95% CI 1.47–2.97]) and or more than 1 mg daily (RR 3.16 [95% CI 1.92–5.20]). Rare and uncertain associated harms include cytopenia and neuromyotoxicity. Colchicine has a narrow therapeutic index, and overdose can be fatal[296, 298].

Values and Preferences: The systematic review of patient values and preferences[9] and direct patient and caregiver input showed that most patients prioritize rapid and sustained symptom control over minor burden or harms. The panel therefore inferred that there is probably no important variability in patient values and preferences when considering add-on colchicine.

Contextual factors: Colchicine at 0.5 mg or 0.6 mg once daily doses is accessible, feasible, likely acceptable, low in resource consumption (**Table 8**), and equitable. Colchicine does not require routine bloodwork monitoring, but may be considered in some circumstances (eg. reduced or risk of impairment of renal function). Given colchicine's narrow therapeutic/safety index, clinicians may require baseline bloodwork to evaluate for patient kidney impairment or liver dysfunction requiring dose modification or meeting criteria for contraindication to use.

Summary of rationale: The panel inferred that most well-informed patients with moderate to severe H1-antihistamine- and first- and second-line advanced treatment-refractory CU would place a high value on the possibly larger, albeit uncertain, benefits of other treatment approaches over the certain minor short-term harms and burdens, uncertain rare long-term harms, and uncertain small benefits with adding low-dose colchicine (0.5 to 0.6 mg once daily). The very low certainty for the tradeoff of benefits and harms, contextual factors, and the likely variability in values and preferences drove the conditional recommendation.

Implementation considerations: Dose, kidney function, liver function, and drug interactions are critical considerations. The supplement summarizes practical issues in a 1-2 page handout about how to use colchicine. Doses of 0.5 or 0.6 mg once daily in patients with normal renal function are generally well-tolerated and at low risk for toxic drug levels with most drug interactions. Decrease dose or avoid in patients with kidney insufficiency, liver dysfunction, or concurrent use of strong CYP3A4 or P-glycoprotein inhibitors. Colchicine is contraindicated with use of strong CYP3A4 or p-glycoprotein inhibitors in the setting of renal or hepatic dysfunction. The LODOCO$_2$ and COP-AF clinical trials[294, 298, 299] showed that low-dose colchicine use with statins are generally tolerated. Monitor clinically, and other investigations if needed, for gastrointestinal symptoms, neuromyotoxicity, and blood dyscrasias.

Mechanism of action of colchicine

Colchicine exerts its anti-inflammatory effects primarily by inhibiting microtubule polymerization, thereby disrupting key cellular processes such as neutrophil adhesion, migration, signaling, and inflammasome activation[300]. Through these actions, colchicine downregulates multiple inflammatory pathways, including superoxide production, the RhoA/ROCK pathway, and TNF-α–induced NF-κB signaling, leading to attenuation of the inflammatory response.

DAPSONE

Question 23. Should patients with chronic urticaria who are intolerant, suboptimally responsive, or refractory to a H1-antihistamine and first- and second-line advanced systemic therapies ADD dapsone vs continue as is?

Recommendation 23. In patients with chronic urticaria who are intolerant, suboptimally responsive, or refractory to a H1-antihistamine and first- and second-line advanced systemic therapies, the JTF panel suggests against the use of dapsone (conditional recommendation, very low certainty evidence).

Conditions to consider:

- Exception may be the rare comorbidity requiring dapsone
- Favor against - G6PD deficiency and kidney impairment are risk factors for adverse reactions

- Favor for - Neutrophilic infiltration on urticaria on skin biopsy. Similar to neutrophils on biopsy in predicting CU treatment response to colchicine, the evidence for using neutrophils on biopsy, longer-lasting hives or more painful hives, for predicting CU treatment response to dapsone is very uncertain.

Benefits and harms: The linked systematic review and network meta-analysis of advanced therapies for CU identified 3 RCTs addressing dapsone[8]. They enrolled 103 adults and adolescents with severe refractory CU. In general, dapsone takes 1-3 months to take effect.

Compared to control, low certainty evidence shows that dapsone may have a small, possibly patient-unimportant, effect on urticaria severity (MD -3.91 [95%CI -9.51 to 1.32]) and very uncertain effect on urticaria-related quality of life (MD -9.24 [95%CI -23.28 to 4.80], very low certainty). No data addressed angioedema. In terms of harms, best estimates are derived from systematic reviews addressing the harms of dapsone for a variety of indications[301, 302]. Common adverse reactions include methemoglobinemia, hemolytic anemia, and neutropenia/agranulocytosis. Rare (1-2%)[301, 302] and uncertain reactions include drug rash with eosinophilia and systemic symptoms[20] (DRESS; previously termed separately as dapsone or sulfone hypersensitivity syndrome). Panel experts agreed that their uncontrolled observations were, in general, small to moderate benefits for urticaria control, and a concern for harms and need for monitoring.

Values and Preferences: The systematic review of patient values and preferences[9] and direct patient and caregiver input showed the patients place a high value on improvement in urticaria symptoms and that safety is prioritized over efficacy as the frequency and severity of harms increases. That harms can occur rapidly, within days, while benefits may take several weeks to take effect, led the panel to infer that many patients may have preferences against routine dapsone use. The panel felt that there was likely no important variability in patient values and preferences when considering add-on dapsone.

Contextual factors: Dapsone is accessible, feasible, acceptable, but, given its need for frequent ongoing monitoring, is moderate in resource consumption and may not be optimally equitable.

Summary of rationale: The panel inferred that most well-informed patients with moderate to severe H1-antihistamine- and first- and second-line advanced treatment-refractory CU would place a high value on avoiding the certain harms and not uncertain, possibly small, benefits of adding, rather than not adding, dapsone. The very low certainty for the tradeoff of benefits and harms, contextual factors, and values and preferences drove the conditional recommendation.

Implementation considerations: G6PD, among other laboratory tests, is done at baseline and, if G6PD insufficient, dapsone is avoided. Other G6PD inhibitors include local anesthetics and sevoflurane. Therefore, patients should hold dapsone before procedures involving local anesthetics and discuss with anesthesiologists preoperatively. Panel experts commented that they most often used doses in the range of 25 to 100 mg. Laboratory monitoring is required. The supplement summarizes practical issues in a 1-2 page handout about how to use dapsone.

Mechanism of action of dapsone

Dapsone is a sulfone antibiotic used off-label for anti-inflammatory effects. It modulates granulocyte function, especially neutrophils, by inhibiting the oxidative burst and interfering with peroxidase activity (eg. MPO), which reduces the production of reactive oxygen species (ROS) that contribute to tissue

injury[303]. Dapsone further impairs neutrophil chemotaxis and adherence, and reduces pro-inflammatory chemokine signaling, collectively decreasing granulocyte-mediated inflammation. Its anti-inflammatory and immunomodulatory effects, rather than direct mast cell inhibiting activity, may explain why advocates for its use suggest it primarily in patients with CU wheals associated neutrophilic inflammation. Management of methemoglobinemia, including methylene blue and cimetidine, are reviewed elsewhere[303-305].

SULFASALAZINE

Question 24. Should patients with chronic urticaria who are intolerant, suboptimally responsive, or refractory to a H1-antihistamine and first- and second-line advanced systemic therapies ADD sulfasalazine vs continue as is?

Recommendation 24. In patients with chronic urticaria who are intolerant, suboptimally responsive, or refractory to a H1-antihistamine and first- and second-line advanced systemic therapies, the JTF panel suggests against the use of sulfasalazine (conditional recommendation, very low certainty evidence).

Conditions:

- Favor for - If comorbidity that would also be treated by sulfasalazine. Similar to neutrophils on biopsy in predicting CU treatment response to other interventions for refractory CU, the evidence for using neutrophils on biopsy or autoimmune features, for predicting CU treatment response to sulfasalazine is very uncertain.
- Favor against – in patients that place a higher value on avoiding the need for potentially burdensome and costly (time, financial) clinical and lab monitoring for adverse effects.

Benefits and harms: The linked systematic review and network meta-analysis of advanced therapies for CU identified no RCTs, and 7 non-randomized studies addressing sulfasalazine at doses of 0.5 to 3 grams per day[8]. They enrolled 239 patients with severe refractory CU. In general, sulfasalazine, including its dose-escalation, takes 1-3 months to take effect.

Compared to control, very low certainty evidence shows that sulfasalazine may improve urticaria severity (MD -10.65 [95%CI -20.92 to 0.37], very low certainty). No data addressed urticaria-related quality of life or angioedema. Panel experts commented that, predominantly in the pre-omalizumab era, approximately 20% to 50% of patients might respond with improved urticaria balanced by about 20% to 50% encountering adverse reactions, including abnormal laboratory values[8, 306]. In terms of harms, best estimates are derived from a sulfasalazine's use for rheumatologic conditions and inflammatory bowel disease. Frequent dose-related harms are gastrointestinal (anorexia, nausea, vomiting, diarrhea), headache, and cytopenias. Sulfasalazine use may also cause orange skin and urine discoloration that is reversible upon discontinuation. Rare and uncertain adverse reactions include, similar to dapsone, severe cutaneous adverse reactions, agranulocytosis, and hemolytic anemia. In males, sulfasalazine may reduce male fertility via reversible oligospermia. A combination of RCTs and observational studies spanning the 1960s to 1990s in rheumatoid arthritis suggest, with low certainty, that 25% of patients initiating sulfasalazine will discontinue it within 3 months due to adverse drug reactions.

Values and Preferences: Similar to dapsone, the systematic review of patient values and preferences[9] and direct patient and caregiver input showed the patients place a high value on improvement in urticaria

symptoms and that safety is prioritized over efficacy as the frequency and severity of harms increases. That harms can occur rapidly, within days, while benefits may take several weeks to take effect, led the panel to infer that many patients may have preferences against routine sulfasalazine use. The panel felt that there was likely no important variability in patient values and preferences when considering add-on sulfasalazine.

Contextual factors: Sulfasalazine is accessible and feasible, but, may not be acceptable for many, and, given its need for frequent ongoing monitoring, is moderate in resource consumption and may not be optimally equitable.

Summary of rationale: The panel inferred that most well-informed patients with moderate to severe H1-antihistamine- and first- and second-line advanced treatment-refractory CU would place a high value on avoiding sulfasalazine's certain harms and not on its uncertain benefits. The very low certainty for the tradeoff of benefits and harms, contextual factors, and values and preferences drove the conditional recommendation.

Implementation considerations: Sulfasalazine is gradually increased over several weeks and titrated according to tolerance. Hemolytic anemia can occur regardless of G6PD status, and therefore G6PD sufficiency is not universally screened for, but local practices may vary. The supplement summarizes practical issues in a 1-2 page handout about how to use sulfasalazine.

Mechanism of action of sulfasalazine

Sulfasalazine is an oral prodrug composed of 5-aminosalicylic acid (5-ASA) linked to sulfapyridine that is commonly used to treat inflammatory bowel disease or autoimmune diseases such as rheumatoid arthritis[307]. After oral administration, colonic bacterial enzymes cleave sulfasalazine into 5-ASA and sulfapyridine. Some sulfasalazine is directly absorbed in the small intestine but largely returned via enterohepatic circulation into bile. Unlike inflammatory bowel disease, where topical 5-ASA activity in the gut is important, the more relevant mechanism in chronic urticaria is systemic immunomodulation from sulfasalazine and absorbed sulfapyridine.

Sulfasalazine has several systemic anti-inflammatory and immunomodulatory effects[307] such as inhibition of NF-κB–dependent inflammatory transcription, reduced TNF-α expression, reduced IL-8 and MCP-1 secretion, possible suppression of lymphocyte activation and function. Additional proposed effects include inhibition of cyclooxygenase and lipoxygenase pathways, reduced prostaglandin and leukotriene generation, suppression of lymphocyte DNA synthesis and IL-2–linked T-cell activation, and impaired neutrophil and macrophage chemotaxis, phagocytosis, and adhesion.

AZATHIOPRINE

Question 25. Should patients with chronic urticaria who are intolerant, suboptimally responsive, or refractory to a H1-antihistamine and first- and second-line advanced systemic therapies ADD azathioprine vs continue as is?

Recommendation 25. In patients with chronic urticaria who are intolerant, suboptimally responsive, or refractory to a H1-antihistamine and first- and second-line advanced systemic therapies, the JTF panel suggests against the use of azathioprine (conditional recommendation, low certainty evidence).

Conditions to consider:

- Favor for (exceptions) - Include when azathioprine will treat more than one condition, if intolerant of other therapies, or considering conception/pregnancy.

Benefits and harms: The linked systematic review and network meta-analysis of advanced therapies for CU identified 2 RCTs[8]. They enrolled 140 adult and adolescent patients with severe refractory CU. In general, azathioprine takes weeks to months to take effect.

Compared to control, low certainty evidence shows that azathioprine may improve urticaria severity (MD -8.07 [95%CI -16.14 to -0.01], low certainty). No data addressed urticaria-related quality of life or angioedema. Panel experts, however, commented that their uncontrolled observations included that the benefits were small and often patient unimportant (very low certainty). In terms of harms, best estimates are derived from azathioprine's use for rheumatologic conditions[281, 287-289]. Frequent dose-related harms are gastrointestinal (anorexia, nausea, vomiting, diarrhea) and cytopenias. Azathioprine has a rare and uncertain association with increased malignancy including lymphoma. Azathioprine during pregnancy and lactation is generally preferred over other immunosuppressive or cytotoxic agents (e.g. mycophenolate or methotrexate) but may still increase the risk of cytopenia, and low T cell receptor excision circles (TRECs) that may be detected during newborn screening in the baby.

Values and Preferences: Similar to the other immunosuppressants considered at this level, the systematic review of patient values and preferences[9] and direct patient and caregiver input showed the patients place a high value on improvement in urticaria symptoms and that safety is prioritized over efficacy as the frequency and severity of harms increases. The panel inferred that there may be important variability in how patients might view the tradeoffs between the uncertain benefits of azathioprine at this level of refractoriness versus its common harms or rare serious ones.

Contextual factors: Azathioprine is accessible and feasible, and may be acceptable for many, but, given its need for frequent ongoing monitoring, is moderate in resource consumption and may not be optimally equitable.

Summary of rationale: The panel inferred that most well-informed patients with moderate to severe H1-antihistamine- and first- and second-line advanced treatment-refractory CU would place a high value on avoiding azathioprine's certain harms and not on its uncertain benefits. The low certainty for the tradeoff of benefits and harms, contextual factors, and values and preferences drove the conditional recommendation.

Implementation considerations: CBC with differential, AST, ALT every 2 weeks for 8 weeks, then every 2 months. TPMT genotyping, and NUDT15 if available, prior to initiation. Caution with allopurinol as co-administration increases azathioprine levels. The supplement summarizes practical issues in a 1-2 page handout about how to use azathioprine.

Mechanism of action of azathioprine

Azathioprine is a purine metabolite that incorporates into DNA in place of guanine and prevents DNA synthesis, thereby suppressing proliferation and function of rapidly dividing cells such as T and B lymphocytes. There are data to suggest it can also affect G-protein signaling and T cell activity independent of proliferation[308, 309]. Azathioprine is used commonly in autoimmune and rheumatologic disorders and transplant rejection prophylaxis. Genetic polymorphisms identified for TPMT and NUDT15 decrease the metabolism of azathioprine such that myelosuppression can be a concern.

METHOTREXATE

Question 26. Should patients with chronic urticaria who are intolerant, suboptimally responsive, or refractory to a H1-antihistamine and first- and second-line advanced systemic therapies ADD methotrexate vs continue as is?

Recommendation 26. In patients with chronic urticaria who are intolerant, suboptimally responsive, or refractory to a H1-antihistamine and first- and second-line advanced systemic therapies, the JTF panel suggests against the use of methotrexate (conditional recommendation, very low certainty evidence).

Conditions:

- Favor for (exceptions) - If methotrexate can treat multiple conditions simultaneously (e.g. rheumatologic disease, specific dermatologic conditions including concomitant moderate-severe atopic dermatitis [eczema]).

Benefits and harms: The linked systematic review and network meta-analysis of advanced therapies for CU identified 2 RCTs[8]. They enrolled 104 adult and adolescent patients with severe refractory CU. In general, methotrexate takes weeks to months to take effect.

Compared to control, very low certainty evidence shows that methotrexate may make little to no difference to urticaria-related quality of life (MD -4.03 [95%CI -15.92 to 7.85], very low certainty). No data directly addressed urticaria-activity or angioedema. Panel experts commented that their uncontrolled observations included that about 25% to 50% may respond with improved urticaria (very low certainty). In terms of harms, best estimates are derived from methotrexate's use for rheumatologic and cardiovascular conditions [281, 287-289]. Studies addressing methotrexate in cardiovascular disease, psoriasis, psoriatic arthritis, and inflammatory bowel disease show probably no important increase in mortality in 1 to 2 years. The Cardiovascular Inflammation Reduction Trial was a 5-year RCT with 4786 patients with known cardiovascular disease and diabetes or metabolic syndrome, found that 87% of patients taking methotrexate experienced an adverse event, compared with 82% of patients taking placebo (HR 1.17 [95% CI, 1.10- 1.25]). Methotrexate increased risks for skin cancer (RD 2%), gastrointestinal (RD 3%), infection (RD 4%), pulmonary (RD 3%), and hematologic adverse events (RD 18%). In a meta-analysis of 68 trials (6938 patients), methotrexate, compared with placebo or standard care, increased the risk of one or more adverse events (RR 1.13 [95% CI, 1.04-1.2])[310]. Frequent harms are oral ulcers, gastrointestinal symptoms (anorexia, nausea, vomiting), and cytopenias. Methotrexate has a rare and uncertain association with increased interstitial lung disease, and malignancy including lymphoma. Harms, such as hepatotoxicity, can be from cumulative exposure. Methotrexate is contraindicated in lactation and pregnancy.

Values and Preferences: Similar to the other immunosuppressants considered at this level, the systematic review of patient values and preferences[9] and direct patient and caregiver input showed the patients place a high value on improvement in urticaria symptoms and that safety is prioritized over efficacy as the frequency and severity of harms increases. The panel inferred that there may be important variability in how patients might view the tradeoffs between the uncertain benefits of methotrexate at this level of refractoriness versus its common harms or rare serious ones.

Contextual factors: Methotrexate is accessible and feasible, and may be acceptable for some, but, given its need for frequent ongoing monitoring, is moderate in resource consumption and may not be optimally equitable.

Summary of rationale: The panel inferred that most well-informed patients with moderate to severe H1-antihistamine- and first- and second-line advanced treatment-refractory CU would place a high value on avoiding methotrexate's certain harms and not on its uncertain benefits. The low certainty for the tradeoff of benefits and harms, contextual factors, and values and preferences drove the conditional recommendation.

Implementation considerations: Methotrexate can be administered weekly as subcutaneous injection or as an oral dose. Folic acid (e.g. 1 mg/day to start, with escalation up to 5 mg/day) is taken on all other days of the week. Avoid, or use extreme caution, if being added to another immunosuppressant. The supplement summarizes practical issues in a 1-2 page handout about how to use methotrexate.

Mechanism of action of methotrexate

While the precise mechanism of action for methotrexate (MTX) in chronic urticaria remains largely unknown, several anti-inflammatory and immunomodulatory pathways have been proposed. *In vitro* studies show that MTX does not directly inhibit histamine release from basophils or mast cells, although a reduction in heparin, a component of mast cell granules, synthesis has been observed in rat mast cells[311]. MTX can suppress immunoglobulin production, including IgE, IgG, IgM, and IgA, suggesting that it could have benefit in both Type 1 autoallergic and Type IIb autoimmune CU[312], albeit see cavetas in the Classification section in the introduction. Nevertheless, it is believed that the clinical effect likely occurs through broader systemic anti-inflammatory pathways rather than a direct effect on mast cells or basophils.

MTX also has an effect on enhancing adenosine release, inhibiting JAK/STAT pathways, suppressing NF-κB, and dampening T cell function[313, 314] that may inhibit leukocyte chemotaxis as well as mast cell and basophil activation. Further, MTX reduces the expression of a number of pro-inflammatory cytokines (e.g. TNF-α, IFN-γ, IL-4, IL-13, and GM-CSF) from whole blood at concentrations achieved in patients taking the drug[315]. This broad dampening of the immune pathways may translate into lowering overall urticaria activity.

Discussion

Limitations of these guidelines

Limitations of these guidelines include focusing on the most common aspects of CU management. Though we prioritized addressing which specific tests to order at diagnosis, if refractory to various therapies, and for screening, the specific systematic reviews for these are ongoing and will be addressed in the future. Therefore, in a living guideline update, we may issue new recommendations addressing these common questions. The guideline panel, however, agreed on the conceptual framework that doing investigations has two distinct purposes: (1) diagnosis, such as ruling out key competing diagnoses or occult disease that may drive urticaria activity, and (2) prognosis, such as prediction of treatment response (e.g. good, fair, or poor response). This may entail absolute effects of treatment response, or the less common scenario of relative treatment effect modification. Living guideline updates will address these concepts, as well as other new, practice-changing evidence.

We did not address Traditional, Complementary or Integrative medicines[316] or Indigenous Ways of Knowing[317]. As these interventions or others become more commonly used, we will address them in subsequent living guidelines in which individual recommendations are updated or added as new evidence arises. Future research may provide robust evidence regarding these interventions.

CU, like many other medical fields, lacks robust evidence for safety of medications during pregnancy and breastfeeding. Well-conducted studies to address this population are critically required. Another issue is that many trials in CU are placebo-controlled, which may be most appropriate during early drug development, but specific funding and investigations must be promoted - through professional organizations, government organizations (e.g. NIH/NIAID), and private organizations - to promote comparative effectiveness and safety of approved medications and their optimal use in treatment pathways. Robust data addressing patients who are pregnant, and that, in general, address comparative effectiveness may inform future guideline recommendations.

Recommendations for future research

By reviewing the cumulative data addressing CU to date, the panel made key research recommendations. Some of the methodological recommendations parallel those research recommendations for atopic dermatitis[32]. The **Guideline main text** and **Appendix** address research needs for specific interventions.

Optimize study designs

1. Given the waxing and waning nature of CU, including spontaneous remission, studies in H1-antihistamine-refractory CU should be at least 16 weeks in length. Those that incorporate continued use of an intervention with the objective to sustain/maintain disease control, or that represent pragmatic disease management strategies, should be at least a year in duration. Limiting the burden of interventions and trial participation will be essential to study retention.
2. The comparator in RCTs must be standard of care with or without an added active comparator. Given omalizumab as a current first-line biologic, and with multiple biosimilars emerging or available, active comparators should at least include omalizumab at standard doses. Additional active comparators (e.g. updosed omalizumab, dupilumab, remibrutinib, cyclosporine, or other advanced step treatments) are preferable.

3. New studies directly testing optimal treatment of patients refractory to any one first-line advanced systemic are required. Robust RCTs addressing combination therapies are also required. An implication of the uncertain evidence for multiple conventional immunomodulators and immunosuppressants is that their specific effects in CU have to be reappraised in new, large RCTs.
4. The evidence for updosing remains low certainty. New robust RCTs must specifically address and report the rate of conversion of patients refractory to 2x dose of H1-antihistamine that respond to 4x doses.
5. Understanding the mechanisms driving refractoriness and response to therapy are critical. There is need for further study of biomarkers and prediction of treatment response for multiple therapeutic agents.
6. Long-term remission as an outcome required. Definition and new endpoints.
7. CU subtype and endotype specific therapies, such as robust investigation, including randomized clinical trials, that directly test the hypothesis of whether autoantibodies (specific ones or as a whole) are pathogenic, e.g. does specifically reducing autoantibodies improve urticaria activity and induce long-term resolution (remission, cure)? Specific management strategies for CIndU (e.g. cholinergic) need to also be investigated. When treatments may work for multiple types of CU, basket trials, where multiple subtypes are enrolled simultaneously under a single master protocol and individually powered such that there is sufficient power to credibly estimate potential subgroup differences, may be more efficient than separate individual RCTs.

Improve data collection, analysis, and reporting

8. Studies should report, in tabular format, the mean values, SD, and number of participants analyzed, the number missing (including if they were imputed for the analysis), for baseline, each analyzed time point, and absolute change from baseline values of all continuous outcomes. The change from baseline value should clearly report how it was calculated, and whether all corresponding statistical assumptions are met (e.g. no baseline by treatment interaction in ANCOVA [linear mixed] models). ANCOVA, or similar regression-based models, with change from baseline as the outcome variable and covariates at minimum being baseline value and treatment group assignment should be considered for statistical analyses of continuous outcomes. Additional analyses such as responder analyses (e.g. UAS7=0, UAS7<6, UCT<12) should be part of the main trial report, but should be reported in addition to, not as a replacement for, the continuous outcome data.

Group	Measure	n analyzed	Mean CfB	SD CfB	Effect measure	n/N [responder threshold 1]	n/N [responder threshold 2]	n/N [responder threshold 3]
Intervention	UAS7				\			
Control	UAS7				MD (95%CI) *			
Intervention	…	…	…	…	\	…	…	…
Control	…	…	…	…	RR (95%CI)*	…	…	…

Table 9. Example template table for reporting outcomes in studies addressing CU. Responder thresholds could represent, for example, UAS7=0, UAS7<6, UCT<12, or, for binary outcomes the number with an event and the number at risk, or count outcomes, the number of events and cumulative duration of follow up time. Table 1 of the study should report the corresponding n, mean, and SD of the baseline values per group, or for count outcomes the mean and SD of the rate. Additional columns could be added to address multiple time points (e.g. baseline, end of randomized treatment period, and CfB), and

to specify whether the analysis is for the overall study population or subgroups. Graphical displays (e.g. figures depicting urticaria activity over time) should address the same data elements. CfB, Change from baseline. MD, mean difference between groups. RR, risk ratio. 95%CI, 95% confidence interval. The table can be adapted for other summary measures, or, predictors of treatment response. *Investigators should specify ANCOVA, MMRM, or the specific regression model used, any covariates adjusted or interaction terms.

Focus on patient-important benefit and harm outcomes

9. New studies must uniformly report incidence of angioedema and health utilization (e.g. urgent clinician visit, or emergency room visit). A core outcome set may promote such data collection.
10. Where there are treatment safety concerns, studies should be of sufficient length to, at least, address cancers and thrombosis, i.e. robust multi-year comparative studies. The framework addressing the safety of TCIs presented in the **Guideline main text**, along with the **Appendix,** provides additional study design considerations.
11. Adverse events (AEs) such as worsening of baseline CU, or new episodes of angioedema should be differentiated from other AEs, i.e. from possible treatment-induced harms. Due to the relapsing nature of CU, studies should separate adverse reactions from worsening of pre-existing CU (or, for instance, angioedema episodes) as this obfuscates assessment of treatment-specific harms (e.g. placebo experiences more adverse events due to worsening CU, while the intervention may improve in CU and therefore the study ends up reporting that the treatment group, compared to the placebo group, had less overall adverse events). This further reinforces the need for active comparator trials.

What is new in these AAAAI/ACAAI JTFPP Chronic Urticaria guidelines and what are others saying?

This JTFPP CU guideline advances trustworthy allergy-immunology guideline[26, 28, 29, 43, 318, 319] development[1] by its foundation in systematic reviews of the evidence, engagement of a multidisciplinary panel, adherence to a rigorous guideline development process, and the integration of patient and caregiver perspectives throughout. This guideline is distinguished from prior guidelines[14, 15, 23, 138, 320, 321]. The 2026 JTF guidelines emphasizes clear translation of evidence into clinically actionable, context-sensitive recommendations and introduces novel approaches to facilitate knowledge translation and mobilization[12, 322]. The 2026 JTF guidelines also explicitly addresses several limitations of prior urticaria clinical practice guidelines identified in a global systematic review and critical appraisal[3].

The current guideline also differs from our previous guidelines in several ways. The 2014 Chronic Urticaria guideline covered a broad range of topics, including diagnosis, trigger factors, and treatments, and represented a revision of the 2000 guideline. In contrast, the 2026 guideline focuses on diagnosis, outcome measures, pathophysiology and mechanisms, comorbidities, prognosis, and stepwise treatment regimens. The 2014 guideline used a now-outdated system for rating medical evidence, relying on categories of evidence to determine the strength of recommendations (A, B, C, D). The 2026 guideline adopts GRADE (recommend for, suggest for, suggest against, recommend against), fulfills explicit requirements for proper use of GRADE[10], and follows principles of trustworthy guideline development, including explicit management of potential conflicts of interest, consideration of equity, diversity, and inclusiveness, multistakeholder involvement, and an emphasis on incorporating the patient voice in shaping recommendations. Since the publication of the 2014 guideline, multiple new therapies,

including several biologics and immunomodulators, have emerged and are comprehensively addressed in the 2026 guideline. The 2026 update also provides more guidance on shared decision-making and practical considerations. In addition, the JTF guidelines incorporate expert opinion and complement associated reviews[21, 56].

In 2015, the British Society for Allergy and Clinical Immunology published a guideline for the management of CU. This guideline was developed through a web-based consensus process and covered clinical classification, etiology, diagnosis, investigations, and treatment guidance. It recommended a standard dose of a non-sedating H1-antihistamine as first-line therapy, with up-dosing of a single H1-antihistamine considered in case of inadequate response. In 2019, the Italian Society of Pediatrics (SIP), the Italian Society for Pediatric Allergy and Immunology (SIAIP), and the Italian Society of Pediatric Dermatology (SIDerP) developed a guideline focused on children, providing recommendations on diagnosis and management based on the Italian National Guideline (PNLG) methodology. In 2021, the British Association of Dermatologists also published a guideline for the management of people with CU. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI also published two guidelines, covering the definition, classification, diagnosis, and management of urticaria. All three guidelines strongly recommended adding omalizumab for patients with CU who are unresponsive to high-dose second-generation H1-antihistamines. In addition, the 2026 JTF guideline provides stepwise, evidence-based recommendations across different treatment stages and patient scenarios, ranging from treatment-naïve CU to H1-antihistamine-refractory and advanced disease, with clear guidance on medication selection, escalation, switching strategies, and special clinical situations.

Revision or adaptation of the guidelines

After publication of these guidelines, the JTF will maintain them through surveillance for new evidence, ongoing review by experts, and regular revisions[2]. This may include, for example, formal assessment of traditional, complementary and alternative medicines, or new treatments for CU (e.g. new BTK inhibitors, anti-KIT targeting antibodies, or other therapies).

Updating or adapting recommendations locally: Adaptation of these guidelines will be necessary in many circumstances. These adaptations should be based on the associated evidence-to-decision frameworks detailed throughout the **Guideline main text**.

The 2026 AAAAI/ACAAI JTF guidelines support achieving optimal outcomes in CU.

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