Appendix Supplement to the JTF CU Guidelines

Title

Chronic Urticaria (Hives, Itch, Swelling) 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 Golden MDCM[22], Marcus Shaker MD MS[23], Jonathan A. Bernstein MD[2], Caroline C. Horner MD MSCI[24], Jay Lieberman MD[25], Matthew A. Rank MD[26], Julie Wang MD[27], Giselle Mosnaim[28], Anne Ellis MD MSc[29], Elissa Abrams[30], Dennis Ledford MD[31], Katherine 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, Kimberly Legault, and Mark Matsos. Evidence in Allergy group evidence synthesis team members and additional collaborators appear in acknowledgements.

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

Detailed in the Methods and Appendix, the Guidelines followed JTFPP policies and international standards for addressing potential conflicts of interest. All JTFPP members' COI are available publicly at https://www.allergyparameters.org/

Sponsors/Funding

AAAAI/ACAAI Joint Task Force on Practice Parameters, https://www.allergyparameters.org/

Appendix Table of Contents

How is a trustworthy guideline made by the AAAAI/ACAAI JTFPP?

The Institute of Medicine laid out how trustworthy guidelines should be made and created key standards[1] as outlined in **Table E1** below. The standards, widely adopted by the international guideline community, are similar to those developed by the Guideline International Network (G-I-N) and McMaster University. These guidelines also fulfill requirements for claiming proper use of GRADE[2].

Table E1: Summary of Institute of Medicine standards for trustworthy guidelines and how the JTFPP Chronic Urticaria guidelines address them

1. Establishing transparency ***"The processes by which a CPG is developed and funded should be detailed explicitly and publicly accessible"***
• The guideline methods are available and published with additional details in the supplement. • The guideline and methods are open-access.
2. Managing conflicts of interest ***"Prior to selection of the guideline development group, individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity....",***
• Interests of each panel member are declared and published with the recommendations. • No one with financial interests in the past two years - as judged by the panel chairs and oversight by the methods team and JTFPP - participated in formulating or drafting recommendations. • Intellectual conflict of interests followed the same standards as financial conflicts of interest. Such conflicts include having taken a strong position on the issue, for example by a written forceful editorial, commentary, or conflicts related to performing a primary research study on the topic. • The co-chairs had methods expertise, a clinical background, and addressed by recusal any financial or intellectual interests declared. We planned that if a potential conflict among all chairs arose, then they would be recused for that recommendation and would be replaced by the methods resource person (GG) for the time required – this process was not encountered in making this guideline. • Pharmaceutical companies had no role in these recommendations. The guideline group had the ability, but not obligation, to consider public comments, including by companies, to the draft guidelines.
3. Guideline Development Group Composition ***"The guideline development group should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG"***
• The panel prioritized equity, diversity and inclusiveness through public calls for patient and healthcare provider engagement, gender and age balance, geographic diversity, balance of tertiary care, community, and rural representation, and inclusion of multiple stakeholders (front-line clinicians [pediatricians, internists, family physicians, emergency room physicians, nurses, pharmacists], patient and caregiver partners, patient advocacy groups, allergists/immunologists and dermatologists, methodologists). • The panel facilitated patient and public involvement by including patient experience, via patient and family partners and systematic reviews on values and preferences[3] to guide outcome choices and the relative importance of each outcome. • Patient and family partners were given priority during panel meetings and had an explicit role in vetting final values and preferences judgements.
4. Clinical Practice Guideline–Systematic Review Intersection ***"CPG developers should use systematic reviews that meet standards set by the IOM. Guideline development group and systematic review team should interact regarding the scope, approach, and output of both processes"***
• Each recommendation is based on one or more high-quality systematic reviews (SRs) developed and published in parallel with, or in advance of, the JTFPP CU Guidelines. • The evidence synthesis team and guideline are editorially independent from the sponsor/funder, with explicit agreement that the team considers JTF/funder feedback but has no obligation to incorporate it. • The guideline panel and systematic review teams interacted to facilitate communication and continuity in the process.
5. Establishing Evidence Foundations for and Rating Strength of Recommendations ***"For each recommendation: explain underlying reasoning, including a clear description of potential benefits and***

harms, a summary of relevant available evidence and description of the quality., explain the part played by values, opinion, theory, and clinical experience in deriving the recommendation, "provide rating of strength of recommendations"

- The GRADE approach[4] provided the framework for establishing evidence foundations and rating strength of recommendations. For each recommendation, systematic and transparent assessments were made across the following key factors:
  - Absolute benefit and harms for all patient-important outcomes of a particular action through structured evidence summaries (e.g. GRADE Summary of Findings tables)
  - Certainty (quality) of the evidence
  - Values and preferences of patients
  - Resources and other considerations (e.g. feasibility, applicability, equity)
- Each outcome included an effect estimate and confidence interval, with a measure of certainty in the evidence, as presented in Summary of Findings tables. If such data were not available, narrative summaries were provided.
- A summary of the underlying reasoning and all additional information (e.g. key factors, practical advice, references) is available and expanded on in the supplement. Summaries include how theory (e.g. pathophysiology) and clinical experience played into the evidence assessment and recommendations.
- Recommendations were rated either weak/conditional or strong, as defined by GRADE.
- If the panel members disagreed on evidence assessment or strength of recommendations, the panel planned to follow a structured consensus process customized to the GRADE system and planned to report any final differences in opinion, with their rationale, in the online supplement. However, the panel reached consensus on all recommendations.

6. Articulation of recommendations
"Recommendations should be articulated in a standardized form detailing precisely what the recommended action is, and under what circumstances it should be performed, and so that compliance with the recommendation(s) can be evaluated"

- Each recommendation appears in the infographic in the JTFPP Chronic Urticaria Guidelines and is available in standardized formats in the main text, articulated to be actionable based on best current evidence on presentation formats of guidelines.
- There is a statement included in each summary article in the Journal that these are recommendations to provide clinicians with guidance. They do not form a rigid mandate of action and should be contextualized in the healthcare system a clinician works in, and/or with an individual patient.

7. External review
"External reviewers should comprise a full spectrum of relevant stakeholders...., authorship should be kept confidential....., all reviewer comments should be considered....a rationale for modifying or not should be recorded in writing.... a draft of the recommendation should be made available to general public for comment.."

- XX external peer-reviewers reviewed the guideline before publication, and, together with XX public commentators, provided peer-review. Each had access to all the information in the guideline package. Each linked systematic review followed standard peer-review policies and processes.
- The guideline was posted for public comment for several weeks and feedback incorporated.
- The JTFPP, with methodological and content expertise, reviewed the Guideline publication and the systematic reviews.
- The JTFPP guideline panel was asked to read and respond to the peer-review comments and make amendments where they judged reasonable.

8. Updating
"The date for publication, systematic review and proposed date for future review should be documented, the literature should be monitored regularly and the recommendation should be updated when warranted by new evidence"

- The JTFPP monitors each guideline and provides scheduled updates in situations where the evidence suggests a change in practice.
- This JTFPP guidance represents living guidance, with a commitment to publish updated recommendations based on new and practice-changing evidence emerging after the first recommendations are published. The systematic review and meta-analyses produced by the Evidence in Allergy Group, commissioned by the AAAAI/ACAAI to be living syntheses, may inform the development of new or updated recommendations on a systematic basis according to need arising in the global community.

86

87

Addressing potential conflicts of interest

Disclosures

All panel members completed JTFPP and World Health Organization disclosure forms for financial and intellectual conflict of interests. These forms were reviewed by the guideline co-chairs and JTFPP. Any disclosed conflicts were assessed and managed according to JTFPP policies. EIA collaborators also assess and manage disclosures according to their established criteria by the high standards of JTFPP and similar guideline efforts (e.g. BMJ Rapid Recommendations).

Those with relevant conflicts of interest to the guideline question participated in the discussion about the scientific evidence and practical issues or implementation considerations and avoided giving judgmental statements that would suggest a specific direction or strength of recommendation during the discussions. They also recused themselves from the formal development of strength and direction of recommendations. Those without potential conflicts drafted the wording of the guideline recommendations. All panel members then provided input on the guideline in its entirety and its corresponding revisions. During revisions, the guideline panel did not change the population, intervention or comparator the recommendation addressed, the strength of recommendation, or its direction. All panel members and the JTFPP approved the final guideline.

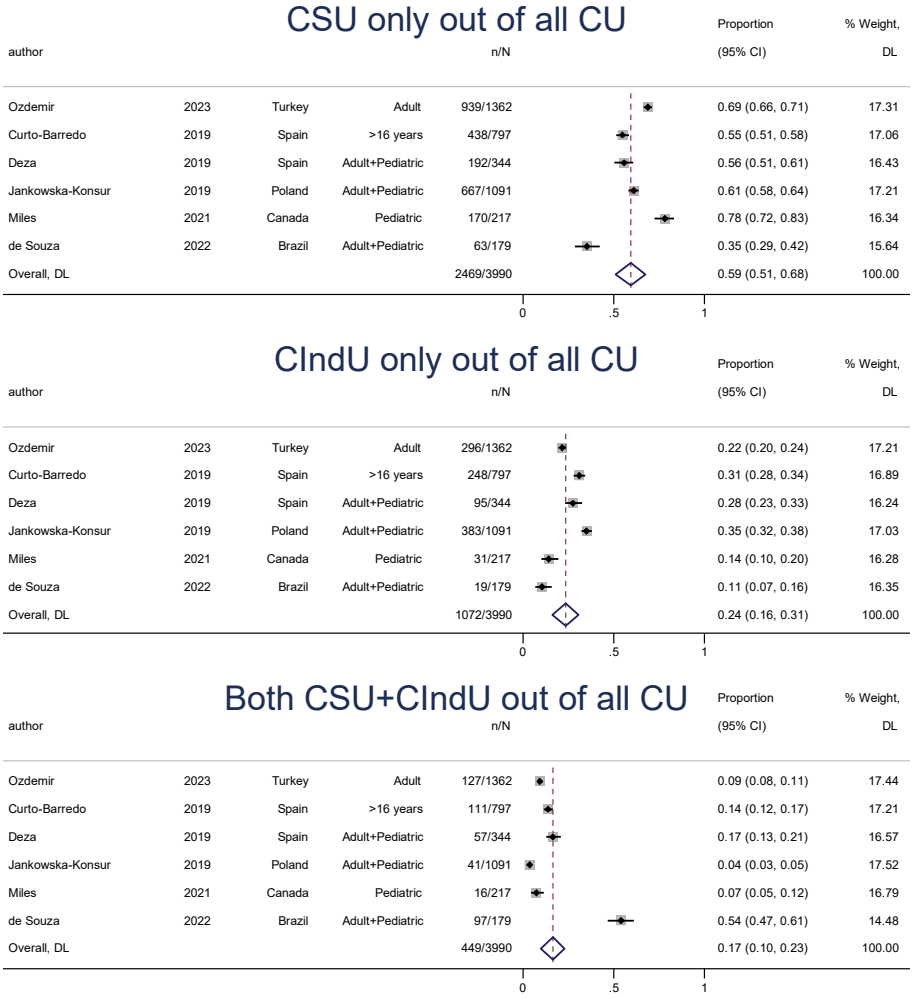
Recusals for each group of recommendations

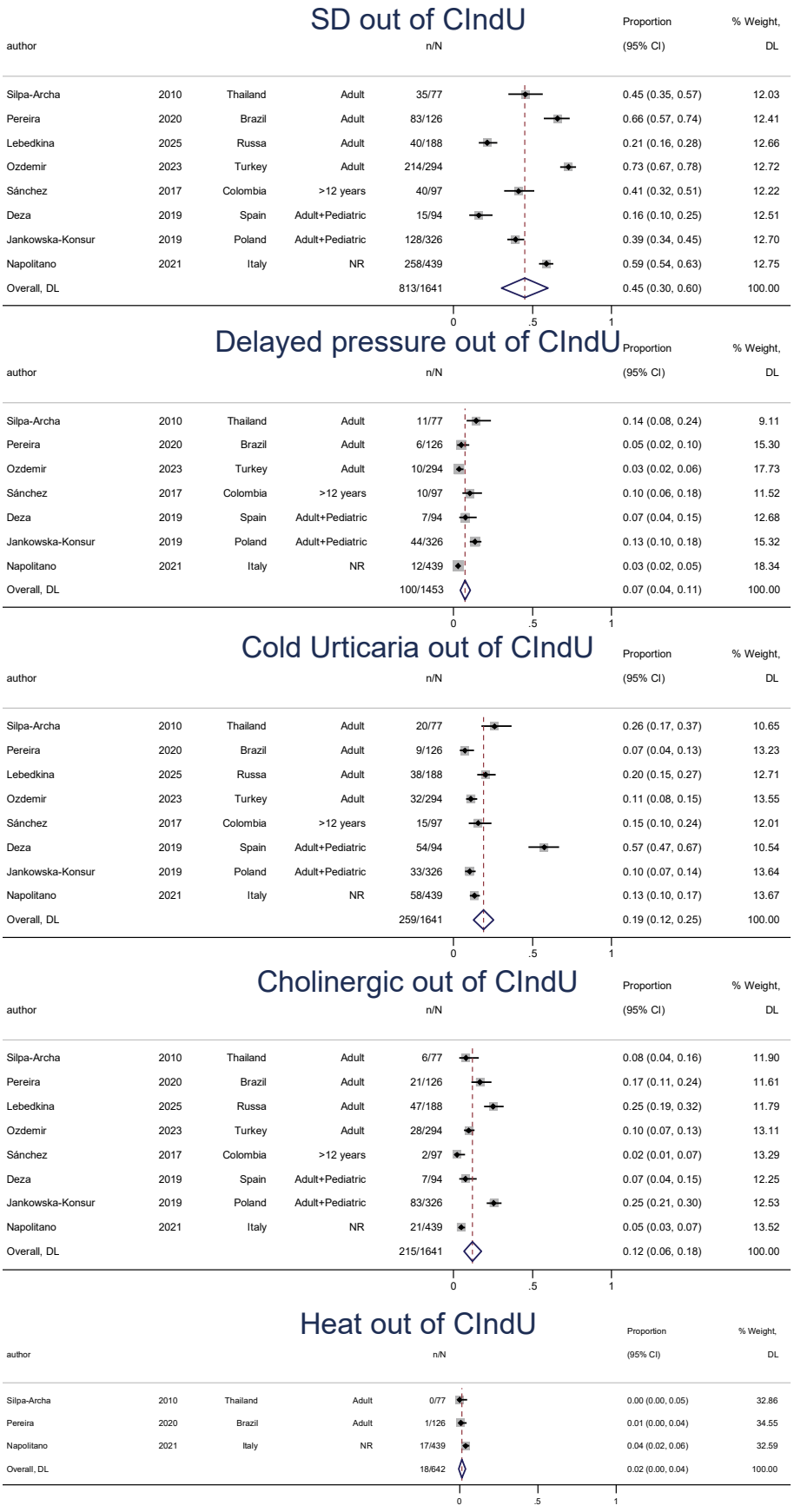
COI	Financial	Intellectual
Antihistamines	Susan Waserman Moshe Ben-Shoshan	Susan Waserman
Topical Corticosteroids	-	-
Leukotriene Antagonists	-	-
Vitamin D	-	-
UV Light	-	-
Systemic Corticosteroids	-	-
Biologics (Omalizumab, Dupilumab)	David M Lang Lisa A Beck Sarbjit S Saini Sameer K Mathur Susan Waserman Moshe Ben-Shoshan Jonathan A Bernstein Rachel Asiniwasis	David M Lang Lisa A Beck Sarbjit S Saini Susan Waserman Jonathan A Bernstein
Remibrutinib	David M Lang Lisa A Beck Sarbjit S Saini Sameer K Mathur Susan Waserman Moshe Ben-Shoshan Jonathan A Bernstein Rachel Asiniwasis	David M Lang Lisa A Beck Sarbjit S Saini Susan Waserman Jonathan A Bernstein
Cyclosporine	David M Lang Lisa A Beck Sarbjit S Saini Sameer K Mathur Susan Waserman Moshe Ben-Shoshan Jonathan A Bernstein Rachel Asiniwasis	David M Lang Lisa A Beck Sarbjit S Saini Susan Waserman Jonathan A Bernstein

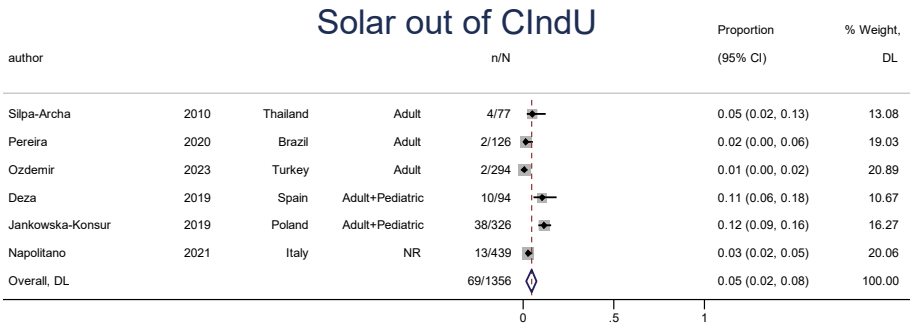
Colchicine	-	-
Hydroxychloroquine	-	-
Dapsone	-	-
Sulfasalazine	-	-
Mycophenolate	-	-
Azathioprine	-	-
Methotrexate	-	-

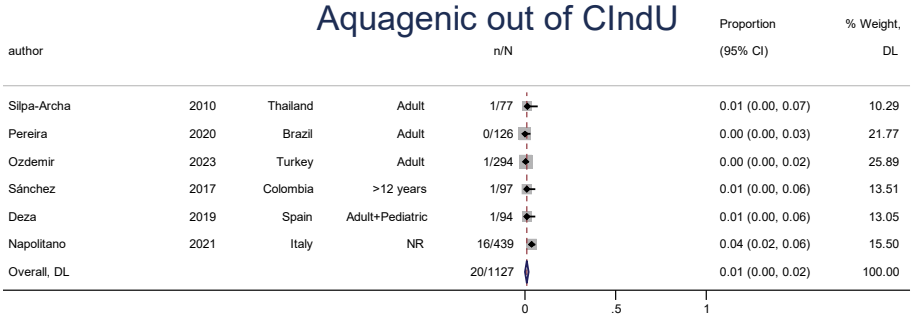
No Evidence in Allergy Group members involved in guideline development had relevant conflicts of interests.

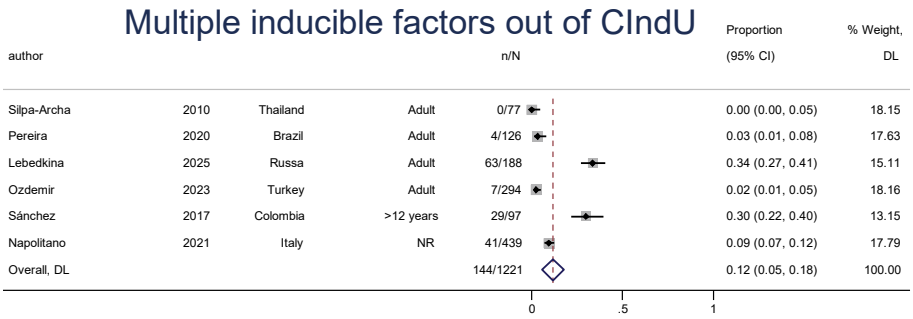
Meta-analyses of prevalence of urticaria subtypes among chronic urticaria




SD out of CIndU
author
n/N
Proportion (95% CI)
% Weight, DL
Silpa-Archa 2010 Thailand Adult 35/77 0.45 (0.35, 0.57) 12.03
Pereira 2020 Brazil Adult 83/126 0.66 (0.57, 0.74) 12.41
Lebedkina 2025 Russa Adult 40/188 0.21 (0.16, 0.28) 12.66
Ozdemir 2023 Turkey Adult 214/294 0.73 (0.67, 0.78) 12.72
Sánchez 2017 Colombia >12 years 40/97 0.41 (0.32, 0.51) 12.22
Deza 2019 Spain Adult+Pediatric 15/94 0.16 (0.10, 0.25) 12.51
Jankowska-Konsur 2019 Poland Adult+Pediatric 128/326 0.39 (0.34, 0.45) 12.70
Napolitano 2021 Italy NR 258/439 0.59 (0.54, 0.63) 12.75
Overall, DL 813/1641 0.45 (0.30, 0.60) 100.00
0 .5 1
Delayed pressure out of CIndU
author
n/N
Proportion (95% CI)
% Weight, DL
Silpa-Archa 2010 Thailand Adult 11/77 0.14 (0.08, 0.24) 9.11
Pereira 2020 Brazil Adult 6/126 0.05 (0.02, 0.10) 15.30
Ozdemir 2023 Turkey Adult 10/294 0.03 (0.02, 0.06) 17.73
Sánchez 2017 Colombia >12 years 10/97 0.10 (0.06, 0.18) 11.52
Deza 2019 Spain Adult+Pediatric 7/94 0.07 (0.04, 0.15) 12.68
Jankowska-Konsur 2019 Poland Adult+Pediatric 44/326 0.13 (0.10, 0.18) 15.32
Napolitano 2021 Italy NR 12/439 0.03 (0.02, 0.05) 18.34
Overall, DL 100/1453 0.07 (0.04, 0.11) 100.00
0 .5 1
Cold Urticaria out of CIndU
author
n/N
Proportion (95% CI)
% Weight, DL
Silpa-Archa 2010 Thailand Adult 20/77 0.26 (0.17, 0.37) 10.65
Pereira 2020 Brazil Adult 9/126 0.07 (0.04, 0.13) 13.23
Lebedkina 2025 Russa Adult 38/188 0.20 (0.15, 0.27) 12.71
Ozdemir 2023 Turkey Adult 32/294 0.11 (0.08, 0.15) 13.55
Sánchez 2017 Colombia >12 years 15/97 0.15 (0.10, 0.24) 12.01
Deza 2019 Spain Adult+Pediatric 54/94 0.57 (0.47, 0.67) 10.54
Jankowska-Konsur 2019 Poland Adult+Pediatric 33/326 0.10 (0.07, 0.14) 13.64
Napolitano 2021 Italy NR 58/439 0.13 (0.10, 0.17) 13.67
Overall, DL 259/1641 0.19 (0.12, 0.25) 100.00
0 .5 1
Cholinergic out of CIndU
author
n/N
Proportion (95% CI)
% Weight, DL
Silpa-Archa 2010 Thailand Adult 6/77 0.08 (0.04, 0.16) 11.90
Pereira 2020 Brazil Adult 21/126 0.17 (0.11, 0.24) 11.61
Lebedkina 2025 Russa Adult 47/188 0.25 (0.19, 0.32) 11.79
Ozdemir 2023 Turkey Adult 28/294 0.10 (0.07, 0.13) 13.11
Sánchez 2017 Colombia >12 years 2/97 0.02 (0.01, 0.07) 13.29
Deza 2019 Spain Adult+Pediatric 7/94 0.07 (0.04, 0.15) 12.25
Jankowska-Konsur 2019 Poland Adult+Pediatric 83/326 0.25 (0.21, 0.30) 12.53
Napolitano 2021 Italy NR 21/439 0.05 (0.03, 0.07) 13.52
Overall, DL 215/1641 0.12 (0.06, 0.18) 100.00
0 .5 1
Heat out of CIndU
author
n/N
Proportion (95% CI)
% Weight, DL
Silpa-Archa 2010 Thailand Adult 0/77 0.00 (0.00, 0.05) 32.86
Pereira 2020 Brazil Adult 1/126 0.01 (0.00, 0.04) 34.55
Napolitano 2021 Italy NR 17/439 0.04 (0.02, 0.06) 32.59
Overall, DL 18/642 0.02 (0.00, 0.04) 100.00
0 .5 1


Solar out of CIndU
author
n/N
Proportion (95% CI)
% Weight, DL
Silpa-Archa 2010 Thailand Adult 4/77 0.05 (0.02, 0.13) 13.08
Pereira 2020 Brazil Adult 2/126 0.02 (0.00, 0.06) 19.03
Ozdemir 2023 Turkey Adult 2/294 0.01 (0.00, 0.02) 20.89
Deza 2019 Spain Adult+Pediatric 10/94 0.11 (0.06, 0.18) 10.67
Jankowska-Konsur 2019 Poland Adult+Pediatric 38/326 0.12 (0.09, 0.16) 16.27
Napolitano 2021 Italy NR 13/439 0.03 (0.02, 0.05) 20.06
Overall, DL 69/1356 0.05 (0.02, 0.08) 100.00
0
.5
1


Aquagenic out of CIndU
author
n/N
Proportion (95% CI)
% Weight, DL
Silpa-Archa 2010 Thailand Adult 1/77 0.01 (0.00, 0.07) 10.29
Pereira 2020 Brazil Adult 0/126 0.00 (0.00, 0.03) 21.77
Ozdemir 2023 Turkey Adult 1/294 0.00 (0.00, 0.02) 25.89
Sánchez 2017 Colombia >12 years 1/97 0.01 (0.00, 0.06) 13.51
Deza 2019 Spain Adult+Pediatric 1/94 0.01 (0.00, 0.06) 13.05
Napolitano 2021 Italy NR 16/439 0.04 (0.02, 0.06) 15.50
Overall, DL 20/1127 0.01 (0.00, 0.02) 100.00
0
.5
1


Multiple inducible factors out of CIndU
author
n/N
Proportion (95% CI)
% Weight, DL
Silpa-Archa 2010 Thailand Adult 0/77 0.00 (0.00, 0.05) 18.15
Pereira 2020 Brazil Adult 4/126 0.03 (0.01, 0.08) 17.63
Lebedkina 2025 Russa Adult 63/188 0.34 (0.27, 0.41) 15.11
Ozdemir 2023 Turkey Adult 7/294 0.02 (0.01, 0.05) 18.16
Sánchez 2017 Colombia >12 years 29/97 0.30 (0.22, 0.40) 13.15
Napolitano 2021 Italy NR 41/439 0.09 (0.07, 0.12) 17.79
Overall, DL 144/1221 0.12 (0.05, 0.18) 100.00
0
.5
1

117

Implementation Guidance

This appendix provides practical, clinician-facing guidance to support implementation of the 2026 AAAAI/ACAAI JTF Chronic Urticaria recommendations in routine care. Each section is intended to accompany, not replace, the main guideline recommendations and should be interpreted together with the recommendation strength, certainty of evidence, qualifying remarks, and shared decision-making considerations in the main text. The handouts summarize common dosing approaches, safety issues, monitoring needs, access and feasibility considerations, special population issues, and situations in which a therapy may be unavailable or undesirable. They are designed to help clinicians individualize treatment, counsel patients, document rationale for treatment escalation or de-escalation, and coordinate care across allergy/immunology, dermatology, primary care, emergency medicine, pharmacy, and other settings. They also highlight research needs for each intervention studied.

The treatment-specific sections follow the general guideline sequence:

- Focused diagnosis and avoidance of unnecessary testing
- Oral second-generation H1-antihistamines and selected adjunctive strategies
    - Leukotriene antagonists
    - Topical corticosteroids
    - Vitamin D solely for CU
    - UV light therapy (Narrow-band UVB)
- Management of acute flares and avoidance of maintenance systemic corticosteroids
- First-line advanced systemic therapies
    - Omalizumab
    - Dupilumab
    - Remibrutinib
- Second-line advanced strategies, including:
    - Omalizumab dose or frequency adjustment
    - Switching among first-line advanced therapies
    - Calcineurin inhibitors
- Later-line options for refractory chronic urticaria
    - Hydroxychloroquine
    - Mycophenolate
    - Sulfasalazine
    - Dapsone
    - Colchicine
    - Azathioprine
    - Methotrexate

These implementation materials should not interpreted a rigid mandate and sole source of information for decision-making. Patients and clinicians, however, may find them helpful resources. The resources may evolve with updates in the evidence.

Practical information for testing at initial chronic urticaria visits

Summary of routine screening tests for occult disease in chronic urticaria

Patients often see multiple clinicians and develop concerns regarding their overall health, including potential health anxiety, before reaching an official diagnosis of chronic urticaria. Understandably, both clinicians and patients have raised questions as to what is driving chronic urticaria and whether it is a sign of a sinister occult disease.

Analogous scenarios arise in other diseases: occult cancer in unprovoked venous thromboembolism, occult cancer and the sudden appearance of multiple seborrheic keratoses that rapidly increase in size and number (sign of Leser-Trélat). If and how clinicians should screen patients with a new diagnosis of chronic urticaria has been unclear. Existing clinical practice statements often mix screening for occult diseases with tests that might help predict whether a patient will respond to a specific treatment for urticaria. Thus, previous guideline recommendations ranged from no routine additional investigations (e.g. skin prick tests, blood tests) to extensive blood tests with or without other types of investigations (e.g. imaging). As standard in the routine practice of medicine, all routine clinical visits include a general history with review of systems and physical exam.

To reduce harms of tests for screening for other conditions in patients with chronic urticaria

While allergies (e.g. allergic rhinitis) are common among the general population and those with CU, skin prick testing and serum specific-allergen IgE testing can produce false positives, and it is implausible that CU, especially CSU, is driven by contact urticaria. Hence, the rationale and interpretation of any allergen-specific testing should be made clear to patients. Routine allergen testing in CU without a clear clinical history suggestive for a temporal relationship between exposure to an allergen and the onset of hives or angioedema increases resource use (time and financial) and can lead to unnecessary anxiety and ineffective environmental avoidance strategies.

Similarly, unless directed by abnormal features of the history and physical, untargeted or non-specific blood or other investigations increase costs and resource use with the potential harm and burden from false-positive tests and follow-up more invasive investigations.

As stated above, the desire for testing is often driven by the aim to understand what is causing the recurrent nature of itch, hives, swelling or all three, and to gain self-efficacy. Clinicians should therefore focus on explaining the self-resolving nature and course of CU.

When routine blood testing is undesirable

No laboratory testing is required if there are no suspected occult diseases based on history, review of systems, and physical examination.

Implementation practical considerations

- **Emotional well-being, coordination of care:** Unnecessary blood or other tests promote overmedicalization and diverts attention away from the core issue – that hives are more so internal disease processes rather than being driven by some external stimulus.
- **Costs and access:** Unnecessary testing increases resource (e.g. financial and time) use.
- **Tests and visits:** Unnecessary tests may lead patients to attend additional hospital or clinic sites for evaluation.

Evaluation

Patients with CU may require routine follow up (e.g. depending on treatment response). As is the case in the routine practice of medicine, such evaluations include routine history including review of systems and physical exam. As stated above, untargeted investigations increase multiple burdens to patients and the healthcare system.

The main text guideline table presents common mimickers of CU (e.g. autoinflammatory syndromes, Schnitzler's syndrome, urticarial vacuities, papular urticaria, bradykinin-mediated angioedema), clues suggesting their possible diagnosis, and investigations.

Note that these issues address diagnosis of CU and ruling out underlying conditions with screening tests. A separate question is whether laboratory tests predict response to CU treatments (addressed in separate forthcoming guidance).

Research needs

Implementation science strategies may be required for optimal dissemination and implementation into routine clinical practice.

Adaptation

These findings are likely applicable globally and adapted to many local contexts. For example, in regions where parasitic infections are endemic, symptom- and risk-directed testing may be warranted.

Summary of Findings – Tests for occult disease in chronic urticaria

Evidence addressing occult diseases among patients with CU is presented in the guideline main text.

Practical information: Using H1-, H2-, and combined antihistamine

Summary of how to use oral H1- and H2- antihistamines for chronic urticaria

Cetirizine, levocetirizine (US, not Canada), loratadine, desloratadine, fexofenadine, and, in Canada (not US), rupatadine and bilastine, are available second-generation H1-antihistamines (SGAH). For CU, they are initially administered at their licensed once daily dose, and can be up-dosed to 4 times their FDA/Health Canada-recommended standard daily dose as needed.

Generic (Brand)	Adult Dose (Daily)	Pediatric Dose (Daily)	Renal / Hepatic Adjustment for adults	OTC / Rx	Approx. Cost
Cetirizine (Reactine/Zyrtec)	10 mg	6 mo-5 yrs: 2.5-5 mg	CrCl <30 mL/min: 5 mg daily	OTC	$8-12 gen; $15-20 brand
Levocetirizine (Xyzal) [US]	5 mg	6 mo-5 yrs: 1.25-2.5 mg; 6-11 yrs: 2.5 mg	CrCl <30 mL/min: 2.5 mg daily	OTC	$10-15 gen; $18-25 brand
Loratadine (Claritin)	10 mg	2-9 yrs: 5 mg	Severe liver and 30kg+: 5 mg daily or 10 mg every 2 days; Severe liver and <30kg: 5 mg every other day	OTC	$8-12 gen; $15-20 brand
Desloratadine (Aerius/Clarinex)	5 mg	6-11 mo: 1 mg; 1-5 yrs: 1.25 mg; 6-11 yrs: 2.5 mg	Severe hepatic/renal impairment: 5 mg every other day	OTC (CA) Rx (US)	CA: $14-20 US: $15-40
Fexofenadine (Allegra)	180 mg (or 60 mg bid)	2-11 yrs: 30 mg bid	Renal impairment: 60 mg daily	OTC	$10-15 gen; $18-25 brand
Bilastine (Blexten) [Canada]	20 mg	4-11 yrs, 16kg+: 10 mg; 12-17 yrs: 20 mg	Avoid in severe renal impairment and strong P-gp inhibitors (e.g. cyclosporine, diltiazem).	Rx (CA)	$25-35 CAD
Rupatadine (Rupall) [Canada]	10 mg	2-11 yrs: 10-25 kg: 2.5 mg; >25 kg: 5 mg	Avoid in severe hepatic/renal impairment; caution with strong CYP3A4 inhibitors	Rx (CA)	$50-70 CAD/30 tabs; $33 CAD /120 mL

1st generation antihistamines that are recommended against include Diphenhydramine (Benadryl), Chlorpheniramine (Chlor Trimeton), Hydroxyzine (Atarax, Vistaril), Clemastine (Tavist), Cyproheptadine (Periactin); a mast cell stabilizer, ketotifen (Zatiden), is included in this category. SGAH available, and unique to, other world regions include ebastine, mizolastine, olopatadine (oral), bepotastine (oral), and azelastine (oral).

H2-receptor antagonists (H2RAs), such as famotidine (e.g. Pepcid AC), are technically also antihistamines but are primarily used as OTC antacids (e.g. for heart burn). They may be used in combination with SGAH for CU. Exactly how H2RAs work in CU and allergy remains unclear.

While tachyphylaxis (loss of drug effect with continued use over time) to H2RAs is recognized for its antacid effects, evidence shows no tachyphylaxis occurs with SGAH for CU or allergy.

To reduce harms of H1- and H2-antihistamines

- Use a SGAH with, on average, fewest adverse effects (e.g. sedation, drowsiness, dry mouth) such as (in alphabetical order) bilastine, desloratadine, or fexofenadine. Other SGAH in the table above have a slightly higher risk of sedative/cognitive adverse reactions, but they are far lower compared to first generation H1 antihistamines.
- Use the lowest dose that reliably controls CU activity and severity.
- Avoid first-generation H1-antihistamines (listed above) since they increase sedation, delirium, reaction time, seizure, cognitive impairment, dry mouth, urinary retention and can persist for 24-48 hours. They also have abuse potential and can be life-threatening.
- Consider patient age, drug- drug interactions, and comorbidities (e.g., kidney and liver disease, cognitive impairment or dementia), as well as patient's preferences and values.
- For H2-antihistamines, cimetidine has the greatest potential among these agents for significant drug-drug interactions through its inhibition of several cytochrome P450 oxidase pathways and other metabolic pathways such as organic compound inhibitors.
- Keep antihistamine regimens simple by preferring to use a single oral H1 antihistamine for daily and on-demand use (e.g. only a single SGAH agent, not SGAH and a 1st generation antihistamine like diphenhydramine [Benadryl in USA and Canada]).

When H1- and H2-antihistamines are unavailable or undesirable

When one SGAH or H2RA is not available due to cost or formulary restrictions, there are alternative agents in the same class that can be used with similar efficacy. Patients and clinicians should consider the differences in adverse reactions (e.g. sedation), noted above and in the guideline main text, among the various SGAH. Similar considerations apply to accounting for impaired renal or liver (hepatic) function. The guideline, however, suggests against H2RAs.

When H1- and H2-antihistamines may not be a good option

The only contraindication for using H1- or H2 antihistamines is very rare allergic hypersensitivity reactions, which may be to medication or non-medication components (e.g. coloring, filler).

Implementation practical considerations

- **Medical routine:** Dosing SGAH can be once daily, and up to 4-times the standard once-daily dose (similar daily drug levels are predicted if taken as one dose at breakfast, lunch, dinner, and bedtime, or double-dose in morning and afternoon/evening). Patients with rare, but severe, CU (e.g. severe angioedema) may prefer to take a single double-dose on demand. If attacks, however, are frequent (e.g. weekly), daily dosing may be more effective than solely on-demand dosing.
- **Adverse effects:** Avoid first-generation H1 antihistamines. The SGAH with lowest sedative adverse reaction potential are, on average, bilastine, desloratadine, and fexofenadine. Cetirizine and levocetirizine have a rare and uncertain association with isolated itch if suddenly discontinued. If this occurs, taper cetirizine rather than suddenly discontinuing.
- **Drug interactions:** Avoid Grapefruit juice with SGAH (e.g. bilastine). Adjust dosing, as applicable per each SGAH, for impaired liver or kidney function.
- **Food and drinks:** Most H1-antihistamines are not importantly affected by food.
- **Cost and access:** Most SGAH and H2-antihistamines are OTC and low cost (less than $1 per dose). Purchasing in bulk (e.g. Costco, Sam's Club, or generic rather than brand medications) or direct (e.g. CostPlusDrugs) may offer optimally affordable treatment regimens. Clinicians should prescribe sufficient amounts and refills according to patient disease activity and severity.
- **Pregnancy and lactation:** The available data show that SGAH are safe for women who are pregnant or breastfeeding (e.g. impact on milk supply and excretion), albeit less evidence exists for bilastine and rupatadine, or for SGAH at 4x the standard daily dose.

Evaluation

Standard evaluation of treatment response (see guideline introduction for outcome measures) may occur over 2 to 4 weeks to determine complete or partial control and any adverse effects.

Research needs

Many insurers demand a trial of 4x dosing of antihistamines before approving advanced therapies, but this is not strictly supported by RCTs. The available biologics and other advanced treatments approved for CU largely studied patients refractory to a single standard dose of H1 antihistamine, not strictly 4x doses. Thus, the precise benefits and harms of 4x dosing, compared to 1x dosing, or advanced therapies (e.g. biologics, remibrutinib) need robust RCTs.

Adaptation

These findings are likely applicable globally and can be adapted to many local contexts. Some region-specific SGAH are presented in the Table and main text.

Summary of Findings – Antihistamines for chronic urticaria

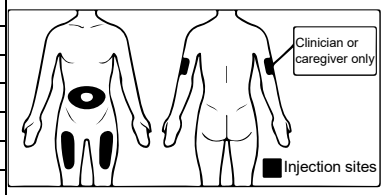
The systematic review and network meta-analyses compares the efficacy and safety of all available H1 and H2 antihistamines, mast cell stabilizers, and their combinations among patients with CU[5]. Their findings are summarized in the guideline main text.

Practical information for using omalizumab for chronic urticaria

Summary of how to use omalizumab (Xolair, Omlyclo, and biosimilars)

- Omalizumab is a recombinant, humanized monoclonal antibody targeting IgE for patients with CU uncontrolled by, or intolerant of, antihistamines.
- Omalizumab should be stored at 2-8°C (36-46°F) and, before administration, unopened at room temperature for 20 minutes to warm up. Do not use heat or water to warm.
- Omalizumab is administered, similar to insulin injections for diabetes, subcutaneously using clean technique by either a clinician (physician office, injection center), or, after adequate training and observation, patients or caregivers.
- Available syringes are routine office syringes and use of a shaker to resuspend dry-powder omalizumab, pre-filled syringes, or autoinjectors (pens).
- It is generally advisable to continue antihistamines when adding omalizumab.
- Omalizumab is dosed, without a loading dose, usually every four weeks. In contrast to omalizumab for asthma, dosing is not based on body weight or serum total IgE level.
- FDA and Health Canada recommend initiating dosing in a healthcare setting for patient monitoring due to an uncertain rare possibility of systemic allergic reactions. Whether this is necessary for all patients, its added value, and time- and resource-tradeoffs, however, remains unclear and are likely preference-sensitive. There is no absolute requirement for patients to carry emergency epinephrine (e.g. injectable or intranasal). Due to the rarity of such events, the limited available suggest that 20% of patients that experience a systemic reaction after omalizumab may tolerate it again.
    - It is uncertain whether a history of anaphylaxis unrelated to omalizumab is a risk factor for systemic reactions to omalizumab.
    - Recognizing that uncontrolled CU can often be confused with anaphylaxis, and that, anaphylaxis, in general, is commonly misdiagnosed, the above suggestions are uncertain and therefore, likely preference sensitive rather than mandates.

Omalizumab Dosing	**Xolair (prefilled syringe, autoinjector; similar for lyophilized powder)**			**Omlyclo (prefilled-syringe only)**	
Syringe doses (color)	75 mg (Blue)	150 mg (Purple)	300 mg (Grey)	75 mg (Yellow)	150 mg (Blue)
75 mg	1			1	
150 mg		1			1
225 mg	1	1		1	1
300 mg			1		2
375 mg	1		1	1	2
450 mg		1	1		3
525 mg	1	1	1	1	3
600 mg			2		4



Equivalent Xolair and Omlyclo doses can be achieved with different combinations of 150 or 300 mg of syringes.

To reduce harms of omalizumab

Although the frequency of anaphylaxis from omalizumab injections in post-marketing reporting has been quite low (estimated at around 0.2% of patients), it remains advisable that all patients be counseled on the signs and symptoms of anaphylaxis, how to seek emergency care, and if prescribed, how to use emergency epinephrine.

When omalizumab is unavailable or undesirable

Dupilumab and remibrutinib are other FDA-approved systemic treatments to manage antihistamine-unresponsive CU. Other off-label treatments options include, but are not limited to, cyclosporine, mycophenolate, sulfasalazine, dapsone, colchicine, and hydroxychloroquine.

When omalizumab may not be a good option

- If there is severe or recurrent hypersensitivity to it or its components.
- If there is no response to omalizumab after about a 4-6 month treatment course.

Implementation practical considerations

- **Medication routine:** After sustained control of CU, which can be seen within the first weeks after injection, typically obvious within about 4 months of treatment and can continue to improve over a year, the injections can be attempted to be tapered (e.g. every 5 weeks, then, if continued control, every 6 weeks, and so on). If controlled at dosing every 8 to 12 weeks, a temporary pause can trialed to see if there is sustained control off omalizumab.
  Antihistamines are typically continued as routine and on-demand while on omalizumab and may be tapered as control is achieved.
- **Procedure and device:** Omalizumab is administered by injection subcutaneously and may, with training, be self-administered. The first 3 injections may have an in-person observation period of 2 hours each. Omalizumab must not be frozen.
- **Coordination of care:** Patients either pick up the medication or have it shipped to their home by specialty pharmacies. Given its high cost and temperature storage needs, it is helpful to plan ahead to retrieve the medication in a timely manner.
- **Travel and driving:** Since biologics are usually stored at around 4°C, some patients adjust their travel schedules to fall around injection dates and avoid travelling with it. Alternatively, patients can travel with omalizumab in a bag with ice packs and a thermometer, or, if kept at room temperature as per above, can be used within 2 days.
- **Adverse effects:** The most common effect is mild injection site discomfort. Very rare systemic reactions can occur in about 0.2%. There is no credible increase in heart attack, stroke, or blood clots.
- **Pregnancy and lactation:** The limited available data suggest omalizumab is safe in pregnancy (comparable birth characteristics to those not on omalizumab). Omalizumab is approved as safe for use in patients aged 1 year and above; individuals less than one year may be exposed via placental transfer and breastfeeding and there is no compelling theoretical or clinical evidence of harm.
- **Costs and access:** Insurers typically cover the cost of Xolair and Omlyclo (ranging about $5,000 to $30,000 per year). Omlyclo may be less expensive. Company patient support programs can facilitate insurance negotiation, medication delivery, and training.

Research needs

Robust direct RCT comparisons among advanced systemic treatments (higher than standard doses of omalizumab [e.g. 600 mg q4wks, or 300 to 450 mg q2wks], new medications and conventional immunosuppressives) as well as combination treatments are required to address patients with severe refractory CU or those with partial response to omalizumab. Credible predictive biomarkers for treatment response may also inform optimal therapy. Studies should include children and patients that are pregnant, become pregnant, and those that are nursing.

Evaluation

Standard structured evaluation of treatment response (see guideline introduction for outcome measures) and adverse reactions occurs over 8 to 16 weeks to determine complete or partial control and any adverse effects. As described above, if there is sustained control (e.g. 3-6 months) of CU, the time interval between doses may be gradually extended to evaluate if control continues with less frequent dosing.

Adaptation

These findings are likely applicable globally and can be adapted to many local contexts.

Summary of Findings – Omalizumab for chronic urticaria

The systematic review and network meta-analyses compares the efficacy and safety of all available advanced systemic treatments for CU[6]. Their findings are summarized in the guideline main text.

Practical information for using leukotriene antagonists for CU

Summary of how to use antileukotrienes for chronic urticaria

- Leukotriene receptor antagonists (LTRA, e.g. montelukast [Singulair]) are oral medications that inhibit the CysLT1 receptor, thus blocking the effects of the leukotriene LTC_4. Montelukast is currently the most commonly used LTRA in the US and Canada.
- Zileuton (Zyflo; available in US, not Canada) inhibits the enzyme 5-lipooxygenase that produces leukotrienes and therefore inhibits the action of LTB_4, LTC_4 and LTD_4.
- Antileukotrienes may be added to CU therapy with antihistamines. Few studies suggest a similar small benefit when added to antihistamines for acute flares of chronic urticaria or acute urticaria.
- In most world regions, antileukotrienes are approved for marketing for allergic rhinitis and asthma and are used off-label for urticaria. Off-label means that there may be numerous studies of the medication, but the producer of the drug did not pursue formal permission to make a health claim with government regulators to market the drug for urticaria specifically. Many routine practices in medicine use medications off-label.
- Antileukotrienes such as montelukast were typically dosed in the evening to coincide with when peak leukotriene synthesis occurs, but studies suggest morning or evening dosing has similar effects due to the medication's long duration of action.

Drug	**Montelukast**	**Zafirlukast**	**Pranlukast**	**Zileuton**
Brand Names	Singulair	Accolate	Onon (Japan), Azlaire	Zyflo, Zyflo CR
Mechanism	Leukotriene receptor antagonist			Synthesis inhibitor
Availability - US	Yes	Yes	No	Yes
Availability - Canada	Yes	No	No	No
Availability - EU/UK	Yes	No	No	No
Boxed Warning?	Rare*, uncertain neuropsychiatric effect	No, but warning for liver toxicity	No	No, but warning for liver toxicity
Food / Drug Interactions	No meal changes; CYP interactions	Take 1-2 hrs before meals; CYP interactions	Take after meals; CYP interactions	Take with meals; CYP interactions
Adult Dose	10 mg once daily (evening usually)	20 mg twice daily	225 mg twice daily	2400 mg per day (Zyflo CR 1200 mg twice daily; Zyflo 600 mg 4x per day)
Pediatric Dose	15+ years: 10 mg; 6-14 years: 5 mg; 6 mo-5 years: 4 mg; All are once daily	≥5 years: 10 mg twice daily	7-10 mg/kg/day (divide total dose over twice per day; max 450 mg per day)	Not approved under 12 years
Dose Adjustment - Renal Impairment	No	No	Not required	No
Dose Adjustment - Hepatic Impairment	Not unless severe	Contraindicated in liver impairment including cirrhosis	Caution, monitor liver enzymes/function	Contraindicated in active liver disease
Monitoring Requirements	Monitoring for neuropsychiatric events	None specified, consider neuropsychiatric	None specified, consider neuropsychiatric	Liver function tests every 3 months. Consider neuropsychiatric
U.S. Approximate Price per Tablet	$0.40 - $0.90 (generic)	$1.12 (10 mg), $1.34 (20 mg)	Not available	$2.00 - $4.00 (Zyflo CR)

*The FDA's montelukast boxed warning discussing and monitoring for rare mental health side effects, including suicidal thoughts or actions, aimed to acknowledge conflicting data about these rare events, the uncertainty in the evidence, to raise awareness about considering pre-existing patient mental health comorbidity before prescribing, for monitoring when using, and to consider the balance of potential benefits and harms when using it.

To reduce harms of LTRA

In March 2020, the FDA required a boxed warning for the use of montelukast, in part due to uncontrolled post-marketing reports of mental health side effects, including suicidal thoughts or

actions. Although these side effects are rare and the association uncertain, discontinue montelukast if there are any concerns about mental health changes, including behavioral changes, hallucinations, or nightmares. The list of possible neuropsychiatric events has expanded over time and is becoming increasingly broad:

- agitation, including aggressive behavior or hostility,
- attention problems
- bad or vivid dreams
- depression
- disorientation or confusion
- feeling anxious
- hallucinations (seeing or hearing things that are not really there)
- irritability
- memory problems
- obsessive-compulsive symptoms
- restlessness
- sleepwalking
- stuttering
- suicidal thoughts and actions
- tremor or shakiness
- trouble sleeping
- uncontrolled muscle movements

For other antileukotrienes, use with caution with any liver disease or dysfunction.

Implementation practical considerations

- **Medication routine:** Before starting montelukast, patients and clinicians should discuss and evaluate any pre-existing mental health comorbidities and rare uncertain future harms. The medication is usually taken by mouth once or twice per day.
- **Adverse effects:** Antileukotrienes are generally well tolerated. Montelukast's boxed warning encourages shared decision-making. For zileuton, monitor liver enzymes and function.
- **Emotional well-being, social life and relationships:** If serious mental health changes occur, discontinue the antileukotriene and patients should discuss with clinicians.
- **Food and drinks:** Montelukast does not require timing around meals. Other antileukotrienes do (each varies, see table above).
- **Pregnancy and nursing:** If the potential benefits outweigh the potential harms, montelukast can be used in pregnancy and nursing. Other antileukotrienes are generally avoided in pregnancy and nursing due animal data suggesting potential harm (e.g. zafirlukast), or liver toxicity (e.g. zileuton), and lack of direct clinical safety data.

Research needs

Robust direct RCT comparisons of antileukotrienes added to antihistamines for mast cell-mediated angioedema (with or without hives), as well as combination treatments (e.g. added to omalizumab or other advanced therapies) are required to address patients with severe refractory CU, especially those with angioedema, and those with partial response to advanced therapies.

Clear and precise definitions of the most patient-important neuropsychiatric safety outcomes are required, followed by robust safety studies to clarify the certainty and magnitude of association, if any, between antileukotrienes for allergy and urticaria and such harm outcomes.

Evaluation

Standard structured evaluation of treatment response (see guideline introduction for outcome measures) and adverse reactions occurs over 8 to 16 weeks to determine complete or partial control and any adverse effects. If using montelukast, monitor for neuropsychiatric effects.

Adaptation

These findings are likely applicable globally and can be adapted to many local contexts.

Summary of Findings – Antileukotrienes for chronic urticaria

The systematic review and network meta-analyses compares the efficacy and safety of all available antileukotrienes, antihistamines, and other therapies for CU[6, 7]. Their findings are summarized in the guideline main text.

Practical information for using systemic corticosteroids for CU

Summary of how to use systemic corticosteroids (e.g. prednisone, dexamethasone)

Systemic corticosteroids (e.g. prednisone, prednisolone, methylprednisolone, and dexamethasone; also called glucocorticoids) are used to treat several conditions, often to address flares of them, and may be effective for acute severe flares of CU.

Most studies addressing systemic corticosteroids for acute urticaria and CU used short courses (<1 week) of high doses (e.g., prednisone 20-40 mg per day in adults or similar)[8]. **Common problems with systemic corticosteroids are rebound flare of the disease after the drug is stopped, the potential for adrenal insufficiency, and that there are multiple recognized harms of using long-term or repeated cycles of systemic corticosteroids**[8-11].

To reduce harms of SCS

- Use safer, effective alternative agents instead of systemic corticosteroids to control CU. Use adjunct SCS only when alternative agents are not effective for treating flares, and only after a trial of antihistamines (see SGAH section above and in guideline main text).
- When prescribing systemic steroids as an add-on to existing therapy (e.g. antihistamines), give for only a short period (i.e., ≤7 days). Avoid long-term or repeated use, even at low doses. Obtain urgent follow up with CU specialist if used.

When SCS are unavailable or undesirable

- In most cases, antihistamines alone provide more effective and safe treatment for CU flares, and adjunct systemic corticosteroids are unnecessary and undesirable.

Implementation practical considerations

- **Medication routine:** Systemic corticosteroids are available in multiple forms, including oral tablets, liquid solutions, and intramuscular injections. With short courses of 10 days or less, the drug can be stopped after the course is complete. Long-term use or repeated cycles, however, require gradual tapering to avoid potentially life-threatening adverse reactions such as adrenal crisis. Tapering instructions may be complex and confusing for patients, so clear guidance, visual aids, and follow-up are important.
- **Adverse effects:** Common adverse reactions of short-term systemic corticosteroids include weight gain and face changes, growth impairment, abdominal pain and acid reflux, headache, anxiety, behavioral changes, and sleep disturbance[12, 13]. Other potential adverse reactions include facial flushing, increased appetite, increased blood pressure, increased blood sugar (including diabetes), infection, and adrenal insufficiency. Long-term use and repeated cycles increase the risk of serious adverse effects, including osteoporosis, bone fracture, type 2 diabetes, cardiac conditions, and cataracts[9, 10]. A study of systemic corticosteroids for asthma found that the risk of most adverse outcomes increased at cumulative exposures between 1.0 to 2.5 g and the risk of some adverse outcomes increased at cumulative exposures as low as 0.5 to 1 g[14]. Short-term use can cause serious events, with less than 30 days of oral steroids being associated with increased risk of sepsis (IRR 5.3; 5 vs 1 per 1000), venous thromboembolism (IRR 3.33; 8 vs 2 per 1000), and bone fracture (1.87; 27 vs 14 per 1000)[15]. Use of systemic corticosteroids in CU specifically has been associated with increased risk of their related adverse effects and higher health care costs[16].
- **Tests and visits:** Monitor for signs of adrenal insufficiency following discontinuation[17, 18] and assess, as needed clinically, with morning serum cortisol, and ACTH stimulation tests[19]. Initiate treatment immediately for suspected adrenal crisis.
- **Recovery and adaptation:** If used daily for more than 4 weeks, do not abruptly stop systemic corticosteroids without guidance from a physician. Adrenal insufficiency can occur following discontinuation of treatment.

- **Coordination of care:** Additional health problems can accumulate with long-term or repeated systemic corticosteroid use that require additional clinicians to coordinate care. If on long-term systemic corticosteroids, special coordination is required for surgeries/procedures, and additional medications may be needed to prevent severe infections or bone loss and fracture.
- **Emotional well-being, Social life and relationships:** It is possible that by relieving acute flares of CU, systemic corticosteroids may help improve quality of life and emotional well-being. Common adverse effects, however, include behavioral and mood changes, such as sleep disturbance, anxiety, not feeling or acting like oneself, mood swings, and irritability (such as anger and impatience). Other adverse effects, such as facial flushing, swelling and weight gain may also cause significant distress to patients.
- **Pregnancy and nursing:** Some studies have reported a potential link between SCS use in pregnancy and increased risk of cleft palate, low birth weight, preterm birth, preeclampsia, or gestational diabetes[20]. However, research findings have been inconsistent, and in many cases, the association has not reached statistical significance. Most pregnant patients prefer trying alternative agents before SCS. If needed, some may be willing to use SCS at the minimally necessary dose and duration and most commonly during the third trimester.
- **Costs and access:** Although SCS are generally inexpensive, they are typically only accessible when prescribed on an urgent basis. Patients may face significant time and travel burdens in seeking treatment for an active flare. Furthermore, prescriptions with tapering schedules may in some cases complicate insurance coverage, and insurance providers may need to be informed of the nuances.
- **Food and drinks:** Patients on systemic steroids commonly experience an increased appetite. Maintain a healthy diet. Taking doses in the morning with breakfast may help mitigate the potential gastrointestinal effects and sleep disturbances.
- **Exercise and activities:** Long-term use of SCS increases the risk of osteoporosis and muscle weakness, which are more prevalent in older adults. These conditions may contribute to an increased risk of injury during exercise and other activities. Older adults in particular may benefit from closer monitoring for changes in bone density and muscle strength, as well as counseling to optimize nutrition and nutritional supplementation (e.g., calcium, vitamin D).

Evaluation

Close clinical monitoring is required to ensure prompt treatment of potential rebound disease or adrenal insufficiency following discontinuation of systemic corticosteroids, as well as transition to a safer long-term control regimen. Patients on long-term or recurrent systemic steroids should be regularly assessed to minimize harms to endocrine function, bone health, growth, cardiovascular health (e.g. dyslipidemia, heart attack), blood sugars and diabetes, and eye health.

Research Needs

Robust RCTs evaluating whether a short course of systemic corticosteroids, compared to placebo and other immunomodulatory agents (e.g. cyclosporine) has any important long-term effect on inducing remission for CU are required.

Adaptation

Systemic corticosteroids are available worldwide, with some evidence suggesting they are overused, and therefore these recommendations encourage their limited and judicious use.

Summary of Findings – Systemic corticosteroids for chronic urticaria

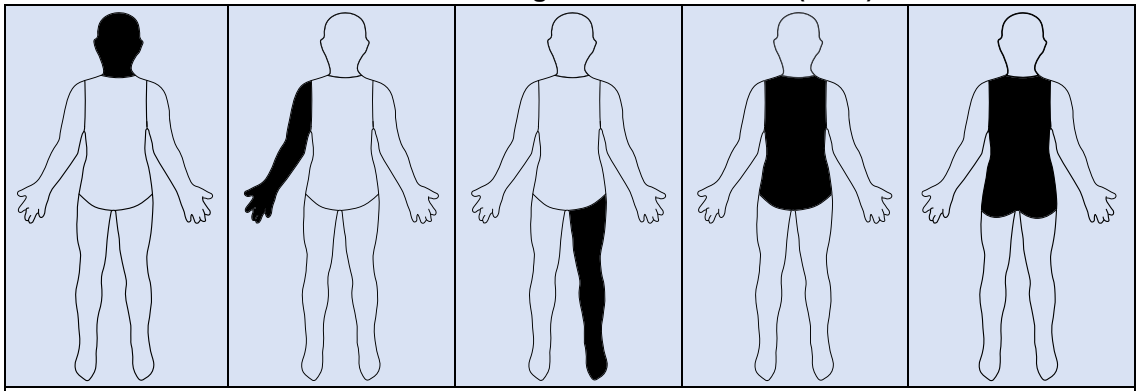
The findings are detailed in the guideline main text and in the associated systematic review[8].

Practical information for using topical corticosteroids for CU

Topical corticosteroids (TCS) are not indicated as a sole or primary treatment for acute urticaria (AU) or chronic urticaria (CU). There is limited evidence for their effectiveness for urticaria[21] and are used for localized, rather than widespread, hives (and not angioedema/swelling). They are indicated for inflammatory skin diseases such as atopic dermatitis and psoriasis. See separate JTF guidance addressing how to use them for atopic dermatitis (Annals Allergy 2023:132, DOI: 10.1016/j.anai.2023.11.009), e.g. for patients with both CU and atopic dermatitis.

Summary of how to use the intervention

Sparingly apply mid- to high-potency TCS to localized areas of hives on the trunk or extremities. When sparingly applied, one fingertip unit (FTU) covers an area of skin approximately equivalent to the back of two adult hands with fingers together.



Age	Average number of adult FTUs +/- 1 to cover each area of the body, classified by age				
3-6 months	1	1	1½	1	1½
1-2 years	1½	1½	2	2	3
3-5 years	1½	2	3	3	3½
6-10 years	2	2½	4½	3½	5
12 years	2½	4	7	5	7
Teen/Adult	2½	4	8	7	9

A **fingertip unit (FTU)** is the amount of cream or ointment squeezed from the index fingertip to its closest crease (distal end of the finger to distal interphalangeal crease). When squeezed from a standard 5 mm diameter tube nozzle, based on sex and gender, 1 FTU covers 2 adult hands with fingers together in area (260-310 cm^2) and uses 0.4-0.5 g of cream/ointment[22-26]. This concept can be helpful when estimating prescription needs and to understand how much topical medication to use.

To reduce harms of TCS in the treatment of CU

- Do not apply mid- to high-potency TCS to the same area more than four times a day.
- Do not apply high-potency TCS to the face or folds (intertriginous areas).
- Do not apply mid- or high-potency TCS daily or several times a day for more than 2-4 continuous weeks.
- Use the lowest potency corticosteroid and for the shortest amount of time required to gain and maintain control of CU. Consider using H1 antihistamines instead (see SGAH).

When TCS may not be a good option

TCS are not a good option for treating patients with widespread skin involvement with hives, or those with angioedema/swelling. Most patients may instead experience greater benefit with little to no harm using oral H1-antihistamines (see SGAH section).

Implementation practical considerations

- **Adverse effects:** Prolonged (almost daily) and non-stop use of TCS, especially high-potency ones, may result in rare side effects, such as skin dyspigmentation, stretch marks, formation of small superficial skin blood vessels (telangiectasia), easy bruising, and persistent redness.
- **Pregnancy and nursing:** When used appropriately, TCS are generally thought to be safe during pregnancy and nursing. TCS should not be applied around the nipples immediately before breastfeeding and might optimally be applied right after a feed is completed. Polymorphic eruption of pregnancy, sometimes called Pruritic Urticarial Papules and Plaques of Pregnancy (PUPPP), is different from the typical evanescent and migratory form of acute and chronic (spontaneous or inducible) urticaria addressed in this guideline. TCS may be effective for PUPPP.
- **Social life and relationships, work and education:** To manage potential concerns about staining clothing or self-consciousness, patients may prefer to apply TCS in private settings (e.g., at home in the morning or before bed) rather than publicly or in work- or school-related environments.

Evaluation

Evaluation of the efficacy of TCS in clinical practice as an intervention for CU is difficult due to the evanescent nature of individual hive lesions. Clinicians must therefore rely on their patients' reports on whether TCS help them manage symptoms associated with localized areas of hives.

Research needs

- Robust RCTs directly addressing efficacy of various potencies of TCS, and other topical anti-inflammatory treatments, as an add-on therapy to oral antihistamines compared to oral antihistamines alone and measured using modern CU measures (e.g. those discussed in the guideline introduction such as UCT and UAS7).

Adaptation

The worldwide availability of TCS facilitates adaptation.

Summary of Findings – Topical corticosteroids for chronic urticaria (hives and itch)

The findings are detailed in the guideline main text and in the associated systematic review[27].

Practical information for using vitamin D solely for CU

Summary of how to use high-dose vitamin D supplementation for CU

Vitamin D is a fat-soluble vitamin important for calcium absorption, bone health, and immune function. Vitamin D supplementation may be indicated for usual non-urticaria reasons, such as documented deficiency and bone health, or other clinical indications. This section addresses some considerations that patients might find important regarding use of vitamin D solely for CU.

The available CU trial evidence is very uncertain, and observed changes in urticaria activity are small and may not be patient-important. A blinded RCT compared vitamin D 4000 IU/day with 600 IU/day, added to cetirizine, ranitidine, and montelukast, and reported improvement over approximately 4 to 8 weeks; however, the evidence did not robustly address angioedema, quality of life, or adverse events. Very high prescription doses, such as 50,000 to 60,000 IU weekly or every 1 to 2 weeks, should not be used for CU alone without a separate clinical indication and monitoring plan.

To reduce harms of vitamin D supplementation for CU

- Do not use very high-dose vitamin D supplementation solely for CU control in patients without a separate indication and clear monitoring plan.
- If vitamin D is used for deficiency or another non-CU indication, use standard dosing and monitoring approaches for that indication rather than escalating solely because of CU symptoms.
    - There is no known optimal dosing or target blood vitamin D level for optimal health benefits (skeletal or non-skeletal).
    - Apart from the known limitations of measuring blood 25-hydroxyvitamin D (25[OH]D or calcidiol) concentrations, vitamin D toxicity is possible when the 25(OH)D level is over 100 ng/mL (>250 nmol/L) in adults ingesting substantial amounts of calcium[28].
    - Endocrine Society 2024 guidelines suggest against routine blood 25(OH)D screening or testing in general population, nor in those with obesity or dark complexion, and multiple other populations considered[29, 30]. It instead recommended empiric vitamin D supplementation in most situations.
- Avoid prolonged, unmonitored use above usual tolerable upper intake levels. For adults and adolescents 9 years and older, the NIH Office of Dietary Supplements, based on a 2011 Institute of Medicine (now National Academies of Sciences, Engineering and Medicine) report[31], lists a tolerable upper intake level of 4000 IU/day from all sources, including food, beverages, and supplements.
- For patients receiving high-dose prescription vitamin D, consider monitoring serum calcium, creatinine/eGFR, and 25-hydroxyvitamin D according to the indication and local practice.
- Counsel patients that vitamin D toxicity is usually due to excessive supplement intake and can cause hypercalcemia, hypercalciuria, kidney stones, renal failure, soft-tissue calcification, cardiac arrhythmias, neuropsychiatric symptoms, nausea/vomiting, weakness, polyuria, and dehydration.

When high-dose vitamin D is unavailable or undesirable

Optimizing the same second-generation H1-antihistamine, and if needed, advancing to therapies with larger benefits and certainty of evidence, such as omalizumab, dupilumab, remibrutinib, or selected later-line agents, is generally preferred over adding high-dose vitamin D solely for CU. Vitamin D may still be continued or started for standard nutritional, pregnancy, bone, renal, endocrine, or deficiency-related indications (skeletal or extraskeletal).

When high-dose vitamin D may not be a good option

High-dose vitamin D may not be a good option for patients with hypercalcemia, hypercalciuria, active kidney stones, significant renal impairment, granulomatous disease or other conditions associated with unregulated vitamin D activation, or patients taking medications that increase hypercalcemia risk, unless managed for a clear indication by an appropriate clinician. It is also not a good option when the intended goal is rapid CU control.

Implementation practical considerations

- **Medication routine:** Vitamin D is taken orally as an over-the-counter or prescription supplement. For non-CU indications, dosing should follow usual clinical guidance.
- **Tests and visits:** No routine blood testing is required and no CU-specific testing is required solely to decide whether to add vitamin D. Guidelines recommend against routine 25(OH)D testing for generally healthy adults. If high-dose vitamin D is used for another indication, monitor symptoms, 25-hydroxyvitamin D, calcium, and kidney function according to that indication and local standards.
- **Adverse effects:** Standard vitamin D supplement doses are generally well tolerated. Toxicity can occur with excessive supplementation.
- **Food and drinks:** Vitamin D is fat-soluble and may be better absorbed with food containing fat, but supplementation instructions should follow the product and clinical indication.
- **Pregnancy and nursing:** Vitamin D at standard doses is commonly already indicated in pregnancy and lactation for usual pregnancy-related health indications.
- **Costs and access:** Standard (low-dose) supplements are widely available and low cost. Most over-the-counter multivitamins contain about 800 to 1000 IU of vitamin D. High-dose prescription supplements may add cost and monitoring burden without sufficient CU-specific evidence.
- **Emotional well-being and self-management:** Patients may reasonably ask about vitamin D because “low vitamin D” is often discussed online. Low vitamin D can coexist with CU but does not prove or guarantee that supplementation will control hives, itch, or swelling.

Evaluation

Standard structured CU evaluation should occur after 4-12 weeks. If doses above recommended intake levels are used, monitor for signs and symptoms of toxicity.

Research needs

- Robust RCTs are needed to determine whether vitamin D supplementation provides patient-important benefit for CU, whether any benefit is limited to patients with documented deficiency, whether there is any effect on angioedema or quality of life, and what dose and duration are optimal and safe.

Adaptation

The worldwide availability of vitamin D facilitates adaptation (including considering, for example, variability in vitamin D exposure due to varied diets, sun exposure, laboratory testing, and regulations).

Summary of Findings – Vitamin D for chronic urticaria

The findings are detailed in the guideline main text and in the associated systematic review[6].

Practical information for using calcineurin inhibitors for CU

Cyclosporine and tacrolimus are calcineurin inhibitors that have been used in a variety of immune-mediated disorders, including off-label use in patients with refractory chronic urticaria[32]. Cyclosporine is a lipophilic cyclic peptide of 11 amino acids, whereas tacrolimus is a macrolide antibiotic[32, 33].

Cyclosporine (Neoral, Sandimmune, Gengraf) reduces activity of immune cells. It may take days to weeks to take effect. Modified cyclosporine (microemulsion form; e.g. Gengraf and Neoral) may deliver more reliable effects compared to unmodified forms (e.g. Sandimmune).

Summary of how to use calcineurin inhibitors (e.g. cyclosporine, tacrolimus) for CU

Cyclosporine dosing for CU starts at 2 to 5 mg/kg. A meta-analysis[34] including 18 studies with 909 patients, and two RCTs[35, 36], concluded that adverse events tend to be dose-dependent and that cyclosporine is effective at low doses (2 to 4 mg/kg/day). Adverse events, which were more frequent with higher doses and longer duration of treatment, occurred in more than half of patients treated with moderate doses (4 to 5 mg/kg/day) of cyclosporine. Many patients with antihistamine- and possibly other advanced treatment-refractory CU may prefer a dose of 3 mg/kg/day, though doses as low around 1 mg/kg/day can be effective in some[34].

Tacrolimus can be initiated at a dose of 1 mg twice daily, with dose escalation every several weeks until improvement or resolution of CSU is observed, or until a maximum dose of 6 mg/day without improvement after 4 weeks of treatment[37].

To reduce harms of calcineurin inhibitors

- Frequent monitoring of blood pressure, blood glucose, complete blood counts, liver enzymes, renal function, electrolytes and extended electrolytes, lipids[38].
- Levels of cyclosporine and tacrolimus may help dosing that minimizes adverse effects. In contrast to solid organ transplantation target drug trough levels (cyclosporine: 75-530 ng/mL, tacrolimus: 5-12 ng/mL), drug trough levels for calcineurin inhibitors in CU are lower but definitive target levels are not established.
- To decrease the chance of nephrotoxicity, an option is to start at lower doses (2-3 mg/kg) and increase the dose as needed. Nephrotoxicity risk is higher at 4 mg/kg or above. Reduce dose if there is acute kidney injury (e.g. rise in creatinine ≥ 25% from baseline).
- During infections, cyclosporine may be stopped or the dose lowered to avoid serious or opportunistic infections. Patients should seek prompt care in case of fever.
- Complete age-appropriate immunizations before initiating therapy[39-41]; give non-live vaccines as usual; depending on dose, avoid live vaccines immediately prior to starting oral calcineurin inhibitors, during their use, and immediately after stopping them.
- Drug-interactions (CYP3A4 and p-gp/ABCB1) include grapefruit and macrolide antibiotics. Use formal drug-interaction program checking with new drugs or herbals.

When calcineurin inhibitors may not be a good option

Other treatment options include omalizumab, dupilumab, remibrutinib, dapsone, colchicine, sulfasalazine, mycophenolate, hydroxychloroquine, and other advanced alternative agents.

- Cyclosporine is contraindicated in patients with poorly controlled hypertension, renal insufficiency, immunodeficiency, and malignancy[42].
- Tacrolimus is contraindicated in patients with hypersensitivity to macrolides and hypersensitivity (e.g. anaphylaxis) to HCO-60 (polyoxyl 60 hydrogenated castor oil)[43].

Implementation practical considerations

These drugs are combined with antihistamines and possibly biologics. Considerations include:

- **Medication routine:** Cyclosporine comes as capsules or a solution and is often taken twice daily. It is dosed by weight, and may be adjusted for age, height, and gender. While the target dose of 4 to 5 mg/kg/day may be more effective and rapid-acting than lower doses (e.g. 2.5 to 3 mg/kg/day), the higher dose also has a higher risk of harms - individualized decision-making is necessary regarding the exact dose to use. Solutions have specific mixing and handling instructions.
- **Adverse effects:** Cyclosporine and tacrolimus common minor adverse events include upset stomach, high blood pressure, tremor, tingling, headache, increased growth of fine hairs, and tender or swollen gums[33, 37, 42, 43]. Kidney and liver function and blood lipids should be monitored. Infections and rare instances of cancer can occur[38, 42]. Tacrolimus may be safer than cyclosporine for patients with cardiovascular co-morbidity[33]. Patients taking cyclosporine should routinely measure their blood pressure at home.
- **Drug interactions:** Caution is appropriate when switching from one formulation of cyclosporine to another, e.g., from Sandimmune to Neoral, the latter of which has increased bioavailability[42]. There are numerous drug-drug interactions[42, 43] that may either reduce (St John's Wort, rifampin, anticonvulsants) or increase (calcium channel blockers, antifungals, macrolides) levels of cyclosporine or tacrolimus, such that the clinician must be alert to administration of concomitant medications. Potassium-sparing diuretics should not be prescribed concomitant with treatment; avoidance of grapefruit and grapefruit juice is also recommended[42, 43]. NSAIDs should also be avoided, due to increased risk of nephrotoxicity.
- **Physical well-being:** Good oral hygiene is important.
- **Pregnancy and lactation:** Though many guidelines addressing cyclosporine or tacrolimus for other conditions deem it relatively safe to continue in pregnancy and lactation, patients with severe CU considering becoming, or who are, pregnant should have an individualized discussion with their clinicians.
- **Cost and access:** Cyclosporine and tacrolimus may be more affordable compared to many other advanced CU treatments.
- **Food and drink:** Avoid dehydration (e.g. drink 1.5 L water per day) to reduce the risk of kidney damage. Avoid grapefruit or other CYP3A4 inhibitors (e.g. macrolide antibiotics).
- **Social life and relationships:** To reduce risk of infection, patients taking cyclosporine may wish to be particularly mindful about avoiding sick contacts or high-risk situations and following infection prevention measures (masking, hand hygiene, vaccinations).
- **Travel and driving:** Use high-quality sunscreen (e.g. broad spectrum, SPF 30 or higher) and wear UV-protective clothing, headwear, and eyewear to reduce the risk of skin cancer and rash.

Evaluation

Standard structured urticaria assessment should occur in approximately 2-4 weeks. Safety may be evaluated via patient report, serial measurements of blood pressure and laboratory tests.

Research needs

- Robust RCTs are required to directly address the efficacy and safety of cyclosporine and tacrolimus regimens alone or added to other advanced systemic therapies (e.g. biologics) for CU control and induction of remission (disease modification).

Adaptation

The worldwide availability of cyclosporin and tacrolimus facilitate adaptation.

Summary of Findings – Calcineurin inhibitors for chronic urticaria

The findings are detailed in the guideline main text and in the associated systematic review[6].

Practical information for using mycophenolate for CU

Summary of how to use the mycophenolate for CU

Mycophenolate (aka mycophenolic acid) is an immunosuppressant (antiproliferative via inhibition of purine biosynthesis) that has long been used to prevent rejection of organ transplants and to treat, off-label, a variety of autoimmune conditions and chronic urticaria (CU) refractory to H1-antihistamines and first- and second-line advanced treatments. Mycophenolate is available in two formulations (see Table).

Characteristic	**Mycophenolate mofetil (MMF; CellCept)**	**Mycophenolic acid delayed-release (MPA; EC-MPS; Myfortic)**
Description	A prodrug that is converted to MPA after absorption	Enteric-coated delayed-release form of mycophenolate sodium delivering MPA
Typical kidney-transplant dosing	1,000 mg twice daily	720 mg twice daily
Available forms	Capsules, tablets, oral suspension, IV	Delayed-release tablets only

EC-MPS has the potential to reduce side effects of diarrhea, but its use has not been reported for treatment of CU. Mycophenolate typically takes weeks to take effect in CU.

To reduce harms of mycophenolate

- During serious infections, mycophenolate may need to be stopped.
- Age-appropriate vaccinations should be completed before initiating therapy.
  - Live attenuated vaccines should generally be avoided during treatment.
- Close monitoring of:
  - Complete blood count with differential
  - Plans for contraception
- Before starting and at each evaluation, check for drug interactions, such as:
  - Decreases in mycophenolate can be seen with antacids, mineral supplements (e.g. magnesium, calcium, iron), sevelamer, bile acid sequestrants, proton pump inhibitors, telmisartan, calcium-free phosphate binders, and rifampin.
  - Increases in mycophenolate may occur with acyclovir, valacyclovir, and probenecid.
  - Mycophenolate may decrease concentrations of hormonal contraceptives, and additional birth control methods should be considered.

When mycophenolate may not be a good option

- Contraindicated in pregnancy and breastfeeding.
- If there is a history of lymphoma
- Active systemic or potentially life-threatening infections
- Low cell counts, especially neutropenia or lymphopenia
- Hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT), inherited as X-linked, such as Lesch-Nyhan and Kelley-Seegmiller syndrome

Implementation practical considerations

- **Medication routine:** MMF comes in tablets, capsules, or an oral suspension. MMF is preferred, due to clinical experience and published literature[44-46]. A typical starting dose for adults is 1000 mg twice a day. Doses as high as 4000-6000 mg/d have been used in CU[45]. In other diseases, EC-MPS has been used, particularly in patients intolerant of gastrointestinal side effects from MMF[47]. A dose of 720 mg of EC-MPS is therapeutically similar to 1000 mg of MMF in other diseases. Absorption is not the same between both drug forms; switch cautiously.
  - Adjust dosing in patients chronic kidney disease (e.g. no more than 2 g per day)

- **Tests and visits:** Before initiation of mycophenolate, a complete blood count with differential, liver function test, creatinine, and urinalysis should be obtained. A complete blood count should be performed 1-2 weeks after the start of therapy. Monitoring of the complete blood count thereafter can be done every 4-8 weeks.
- **Adverse effects:** Gastrointestinal adverse effects, including nausea, diarrhea, and abdominal discomfort, are the most common adverse effects. Over time, gastrointestinal adverse effects tend to improve or resolve. Bone marrow suppression is less common and is dose-related. These adverse effects can often be resolved with dose adjustments. There may be an increased risk of development of lymphoma and other malignancies. Low white cell counts may increase risk of infections.
- **Pregnancy and nursing:** Mycophenolate is strictly contraindicated in pregnancy due to increased risks of first trimester pregnancy loss and congenital malformations. Though the drug label suggests its possible use during breastfeeding, clinical experts generally recommend avoiding using mycophenolate during lactation.
  Mycophenolate may decrease the effectiveness of oral contraceptives (levonorgestrel levels). Additional contraceptive methods may be required.
- **Costs and access:** Mycophenolate is available as a generic medication, and it is generally affordable and widely available.
- **Food and drinks:** High-fat meals can reduce the optimal absorption of mycophenolate, and therefore it is usually recommended to take this medication 1 hour before or 2 hours after meals. However, in patients with gastrointestinal intolerance, taking it with meals may improve tolerability, and dose adjustments can be considered.

Evaluation

A complete blood count should be performed 1-2 weeks after the start of therapy. Standard structured CU assessment should be performed within 4-8 weeks after initiation of therapy. If CU is inadequately controlled, the dose of MMF can be increased by 500-1000 mg/d. Doses as high as 4000-6000 mg/d of MMF have been used in CU. Monitoring of the complete blood count can be done every 4-8 weeks. If gastrointestinal symptoms develop and are mild, no dose adjustment is required, and these adverse effects may resolve over time. With more severe gastrointestinal symptoms, dose adjustments or taking the medication with food can be considered. If cytopenias develop, dose adjustments should be performed, with a repeat complete blood count in 1 week.

Once CU is controlled, the dose can be reduced gradually (e.g., by 500-1000 mg/d of MMF) to the lowest effective dose. Long-term studies of mycophenolate have not been conducted. Clinical experts tend to use mycophenolate for months or years, using shared decision-making.

Research needs

To the extent that mycophenolate is prioritized as an alternative treatment option for severe, refractory CU, robust randomized trials are required to address the existing low and very low certainty evidence and the drug's comparative effectiveness and safety to omalizumab, dupilumab, remibrutinib, and/or cyclosporine in patients refractory to H1 antihistamines alone.

Adaptation

Mycophenolate is available widely and therefore these recommendations can be adapted in many contexts.

Summary of Findings – Mycophenolate for Chronic Urticaria

The findings are detailed in the guideline main text and in the associated systematic review[6].

Practical information for using sulfasalazine for CU

Summary of how to use sulfasalazine for CU

Sulfasalazine is an oral anti-inflammatory 5-aminosalicylic acid derivative that is FDA-approved to treat autoimmune diseases (e.g. ulcerative colitis, rheumatoid arthritis) and may be used off-label for patients with antihistamine refractory CU.

- Target dose for sulfasalazine is typically 2000-3000 mg per day in two divided doses.
- Dosing is initiated in a gradual fashion, beginning with one 500 mg tablet and gradually increasing the daily dose by a 500 mg tablet each week until the target dose is reached.
- A four-to-six-week trial is recommended to determine effectiveness [48-51].
- If on stable dosing, blood tests (CBC, CMP, Urinalysis) are to be monitored weekly-biweekly during the first 3 months, then monthly for 3 months, then every 3 months[52].
- Potential side effects: gastrointestinal discomfort (> 10% of patients), nausea, and headache. There is also the risk for blood dyscrasias such as low white cell counts (including agranulocytosis), and liver injury. Delayed hypersensitivity reactions including severe cutaneous drug reactions such as AGEP, SJS, TEN and DRESS rarely occur.

To reduce harms of sulfasalazine

Folate supplementation should be provided to individuals who are pregnant or could conceive.

When sulfasalazine is unavailable or undesirable

Several alternatives exist for CU patient's refractory to antihistamines including biologics (omalizumab, dupilumab) or cyclosporine.

When sulfasalazine may not be a good option

There is limited data for use in patients with kidney impairment and liver impairment. The drug may lead to oligospermia and reversible infertility in males and may not be preferred in individuals trying to conceive. One should stop the therapy if there is concern for blood dyscrasias or severe cutaneous adverse reactions.

Implementation practical considerations

- **Medication routine:** Tablets should be taken on a regular basis twice daily with expectations for relief in 4-6 weeks from initiation. In diseases like rheumatoid arthritis, sulfasalazine is often used in combination with other drugs, such as methotrexate and hydroxychloroquine. These practices might be extrapolated to CU.
- **Tests and visits:** Weekly blood tests (CBC, LFTs) while uptitrating the dose. Once stabilized, testing is monthly for three months, then every 3 months thereafter. Routine screening for G6PD deficiency (inherited in an X-linked pattern) is not required before initiation of sulfasalazine. Avoid in patients with known G6PD deficiency.
- **Adverse effects:** Gastrointestinal, blood dyscrasias, and rare delayed drug reactions. Taking doses with meals and water may reduce gastrointestinal adverse reactions.
- **Interactions and antidote:** May increase serum concentrations of BCRP/ABCG2 substrates. Supplement folic acid in patients who are pregnant or could conceive.
- **Pregnancy and nursing:** Sulfasalazine maintenance doses may be continued in pregnancy. The manufacturer recommends caution with use in breast feeding.
- **Costs and access:** Widely available and lower costs than biologics, however, blood monitoring may add to overall cost burden.
- **Travel and driving:** Some people become sun-sensitive while on sulfasalazine. Use high-quality sunscreen (e.g. broad spectrum, SPF 30 or higher) and wear UV-protective clothing, headwear, and eyewear to reduce the risk of skin cancer and rash.

Evaluation

Assessment of sulfasalazine efficacy can be direct monitoring of daily symptoms using the UAS7 at the beginning and again 4-6 weeks after reaching the target dose. The UCT could also be substituted at monthly intervals. Optimal duration of therapy is unknown.

Patients should be advised to stop the medication and seek medical advice promptly for fever, sore throat, mouth ulcers, jaundice, severe rash, blistering, or systemic symptoms.

Research needs

To the extent that sulfasalazine is prioritized as an alternative treatment option for severe, refractory CU, robust randomized trials are required to address the existing low and very low certainty evidence and the drug's comparative effectiveness and safety to omalizumab, dupilumab, remibrutinib, and/or cyclosporine in patients refractory to H1 antihistamines alone.

Adaptation

Sulfasalazine is available widely and therefore these recommendations can be adapted in many contexts.

Summary of Findings – Sulfasalazine for Chronic Urticaria

The findings are detailed in the guideline main text and in the associated systematic review[6].

Practical information for using dapsone for CU

Summary of how to use the dapsone for CU

Dapsone is a sulfone antibiotic which exhibits anti-inflammatory properties[53]. Oral dapsone is FDA-approved for leprosy and dermatitis herpetiformis with no minimum age restriction[53]. Off-label uses include urticarial vasculitis[54], bullous dermatoses[55], and antihistamine-refractory chronic urticaria[56-58].

- Typical dosing for urticaria: Ranges from 25 mg to 200 mg/day.
  - Most commonly dosing being in the 50-100 mg/day range.
  - Typical starting dose is 25-50 mg/day. If needed, increase by 25-50 mg/day every 2-4 weeks up to 200 mg/day.
  - Tablets available: 25 or 100 mg
- For most patients, improvement occurs within approximately 1 month, and complete response may take 5 months to occur[56].
- Routine bloodwork monitoring required
- Contraindicated in patients with Glucose 6-phosphate dehydrogenase deficiency (G6PD), inherited as an X-linked genetic condition, due to risk of severe, potentially life-threatening hemolytic anemia and methemoglobinemia[59, 60]

Complete blood counts should be monitored in patients treated with dapsone[57]. Patients taking dapsone frequently experience a mild non-hemolytic anemia. In one review, approximately 80% of patients taking dapsone ≥ 50 mg experience a hemoglobin drop of at least 1 g/dL (10 g/L)[56, 61, 62]. Less frequent side effects include headaches, liver injury, and agranulocytosis[57]. Although exceedingly rare, there are cases of dapsone-induced hemolytic anemia and methemoglobinemia in patients with immune thrombocytopenia and patients with either a stem cell or renal transplant without known G6PD deficiency[63-67].

Human data is limited on the safety of dapsone in pregnancy and breastfeeding. Dapsone crosses the placenta [68, 69] and is excreted in breast milk[70-72]. Dapsone was not shown to be teratogenic in rats or rabbits at dosages up to 192 mg/kg/day or 200 mg/kg/day, respectively[70, 73]. Use of dapsone throughout all trimesters of pregnancy in humans has not been associated with an increased risk of fetal abnormalities[70]. Dapsone can used during breastfeeding; however, hemolytic anemia might occur in newborn infants, especially in those with G6PD deficiency. One case of mild hemolytic anemia attributed to dapsone occurred in a 41-day-old breastfed infant of a mother who was taking dapsone 50 mg daily[71, 74].

To reduce harms of dapsone

To reduce harm from dapsone, a Glucose 6-Phosphate Dehydrogenase (G6PD) quantitative assay should be performed before initiation and dapsone should be avoided in those with G6PD deficiency. Testing during acute hemolysis can lead to a falsely normal G6PD level.

When dapsone may not be a good option

- Glucose–6-phosphate dehydrogenase (G6PD) deficiency: Avoid dapsone since it induces severe and potentially life-threatening hemolysis in patients with G6PD deficiency[53, 57].
- Severe anemia: As dapsone can worsen anemia, avoid it in patients with severe anemia.
- Liver disease: Dapsone has been associated with liver injury, including toxic hepatitis and cholestatic jaundice[75]. Patients with G6PD deficiency may be at increased risk for developing hyperbilirubinemia[75]. When possible, baseline and subsequent monitoring of liver function is recommended; if abnormal, dapsone should be discontinued until the cause of the abnormality is determined[75].

Implementation practical considerations

- **Medication routine:** The typical starting dose is 25-50 mg/day, if needed, increase by 25-50 mg/day every 2-4 weeks up to 200 mg/day. Data is limited on the use of dapsone for urticaria in children. For other indications, the recommended dosing for children under the age of 10 years is 2 mg/kg[53, 76].
- **Tests and visits:** Complete blood counts and comprehensive metabolic panels should be monitored monthly for the first 6 months of therapy, then periodically. Reticulocyte count can be obtained as needed.
- **Adverse effects:** Dapsone should be avoided in individuals with G6PD deficiency, which places patients at risk for severe hemolytic anemia and methemoglobinemia. Liver toxicity and, rarely, muscle weakness (peripheral neuropathy) are possible. Dapsone, a sulfone, is not contraindicated in patients with immediate sulfonamide-allergy as these drugs do not share similar chemical structures[76, 77].
- **Interactions and antidote:** Concurrent use of medications that induce methemoglobinemia, such as certain anesthetics (e.g., benzocaine or lidocaine), is a relative contraindication[53]. Discontinue dapsone prior to surgical procedures due to the risk of methemoglobinemia with anesthetics[53, 77]. Should methemoglobinemia occur, stop dapsone and provide supportive care[53]. Methylene blue or other interventions may be required to reverse toxicity[53, 78]. In cases of accidental or intentional dapsone overdose, activated charcoal can be administered to improve clearance of methemoglobin[53, 79]. Dapsone may cause falsely low hemoglobin A1c (HbA1c) levels.
- **Pregnancy and nursing:** Dapsone may be used during pregnancy and while breastfeeding if the benefits outweigh the risks. Dapsone poses a potential risk to the fetus and is excreted in breast milk[74, 80, 81]. Monitor the infant for signs of hemolysis or jaundice, especially in newborn or premature breastfed infants[74].
- **Costs and access:** Dapsone is generally considered affordable and is available in generic formulation.
- **Food and drinks:** Dapsone can be taken with or without food. Taking with food and/or milk can help to reduce upset stomach.

Evaluation

Structured CU evaluation should occur in 4-6 weeks after starting dapsone. As above, CBC and liver function should be checked within the first month to ensure there is no hemolysis or liver injury, and then routinely thereafter. For example, the drug label suggests, “The FDA Dermatology Advisory Committee recommended that, when feasible, counts should be done weekly for the first month, monthly for six months and semi-annually thereafter.”

Research needs

To the extent that dapsone is prioritized as an alternative treatment option for severe, refractory CU, perhaps those with a neutrophil predominant infiltrate, robust randomized trials are required to address the existing low and very low certainty evidence and the drug’s comparative effectiveness and safety to omalizumab, dupilumab, remibrutinib, and/or cyclosporine in patients refractory to H1 antihistamines alone.

Adaptation

Dapsone is available widely and therefore these recommendations can be adapted in many contexts.

Summary of Findings – Dapsone for Chronic Urticaria

The findings are detailed in the guideline main text and in the associated systematic review[6].

Practical information for using oral BTK inhibitors for CU

Summary of how to use oral BTK inhibitors (remibrutinib)

Bruton's tyrosine kinase (BTK) is a cytoplasmic kinase expressed in selected immune cells, such as mast cells, basophils, B cells, macrophages, and platelets[82]. In mast cells and basophils, it plays an important role in the cell's IgE receptor, subsequent degranulation, and release of histamine and other pro-urticaria mediators. Modern selective BTK inhibitors may have more favorable risk-benefit profiles compared to older BTK inhibitors that were initially developed for cancer[83].

Remibrutinib is a selective, oral, covalent BTK inhibitor approved as an add-on therapy to oral H1-antihistamines for CSU in adult patients who remain symptomatic despite H1 antihistamine treatment[84, 85]. Remibrutinib also inhibits the BTK-related kinases tec protein tyrosine kinase (TEC) and BMX non-receptor tyrosine kinase (BMX). Other BTK inhibitors, such as rilzabrutinib and others, are being evaluated for CSU[86].

Some practical issues about remibrutinib:

Brand name	Rhapsido
Medication form	Oral tablet (yellow, round); bottles of 60 tablets
Wholesale price per pill	$4,521 per 30-day supply, or $55,005.5 per year
Age indication	Adults (18 years old or older)
Drug interaction	Yes, CYP3A4 and p-gp[87, 88]. Metabolized by liver.
Half-life	1-2 h[89]
Dose	25 mg twice daily[85]

When remibrutinib may not be a good idea

- The efficacy of remibrutinib for chronic inducible urticaria is uncertain
- Liver impairment (mild to severe): Avoid use
- Have a bleeding disorder, require antithrombotic including anticoagulants, or at high risk for bleeding

Implementation practical considerations

- **Medication routine:** Do not split, crush, or chew the medication. Take with or without food. Store at room temperature.
- **Adverse effects:** Monitor for signs and symptoms of bleeding (9% remibrutinib vs 2% placebo over 24 weeks) or nasopharyngitis (11% remibrutinib vs 9% placebo over 24 weeks). The most common bleeding events were bruises (petechiae and contusion).
- **Coordination of care:** Stop remibrutinib for 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.
  Interactions: Concomitant use of antithrombotic agents may further increase bleeding
  - Remibrutinib is primarily metabolized by CYP3A4 and inhibits p-gp. Avoid strong or moderate CYP3A4 inhibitors or inducers, or p-gp substrates.
- **Immunization:** Due to the absence of data, and selective immunosuppressive effect of remibrutinib, the drug label recommends avoiding live or live-attenuated vaccines.
- **Pregnancy and nursing:** Avoid in pregnancy and lactation. There are insufficient data for remibrutinib safety in humans. In pregnant rabbits, but not pregnant rats, remibrutinib increased fetal malformations. It is not known whether remibrutinib is excreted into breastmilk or if it is safe to expose newborns to breastmilk from patients using remibrutinib. Animal data suggest no impact to fertility.
- **Cost and access:** Remibrutinib is expensive and can be difficult to access. The drug maker has a patient support program that may help address these barriers.

Evaluation

- Apart from standard structured CSU assessment occurring within approximately 2-12 weeks after initiating remibrutinib, monitor for signs and symptoms of bleeding, upcoming procedures and surgeries, pregnancy plans, vaccinations, liver impairment and drug-interactions.
- No routine laboratory monitoring is required.
- Once control of CU is achieved, optimal remibrutinib and H1-antihistamine tapering is uncertain.

Research needs

- Robust studies to definitively address the residual uncertainty for harms, especially long-term, are required.
- There is a need to establish the optimal dose, age, and monitoring.
- There are also no data regarding their safety in preschool-aged children, during pregnancy, or during lactation/breastfeeding.
- Comparative effectiveness to other first-line advanced treatment options, as well as combination therapy with other first-line and second-line treatment options require definitive randomized clinical trials.
- Whether BTK inhibitors can be used on-demand to effectively treat acute flares of urticaria (acute or chronic), for instance as a safer alternative to systemic corticosteroids, needs to be addressed in robust randomized clinical trials.

Adaptation

The recommendations might be most easily adaptable to high-income countries and settings.

Summary of Findings – Remibrutinib for chronic urticaria

The findings are detailed in the guideline main text and in the associated systematic review[6].

Practical information for using dupilumab for CU

Summary of how to use dupilumab for CU

Dupilumab is a fully human monoclonal antibody that binds IL-4Rα and inhibits signaling of both IL-4 and IL-13. Dupilumab has shown efficacy in numerous conditions in which type 2 inflammation plays a major role, and it is approved for the treatment of asthma, atopic dermatitis (AD), chronic sinusitis with nasal polyposis[90-93], chronic urticaria, among other conditions. Dupilumab is effective in patients with CSU uncontrolled with H1-antihistamines, with or without prior treatment with omalizumab. It is given by injection subcutaneously (like a diabetes needle).

Some practical issues about dupilumab[94]:

Brand name	Dupixent
Injection devices available	Pre-filled syringe, or autoinjector pen Both come in cartons containing 2 syringes or pens
Wholesale price per syringe	A 300 mg dose is approximately $2000 USD
Manufacturer-recommended Dosing	
Adults (>=18 years)	600 mg (2x 300 mg) once, then 300 mg every 2 weeks
Pediatric (6-17 years)	
>=60kg	600 mg (2x 300 mg) once, then 300 mg every 2 weeks
30 to <60 kg	400 mg (2 x 200 mg) once, then 200 mg every 2 weeks
15 to <30 kg	600 mg (2 x 300 mg) once, then 300 mg every 4 weeks
Pediatric (2-5 years)	
15 to <30 kg	200 mg every 4 weeks (no initial loading dose)
5 to <15 kg	300 mg every 4 weeks (no initial loading dose)
Volume administered	300 mg dose = 2 ml 200 mg dose = 1.14 ml

Dupilumab may be particularly helpful if it treats multiple conditions simultaneously.

When dupilumab may not be a good option[95]

- Thus far, data shows that dupilumab may not be effective (low certainty) in addressing angioedema in patients with CSU or in patients who have cold urticaria.
- If there is recurrent or severe conjunctivitis, arthritis or arthralgias, or psoriasis
- If there is new vasculitis, such as eosinophilic granulomatosis with polyangiitis
- If there is known untreated helminth infection

Implementation practical considerations

Dupilumab is combined with oral H1 antihistamines. Considerations include:

- **Medication routine:** Dupilumab is administered subcutaneously. The medication may become effective within days to weeks after the first injection. The first dose will involve injection training. The drug can be self-administered at home or given in a clinic.
  - Keep the medication refrigerated. Remove from the fridge 30-45 minutes before administration and then use immediately. Do not shake and do not freeze.
  - If necessary, dupilumab may be kept at room temperature up to 25°C for a maximum of 14 days.
  - No studies have established the optimal tapering of dupilumab doses among patients with CSU, or the optimal treatment duration.
- **Immunizations:** Non-live vaccines (e.g., Tdap and meningococcal polysaccharide) are safe and efficacious when administered during treatment with dupilumab[94, 96].
  - For live vaccines, the available literature on patients who received vaccinations while using dupilumab overall suggests that live vaccines are safe and that the vaccine efficacy, in general, is not affected by dupilumab[97].

    - Options, for which there is no robust data to inform the optimal approach, include (1) Completing all live vaccine (e.g., MMR, Varicella) immunizations before starting dupilumab, if possible, (2) Holding dupilumab for 12 weeks before and 4 weeks after vaccination[98] (3) Holding dupilumab for 2-4 weeks before immunization, or (4) not modifying the dosing.
- **Tests and visits:** No routine blood monitoring is required.
- **Adverse effects:** Common minor harms include injection site discomfort. Upper respiratory tract infections, herpes infections, nasopharyngitis, conjunctivitis, arthralgia, myalgia, dizziness, diarrhea, anaphylaxis, and serum sickness have rarely been reported. Eosinophilic pneumonia and vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported, but a causal relationship has not been established [94].
- **Coordination of care:** Patients either pick up the medication or have it shipped to their home by specialty pharmacies. Given its high cost and temperature storage needs, it is helpful to plan to retrieve the medication on time.
- **Pregnancy and nursing:** Animal data and limited human data suggest no clear evidence of harm with dupilumab during pregnancy and lactation/breastfeeding[99, 100]. Patients who become pregnant while on dupilumab should discuss with their clinicians about whether to continue or stop the biologic.
- **Costs and access:** Biologics are costly and can be difficult to access. Most biologics companies have patient support programs that will facilitate insurance negotiation, medication delivery, and injection training.
- **Travel and driving:** Since biologics are usually stored at around 4°C, some patients adjust their travel schedules to fall around injection dates and avoid traveling with the medication. Alternatively, patients can travel with dupilumab in a bag with ice packs and a thermometer or keep at room temperature and use it within 14 days (see above).

Evaluation

- Standard structured CSU assessment should occur within approximately 4 weeks after initiating dupilumab treatment. Benefits may be seen within days to weeks of starting therapy and increase over 24 weeks[91]. There is no routine laboratory monitoring required.
- With any change in drug dosing, monitor closely for changes in CSU control.
- In patients with CU and atopic dermatitis treated with dupilumab, monitor for conjunctivitis.

Research needs

- Robust randomized trials, including investigator-initiated, of active interventions (comparative effectiveness research), including omalizumab, remibrutinib, cyclosporine, among others, are critically required to inform optimal care pathways.
- Robust RCTs of combination therapy of dupilumab or other biologics as maintenance therapy, with topical or oral BTK inhibitor used as on-demand therapy for flares, are also required.

Adaptation

The recommendations might be most easily adaptable to high-income countries and settings.

Summary of Findings – Dupilumab for chronic urticaria

The findings are detailed in the guideline main text and in the associated systematic review[6].

Practical information for using narrow-band UVB (NB-UVB)

Summary of how to use phototherapy for CU

NB-UVB therapy is a phototherapy that uses 311-313 nm wavelength light to treat various skin conditions. Limited studies NB-UVB evaluate combination with oral H1-antihistamines in patients with CU inadequately controlled with H1-antihistamines alone[101-103]. Treatments are typically 2 to 3 times per week, and it may take several weeks to months to see an improvement in symptoms. Phototherapy is usually delivered in a clinic setting, but home units may also be prescribed. The efficacy and safety of home units, or their comparability to clinic-based phototherapy, is not clear. In general, the JTF guideline suggests against adding NB-UVB for CU.

To reduce harms of NB-UVB:

- Follow standardized treatment recommendations for frequency and intensity of treatments.
- Carefully monitor the patient's response to treatments, including skin erythema, itching, or burning sensations, and alter UV dose as appropriate to reduce the potential for harm from NB-UVB therapy for the treatment of CU.

When NB-UVB may not be a good option

NB-UVB may not be a good option for patients who:

- Have experienced recurrent or severe burns
- Have light-sensitive conditions or are on photo-sensitive medications
- Have cataracts
- Have current or previous skin cancer, or risk factors for skin cancer (e.g., genetic disorders or syndromes)
- Experience a lack of response to the therapy
- Find the travel or time required or co-pays to do NB-UVB therapy burdensome or impractical

Implementation practical considerations

- **Treatment routine:** Clinic-based NB-UVB requires visits 2–3 times per week. Dosing is based on one's skin type (propensity to tan and/or burn) and the exact dose that elicits redness or a burn. Doses are then adjusted based on treatment response and adverse effects. Each session involves standing in a cabinet containing multiple light bulbs, and treatment times range from less than 5 minutes to up to about 30 minutes. For treatments, patients must undress and wear UV protective goggles and are often given a face visor. Their genitals should be covered.

- **Adverse effects:** Common minor adverse events include local redness or burning, pain, itch, tanning, and increased skin dryness. Severe burns, including swelling and blistering, are possible. Cold sores on the lips can often be prevented with sun-protective lip balm. Premature skin aging and skin cancer are less likely to occur with NB-UVB therapy, compared with other UV phototherapies.
- **Pregnancy and nursing:** NB-UVB therapy is generally considered safe for pregnant and nursing individuals. Narrowband UVB can lower folic acid levels, so pregnant patients should discuss folic acid supplementation with their clinicians and individualize discussions about using NB-UVB therapy in pregnancy.
- **Cost and access:** NB-UVB therapy can be difficult to access, due to the time and travel required to attend specific clinics that have phototherapy units. Such clinics tend to be in urban centers. Home therapy units cost in the range of several thousands of US dollars.
- **Travel and driving:** NB-UVB therapy may require coordination of travel, childcare, and work schedules.
- **Coordination of care:** Between clinic sessions, patients should use high-quality sunscreen (e.g., broad spectrum, SPF 30 or higher) and wear UV-protective clothing, headwear, and eyewear to reduce the risk of skin cancer and rash.

Evaluation

Apart from standard structured disease assessment at approximately 4-week intervals after initiation of therapy, patients should be routinely monitored for signs of sunburn, skin damage, and skin cancer.

Research needs

- To the extent that NB-UVB is prioritized as a competing therapy with first-line advanced therapies (omalizumab, dupilumab, remibrutinib) or second-line advanced therapies such as the calcineurin inhibitor, cyclosporine, robust randomized clinical trials addressing add-on NB-UVB are required to inform optimal care.
    - Increasing confidence in the efficacy and safety of home-based NB-UVB requires robust randomized clinical trials.
- Where NB-UVB imparts any long-term immunomodulatory effect or disease remission in CU remain highly uncertain and will require longer-term trials (e.g. 52 weeks or longer).

Adaptation

The recommendations might be most easily adaptable to high-income countries and settings.

Summary of Findings – NB-UVB for chronic urticaria

The findings are detailed in the guideline main text and in the associated systematic review[6].

Practical information for using hydroxychloroquine for CU

Summary of how to use hydroxychloroquine (Plaquenil) for CU

Hydroxychloroquine (HCQ) is an oral antimalarial and immunomodulatory drug commonly used for systemic lupus erythematosus, chronic discoid lupus erythematosus, rheumatoid arthritis, and related autoimmune inflammatory diseases. It may be used in selected patients with CU that are intolerant, suboptimally responsive, or refractory to H1-antihistamines and a first-line advanced systemic therapy. Benefits may take weeks to months to appear.

A practical adult dose is usually 200 mg once daily to 400 mg/day, given once daily or in two divided doses. To reduce retinopathy risk, avoid long-term average dosing above 5 mg/kg/day actual body weight, and generally do not exceed 400 mg/day.

To reduce harms of HCQ:

- Use the lowest effective dose and avoid long-term average dosing above 5 mg/kg/day actual body weight.
- Complete baseline ophthalmologic assessment within the first year of starting treatment. Retinal screening should occur annually for patients with major risk factors; for lower-risk patients, annual screening can often be deferred until 5 years of treatment.
    - Risk factors for retinal toxicity include daily doses ≥5 mg/kg actual body weight, duration of use greater than 5 years, renal impairment, concomitant tamoxifen, and concurrent macular disease.
- Consider baseline and follow-up ECG when there is congenital or acquired QT prolongation, clinically important cardiac disease, bradycardia, electrolyte abnormalities, prior ventricular dysrhythmia, or concomitant QT-prolonging drugs. Routine ECG screening is not necessary for most otherwise low-risk patients.
- Patients should report vision changes, palpitations, syncope, muscle weakness, severe rash, mood or neuropsychiatric symptoms, or symptoms of hypoglycemia.

When HCQ is unavailable or undesirable

Alternative options depend on where the patient is in the CU treatment pathway and include first-line advanced therapies, switching among first-line advanced therapies, cyclosporine or tacrolimus in selected cases, mycophenolate, or continued advanced standard care. HCQ should not delay therapies with greater certainty or magnitude of benefit when those are available and acceptable.

When HCQ may not be a good option

HCQ may not be a good option in patients with:

- Pre-existing retinal or macular disease that makes monitoring difficult
- No reliable ability to monitor for retinal or macular toxicity if long-term treatment is planned
- Major risk factors for retinopathy that cannot be mitigated
- Congenital or acquired QT prolongation, or other important arrhythmia risk factor
- Significant renal impairment without dose/safety planning
- Prior severe cutaneous adverse reaction or allergy to HCQ.
- Severe or active psoriasis that may worsen

Implementation practical considerations

- **Medication routine:** Take HCQ with food or milk, or at bedtime if nausea is problematic. If gastrointestinal intolerance occurs, consider starting at 200 mg daily or even a lower temporary dose if feasible, then increasing gradually every 1 to 2 weeks as tolerated.

Some scored tablets may be split; do not assume all products can be split and follow local product instructions.
    - HCQ has a long terminal half-life, approximately 1 to 2 months in rheumatologic pharmacology literature, and steady state may take months. Benefit, if any, is expected gradually rather than immediately.
- **Tests and visits:** Use weight-based dose calculation, medication review, pregnancy/lactation discussion, renal function review, cardiac risk review, and an eye-screening plan. Routine bloodwork is not required specifically for HCQ in all low-risk patients, but baseline CBC, liver enzymes, and creatinine are practical when HCQ is used in complex refractory CU, kidney disease, older adults, or when used with other immunomodulators.
    - **Eye monitoring:** Early retinal toxicity can be asymptomatic and that screening aims to identify toxicity before vision is affected. Stop HCQ and obtain urgent ophthalmology input if retinal toxicity is suspected.
    - Routine G6PD testing is not generally required solely for usual-dose HCQ.
- **Adverse effects:** Common effects include nausea, abdominal cramps, vomiting or diarrhea, headache, lightheadedness, itchy rash, and other skin eruptions. Rare but important harms include irreversible retinal toxicity, corneal deposits, cardiomyopathy, QT prolongation or ventricular arrhythmias, severe skin reactions, myopathy or neuropathy, neuropsychiatric reactions, cytopenias, and hypoglycemia. Hyperpigmentation can occur with long-term use, especially on shins, oral mucosa, nails, or forearms.
- **Pregnancy and nursing:** HCQ is commonly continued in pregnancy and lactation for rheumatologic diseases when clinically indicated.
- **Costs and access:** HCQ is generic, widely available, and usually low cost. Eye-screening costs, however, may vary.
- **Travel and driving:** No special travel restrictions are required. HCQ can cause sun sensitivity, so patients should use high-quality sunscreen (e.g., broad spectrum, SPF 30 or higher) and wear UV-protective clothing, headwear, and eyewear.

Evaluation

Apart from standard structured CU assessment after 4-12 week after initiation of therapy, patients should be routinely monitored for HCQ adverse effects.

Research needs

- Robust RCTs are needed to clarify HCQ's comparative effectiveness and safety for refractory CU, optimal dosing and duration, predictors of response, and its role relative to omalizumab, dupilumab, remibrutinib, cyclosporine, and mycophenolate. CU-specific data are needed on whether HCQ blood levels, biomarkers, or comorbid autoimmune disease identify patients more likely to benefit.

Adaptation

HCQ’s availability across many regions facilitates adaptation in many contexts.

Summary of Findings – HCQ for chronic urticaria

The findings are detailed in the guideline main text and in the associated systematic review[6].

Practical information for using colchicine for CU

Summary of how to use colchicine for CU

Colchicine is an oral anti-inflammatory drug used for gout, familial Mediterranean fever, pericarditis, and selected cardiovascular indications. It inhibits microtubule polymerization and affects neutrophil migration, inflammasome activation, and other inflammatory pathways. Though generally not used for CU, it may rarely be used in select patients intolerant, suboptimally responsive, or refractory to H1-antihistamines and first- and second-line advanced systemic therapies. Typically, colchicine is considered only in unusual circumstances, such as when a patient has a separate comorbid indication for colchicine, strongly prefers an oral low-cost option despite uncertain benefits, or when expert review identifies a possible neutrophilic phenotype. The evidence that neutrophilic findings on biopsy predict colchicine response in CU is very uncertain.

If colchicine is used, use low-dose regimens and avoid use when renal or hepatic impairment or interacting medications make toxicity likely. In patients with normal renal and hepatic function, 0.5 mg or 0.6 mg once daily is a practical low-dose approach. Higher doses increase gastrointestinal and systemic toxicity.

To reduce harms of colchicine:

- Review kidney function, liver function, age, frailty, body size, and interacting medications before prescribing.
- Avoid colchicine in patients with renal or hepatic impairment who are also receiving strong CYP3A4 inhibitors or P-glycoprotein inhibitors (e.g. statins, fibrates, cyclosporine, macrolide antibiotics, azole antifungals, protease inhibitors, verapamil, diltiazem); life-threatening and fatal toxicity has been reported in such settings.
- Stop the medication and seek care for severe diarrhea, vomiting, muscle pain or weakness, dark urine, numbness/tingling, unusual bruising or bleeding, fever, or infection symptoms.

When colchicine is unavailable or undesirable

In patients with severe CU refractory to first- and second-line advanced therapies, selected patients may prefer trials of hydroxychloroquine or mycophenolate, or accessing randomized clinical trials addressing new therapies.

When colchicine may not be a good option

Colchicine may not be a good option in patients with:

- Chronic kidney disease
- Liver impairment
- Substantial gastrointestinal disease
- Baseline cytopenias
- Neuromuscular disease
- Older age or frailty with polypharmacy
- Need to use strong CYP3A4/P-glycoprotein inhibitors

Implementation practical considerations

- **Medication routine:** The optimal dose regimen for CU is not known. Dosing for other indications varies and can titrate, as tolerated up to 3 mg per day divided over 1 to 3 doses per day. One approach for CU may be 0.5 mg or 0.6 mg once daily.
- **Tests and visits:** CBC, creatinine, and liver enzymes may be drawn at baseline and periodically.

- **Interactions:** Colchicine is a CYP3A4 and P-glycoprotein substrate. Consider using a formal drug interaction program whenever a new medication or herbal is added.
- **Adverse effects:** The most common adverse effects are dose-dependent diarrhea, abdominal pain, nausea, and vomiting. Serious harms include myelosuppression, leukopenia, thrombocytopenia, pancytopenia, neuromyopathy, rhabdomyolysis, and fatal toxicity, especially with interacting drugs or organ impairment.
- **Pregnancy and nursing:** colchicine may be used in pregnancy and lactation for rheumatologic diseases when clinically indicated. Its use, however, in CU requires risk-benefit discussion given its uncertain benefits and known harms.
- **Costs and access:** Colchicine is generic, widely available, and usually low cost.

Evaluation

Apart from standard structured CU assessment after 4-12 week after initiation of therapy, patients should be routinely monitored for colchicine adverse effects.

Research needs

- Robust RCTs are needed to clarify whether any subgroup of CU benefits from colchicine, whether neutrophilic histology predicts response, and how colchicine compares with other advanced or later-line therapies.

Adaptation

Colchicine's availability across many regions facilitates adaptation in many contexts.

Summary of Findings – colchicine for chronic urticaria

The findings are detailed in the guideline main text and in the associated systematic review[6].

Practical information for using azathioprine for CU

Summary of how to use azathioprine for CU

Azathioprine is an oral purine antimetabolite immunosuppressant used for transplant medicine and several autoimmune diseases. It is not a routine CU therapy. The guideline suggests against using azathioprine rather than continuing advanced standard care for most patients with CU that is intolerant, suboptimally responsive, or refractory to H1-antihistamines and first-line advanced systemic therapy. Azathioprine is most likely to be considered only in selected circumstances, such as when it treats a separate comorbid condition, when other better-supported CU therapies are unavailable or not tolerated, or when reproductive considerations make other later-line immunosuppressive options less acceptable. Expected onset is slow, often weeks to months.

If used, there is no established CU-specific dose and dosing is extrapolated from autoimmune disease regimens. These commonly begin around 1 mg/kg/day and titrate cautiously, with many regimens not exceeding 2 to 2.5 mg/kg/day. Dose should be individualized for comorbidities, kidney/liver function, TPMT/NUDT15 status when known, concomitant medications, and blood counts.

To reduce harms of azathioprine:

- Obtain baseline CBC with differential, liver enzymes, bilirubin, and creatinine/eGFR.
- Assess TPMT status before starting azathioprine. Consider NUDT15 genotyping when available. Reduce dose for intermediate metabolizers and generally avoid azathioprine in poor metabolizers.
- Monitor CBC and liver tests routinely. One approach is CBC with differential and AST/ALT every 2 weeks for the first 8 weeks, then every 1 to 2 months if stable; the FDA label suggests weekly CBCs for the first month, twice monthly for months 2 and 3, then monthly or more often if doses or interacting drugs change.
- Review interacting drugs, including aminosalicylates such as sulfasalazine/mesalamine, ribavirin, co-trimoxazole, ACE inhibitors, warfarin and xanthine oxidase inhibitors.
- Patients should report fever, infection symptoms, sore throat, mouth ulcers, unusual bruising or bleeding, jaundice, severe nausea/vomiting, rash, or neurologic symptoms. Temporarily discontinue azathioprine during severe infection, such as infection requiring intravenous therapy or hospitalization.

When azathioprine is unavailable or undesirable

In patients with severe CU refractory to first- and second-line advanced therapies, selected patients may prefer trials of hydroxychloroquine or mycophenolate, or accessing randomized clinical trials addressing new therapies.

When azathioprine may not be a good option

Azathioprine may not be a good option in patients with:

- Known hypersensitivity to azathioprine or 6-mercaptopurine
- Baseline significant cytopenia
- High malignancy risk
- Important liver disease
- Inability to complete laboratory monitoring, TPMT or NUDT15 homozygous deficiency testing, or unavoidable interacting medications such as febuxostat or full-dose allopurinol without expert dose adjustment.
- Active serious infection

Implementation practical considerations

- **Medication routine:** Azathioprine is usually taken once or twice daily. Taking in divided doses or after meals may improve gastrointestinal tolerability. Response may take 6 to 12 weeks or longer.
- **Tests and visits:** Frequent early lab monitoring is essential. TPMT/NUDT15 testing can identify higher-risk patients but cannot substitute for CBC monitoring.
- **Interactions:** Xanthine oxidase inhibitors are the most important interaction; allopurinol requires major azathioprine dose reduction and close monitoring, and febuxostat is generally not recommended. Aminosalicylates may inhibit TPMT and should be used cautiously. Consider using a formal drug interaction program whenever a new medication or herbal is added.
- **Adverse effects:** Dose-related effects include nausea, vomiting, diarrhea, and cytopenias. Serious harms include severe leukopenia, thrombocytopenia, pancytopenia, hepatotoxicity, pancreatitis, serious infections, progressive multifocal leukoencephalopathy, malignancy including lymphoma, and rare severe hypersensitivity syndromes.
- **Pregnancy and nursing:** Azathioprine may be used in pregnancy and lactation for rheumatologic diseases when clinically indicated. Its use, however, in CU requires risk-benefit discussion given its uncertain benefits and known harms. Potential fetal/neonatal cytopenia and newborn screening effects (e.g. positive new born screening for low T cell receptor excision circles [TRECs]) can occur.
- **Costs and access:** Azathioprine is generic, widely available, and usually low cost. Monitoring, however, may have variable costs.
- **Immunization:** Review immunizations before treatment. For adults starting azathioprine, screen for chronic hepatitis B, hepatitis C, and HIV unless already known or recently assessed; test for latent tuberculosis when risk is increased. Assess varicella immunity in patients without a history of chickenpox, shingles, or varicella vaccination. Live vaccines require individualized planning based on total immunosuppression.
- **Coordination of care:** Azathioprine is not routinely stopped perioperatively, but decisions should be individualized for high-risk procedures or high-risk patients.

Evaluation

Apart from standard structured CU assessment after 4-12 week after initiation of therapy, patients should be routinely monitored for azathioprine adverse effects.

Research needs

- Robust RCTs are needed to clarify whether any subgroup of CU benefits from azathioprine, predictors of response, and how azathioprine compares with other advanced or later-line therapies.

Adaptation

Azathioprine's availability across many regions facilitates adaptation in many contexts.

Summary of Findings – azathioprine for chronic urticaria

The findings are detailed in the guideline main text and in the associated systematic review[6].

Practical information for using methotrexate for CU

Summary of how to use methotrexate for CU

Methotrexate is an oral or injectable antimetabolite and immunomodulatory drug used for rheumatoid arthritis, psoriasis, polyarticular juvenile idiopathic arthritis, and some cancers. It is not a routine CU treatment. Methotrexate should therefore be used for unusual selected circumstances such as a separate comorbid disease for which methotrexate is otherwise indicated or inability to access or tolerate better-supported therapies.

There is no established CU-specific dose. Extrapolated from its use in autoimmune and inflammatory skin diseases, methotrexate is given once weekly for CU. Ensure that the patient can do once-weekly dosing, agree on a specific dosing day, and use clear written instructions. A cautious adult starting dose often used in inflammatory disease is 7.5 mg once weekly, with gradual escalation if needed and tolerated. Co-prescribe folic acid.

To reduce harms of methotrexate:

- Prescribe and counsel once-weekly dosing and agree on a specific day of the week. Daily dosing errors have caused fatal adverse reactions. To reduce risk of errors, prescribe a single tablet strength when possible, commonly 2.5 mg tablets, and avoid ambiguous instructions such as 'as directed.'
- Methotrexate is contraindicated in pregnancy. Effective contraception should be used during methotrexate use and for the recommended post-treatment period. The FDA label advises contraception for females of reproductive potential during treatment and for 6 months after the final dose, and for males with partners of reproductive potential during treatment and for 3 months after the final dose.
- Obtain baseline weight, CBC, liver enzymes and function, creatinine, hepatitis B/C and HIV screening in adults, latent tuberculosis testing when risk is increased, medication review, alcohol-use assessment, and lung history/exam.
    - For adults with risk factors for liver disease, such as alcohol use, diabetes, dyslipidemia, increased BMI, or suspected metabolic dysfunction-associated steatotic liver disease, calculate a non-invasive fibrosis score such as FIB-4 and consider elastography if indicated; this should not delay treatment when methotrexate is otherwise appropriate.
- Monitor CBC, liver tests, and kidney function periodically.
- Counsel patients to report fever, infection symptoms, mouth sores, severe nausea/vomiting/diarrhea, dyspnea/cough, rash, bruising/bleeding, jaundice, marked fatigue, or reduced urine output. Temporarily discontinue methotrexate during severe infection, such as infection requiring intravenous therapy, until recovery.

When methotrexate is unavailable or undesirable

For most patients, methotrexate is undesirable for CU because benefit is uncertain and monitoring/toxicity burdens are substantial. In patients with severe CU refractory to first- and second-line advanced therapies, selected patients may prefer trials of hydroxychloroquine or mycophenolate, or accessing randomized clinical trials addressing new therapies.

When methotrexate may not be a good option

Methotrexate may not be a good option in patients with:

- pregnancy, lactation, patients who could become pregnant without an appropriate contraception and washout strategy
- significant liver disease or heavy alcohol use
- significant renal impairment

- baseline cytopenias
- active serious infection, immunodeficiency, inability to adhere to weekly dosing, inability to complete laboratory monitoring, or concomitant drugs that substantially increase toxicity.
- In patients with possible lung disease, evaluate symptoms and examination findings rather than treating lung disease as an automatic contraindication; specialist input is appropriate when respiratory reserve is limited or pneumonitis would be difficult to distinguish.

Implementation practical considerations

- **Medication routine:** Methotrexate is taken once weekly by mouth or subcutaneous injection. Prescribe folic acid or folinic acid to reduce adverse effects. One possible approach is folic acid 5 mg once weekly, not on the methotrexate day.
- **Tests and visits:** Frequent early lab monitoring is essential. Check CBC, liver enzymes, albumin, and creatinine/eGFR at baseline and periodically; increase monitoring with dose changes or toxicity risk. For adults with liver-disease risk factors, do a fibrosis risk assessment such as FIB-4 and arrange elastography or hepatology input if indicated.
- **Immunization:** Assess vaccination status and infection risk before therapy when feasible. Consider holding methotrexate for up to 2 weeks after vaccination if possible.
- **Interactions:** Review interacting medications carefully, including trimethoprim-sulfamethoxazole, penicillins, NSAIDs in higher-risk settings, proton-pump inhibitors, nephrotoxic drugs, other hepatotoxic drugs, nitrous oxide anesthesia, and live vaccines.
- **Adverse effects:** Common effects include nausea, vomiting, diarrhea, stomatitis/oral ulcers, rash, alopecia, and elevated liver tests. Serious harms include myelosuppression, hepatotoxicity, pulmonary toxicity including interstitial pneumonitis, renal toxicity, severe skin reactions, serious infections, neurotoxicity, and secondary malignancies.
- **Pregnancy and nursing:** Contraindicated in pregnancy breastfeeding. Discuss contraception, washout timing, and pregnancy planning before prescribing to patients who could become pregnant. For male patients trying to conceive, EULAR reproductive guidance considers low-dose methotrexate up to 25 mg/week compatible with paternal exposure, while some product labels remain more conservative.
- **Costs and access:** Methotrexate is generic, widely available, and usually low cost. Monitoring, however, may have variable costs.

Evaluation

Apart from standard structured CU assessment after 4-12 week after initiation of therapy, patients should be routinely monitored for methotrexate adverse effects.

Research needs

- Robust RCTs are needed to clarify whether methotrexate has any patient-important benefit in CU, whether any subgroup benefits, and how benefits and harms compare with advanced therapies and selected later-line options.

Adaptation

Methotrexate's availability across many regions facilitates adaptation in many contexts.

Summary of Findings – methotrexate for chronic urticaria

The findings are detailed in the guideline main text and in the associated systematic review[6].

References

1. Agarwal A, Chen L, Capozza K, Roberts A, Golden DBK, Shaker MS, et al. Trustworthy Patient-Centered Guidelines: Insights From Atopic Dermatitis and a Proposal for the Future. *J Allergy Clin Immunol Pract.* 2022;10:2875-2877.
2. Schünemann HJ, Brennan S, Akl EA, Hultcrantz M, Alonso-Coello P, Xia J, et al. The development methods of official GRADE articles and requirements for claiming the use of GRADE – A statement by the GRADE guidance group. *Journal of Clinical Epidemiology.* 2023;159:79-84.
3. Chu X, Mubasher J, Chen L, Chu AWL, Oykhman P, Brignardello-Petersen R, et al. Patient Values and Preferences in Chronic Urticaria Treatment: A Systematic Review. *JAMA Dermatol.* 2025;161:1264-1272.
4. Chu DK, Golden DBK, Guyatt GH. Translating Evidence to Optimize Patient Care Using GRADE. *J Allergy Clin Immunol Pract.* 2021;9:4221-4230.
5. Chu A, Zhao I, Rayner D, Guyatt G, Liu M, Gao C, et al. COMPARING ANTIHISTAMINES FOR CHRONIC URTICARIA: SYSTEMATIC REVIEW, DOSE RESPONSE, AND NETWORK META-ANALYSIS OF RANDOMIZED TRIALS: Research presented by the AAAAI/ACAAI Joint Task Force on Practice Parameters. *Annals of Allergy, Asthma & Immunology.* 2025;135:S28.
6. Chu AWL, Oykhman P, Chu X, Rayner DG, Bhangal S, Dam A, et al. Comparative efficacy and safety of biologics and systemic immunomodulatory treatments for chronic urticaria: Systematic review and network meta-analysis. *J Allergy Clin Immunol.* 2025;156:1008-1023.
7. Rayner DG, Liu M, Chu AWL, Chu X, Guyatt GH, Oykhman P, et al. Leukotriene receptor antagonists as add-on therapy to antihistamines for urticaria: Systematic review and meta-analysis of randomized clinical trials. *J Allergy Clin Immunol.* 2024;154:996-1007.
8. Chu X, Wang J, Ologundudu L, Brignardello-Petersen R, Guyatt GH, Oykhman P, et al. Efficacy and Safety of Systemic Corticosteroids for Urticaria: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *J Allergy Clin Immunol Pract.* 2024;12:1879-1889.e1878.
9. Bradford Rice J, White AG, Scarpati LM, et al. Long-term systemic corticosteroid exposure: A systematic literature review. *Clin Ther.* 2017;39:2216-2229.
10. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of long-course oral corticosteroids in children. *PloS One.* 2017;12:e0170259.
11. Lima JP, Chowdhury SR, Tangamornsuksan W, Zhai C, Chu X, Matos Silva J, et al. Adverse Events Following Short-Course Systemic Corticosteroids Among Children and Adolescents: A Systematic Review and Meta-Analysis. *JAMA Network Open.* 2025;8:e2534953-e2534953.
12. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short-course oral corticosteroids in children. *Arch Dis Child.* 2016;101:365-370.
13. Chu X, Wang J, Ologundudu L, et al. Efficacy and safety of SCS for urticaria: A systematic review and meta-analysis of randomized clinical trials. *J Allerg Clin Immunol Pract.* 2024;12:1980-1889.e1988.

14. Price DB, Trudo F, Voorhan J, et al. Adverse outcomes from initiation of SCS for asthma: Long-term observational study. *J Asthma Allergy.* 2018;11:193-204.
15. Waljee AK, Rogers MAM, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States: Population based cohort study. *BMJ.* 2017;357:j1415.
16. Ledford D, Broder MS, Antonova E, Omachi TA, Chang E, Luskin A. Corticosteroid-related toxicity in patients with chronic idiopathic urticariachronic spontaneous urticaria. *Allergy Asthma Proc.* 2016;37:458-465.
17. Broerson LH, Pereira AM, Jorgensen JOL, et al. Adrenal insufficiency in corticosteroids use: Systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2015;100:2171-2180.
18. Joseph RM, Hunter AL, Ray DW, et al. Systemic glucocorticoid therapy and adrenal insufficiency in adults: A systematic review. *Semin Arthritis Rheum.* 2016;46:133-141.
19. Nielman LK, Raff H, DeSantis A. Diagnosis of adrenal insufficiency in adults. *UpToDate.* 2024.
20. Bandoli G, Palmsten K, Forbess Smith CJ, Chambers CD. A Review of Systemic Corticosteroid Use in Pregnancy and the Risk of Select Pregnancy and Birth Outcomes. *Rheum Dis Clin North Am.* 2017;43:489-502.
21. Ugwu N, Cheraghlou S, et al. Characterization of outpatient visits and treatments for urticaria in the United States adult population between 1998 and 2016. *J Am Acad Dermatol.* 2022;86:936-938.
22. Finlay AY, Edwards PH, Harding KG. "Fingertip unit" in dermatology. *Lancet.* 1989;2:155.
23. Long CC, Finlay AY. The finger-tip unit—a new practical measure. *Clinical and Experimental Dermatology.* 1991;16:444-447.
24. Long CC, Finlay AY, Averill RW. The Rule of Hand: 4 Hand Areas=2 FTU=1 g. *Archives of Dermatology.* 1992;128:1129-1130.
25. Long CC, Mills CM, Finlay AY. A practical guide to topical therapy in children. *British Journal of Dermatology.* 1998;138:293-296.
26. Bewley A, Dermatol Working G. Expert consensus: time for a change in the way we advise our patients to use topical corticosteroids. *BRITISH JOURNAL OF DERMATOLOGY.* 2008;158:917-920.
27. Chu AWL, Rayner DG, Chu X, Chen L, Dong AYH, Waserman S, et al. Topical corticosteroids for hives and itch (urticaria): Systematic review and Bayesian meta-analysis of randomized trials. *Ann Allergy Asthma Immunol.* 2024.
28. Giustina A, Adler RA, Binkley N, Bouillon R, Ebeling PR, Lazaretti-Castro M, et al. Controversies in Vitamin D: Summary Statement From an International Conference. *J Clin Endocrinol Metab.* 2019;104:234-240.
29. Demay MB, Pittas AG, Bikle DD, Diab DL, Kiely ME, Lazaretti-Castro M, et al. Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2024;109:1907-1947.

30. Shah VP, Nayfeh T, Alsawaf Y, Saadi S, Farah M, Zhu Y, et al. A Systematic Review Supporting the Endocrine Society Clinical Practice Guidelines on Vitamin D. *J Clin Endocrinol Metab.* 2024;109:1961-1974.

31. Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin D, Calcium. The National Academies Collection: Reports funded by National Institutes of Health. In: Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington (DC): National Academies Press (US)

Copyright © 2011, National Academy of Sciences.; 2011.

32. Dai A, Kim SJ. Systemic calcineurin inhibitors tacrolimus and voclosporin: A review of off-label dermatologic uses. *J Am Acad Dermatol.* 2024;90:358-367.

33. Trojan T, Khan DA. Calcineurin inhibitors in chronic urticaria. *Curr Opin Allergy Clin Immunol.* 2012;12:412-420.

34. Kulthanan K, Chaweekulrat P, Komoltri C, et al. Cyclosporine for Chronic Spontaneous Urticaria: A Meta-Analysis and Systematic Review. *J Allergy Clin Immunol Pract.* 2018;6:586-599.

35. Baskan EB, Tunali S, Turker T, Saricaoglu HU. Comparison of short and long term Cyclosporine A therapy in chronic idiopathic urticaria. *J Dermatolog Treat.* 2004;15:164-168.

36. Di Gioacchino M, Di Stefano F, Cavallucci E, et al. Treatment of chronic idiopathic urticaria and positive autologous serum skin test with cyclosporine: clinical and immunologic evaluation. *Allergy Asthma Proc.* 2003;24:285-290.

37. Dorman SM, Regan SB, Khan DA. Effectiveness and safety of oral tacrolimus in refractory chronic urticaria. *J Allergy Clin Immunol Pract.* 2019;7:2033-2034.

38. Khan DA. Alternative agents in refractory chronic urticaria: evidence and considerations on their selection and use. *J Allergy Clin Immunol Pract.* 2013;1:433-440.

39. Kroger A BL, Long S, Sanchez P. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). *Vaccine Recommendations and Guidelines of the ACIP.* Vol 2023. August 3, 2023 ed: US CDC. National Center for Immunization and Respiratory Diseases; 2023.

40. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host. *Clinical Infectious Diseases.* 2013;58:e44-e100.

41. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of Herpes Zoster: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report: Recommendations and Reports.* 2008;57:1-30.

42. FDA. NEORAL® Soft Gelatin Capsules (cyclosporine capsules, USP) MODIFIED (https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/050715s035,050716s038lbl.pdf). 2024.

43. FDA. Prograf (tacrolimus) capsules/injection label (https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050709s031lbl.pdf). 2024.
44. Shahar E, Bergman R, Guttman-Yassky E, Pollack S. Treatment of severe chronic idiopathic urticaria with oral mycophenolate mofetil in patients not responding to antihistamines and/or corticosteroids. *Int J Dermatol.* 2006;45:1224-1227.
45. Zimmerman AB, Berger EM, Elmariah SB, Soter NA. The use of mycophenolate mofetil for the treatment of autoimmune and chronic idiopathic urticaria: experience in 19 patients. *J Am Acad Dermatol.* 2012;66:767-770.
46. Seth S, Khan DA. The Comparative Safety of Multiple Alternative Agents in Refractory Chronic Urticaria Patients. *J Allergy Clin Immunol Pract.* 2017;5:165-170.e162.
47. Sabbatini M, Capone D, Gallo R, Pisani A, Polichetti G, Tarantino G, et al. EC-MPS permits lower gastrointestinal symptom burden despite higher MPA exposure in patients with severe MMF-related gastrointestinal side-effects. *Fundam Clin Pharmacol.* 2009;23:617-624.
48. Orden RA, Timble H, Saini SS. Efficacy and safety of sulfasalazine in patients with chronic idiopathic urticaria. *Ann Allergy Asthma Immunol.* 2014;112:64-70.
49. Jaffer AM. Sulfasalazine in the treatment of corticosteroid-dependent chronic idiopathic urticaria. *J Allergy Clin Immunol.* 1991;88:964-965.
50. Engler RJ, Squire E, Benson P. Chronic sulfasalazine therapy in the treatment of delayed pressure urticaria and angioedema. *Ann Allergy Asthma Immunol.* 1995;74:155-159.
51. McGirt LY, Vasagar K, Gober LM, Saini SS, Beck LA. Successful treatment of recalcitrant chronic idiopathic urticaria with sulfasalazine. *Arch Dermatol.* 2006;142:1337-1342.
52. Chakravarty K, McDonald H, Pullar T, Taggart A, Chalmers R, Oliver S, et al. BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. *Rheumatology (Oxford).* 2008;47:924-925.
53. Lovell KK, Momin RI, Sangha HS, Feldman SR, Pichardo RO. Dapsone Use in Dermatology. *Am J Clin Dermatol.* 2024;25:811-822.
54. Fortson JS, Zone JJ, Hammond ME, Groggel GC. Hypocomplementemic urticarial vasculitis syndrome responsive to dapsone. *J Am Acad Dermatol.* 1986;15:1137-1142.
55. Wolf R, Tüzün B, Tüzün Y. Dapsone: unapproved uses or indications. *Clin Dermatol.* 2000;18:37-53.
56. Liang SE, Hoffmann R, Peterson E, Soter NA. Use of Dapsone in the Treatment of Chronic Idiopathic and Autoimmune Urticaria. *JAMA Dermatol.* 2019;155:90-95.
57. González P, Soriano V, Caballero T, Niveiro E. Idiopatic angioedema treated with dapsone. *Allergol Immunopathol (Madr).* 2005;33:54-56.
58. Stanaland BE. Treatment of patients with chronic idiopathic urticaria. *Clin Rev Allergy Immunol.* 2002;23:233-241.

59. Dziewulska KH, Reisz JA, Hay AM, D'Alessandro A, Zimring JC. Hemolysis and Metabolic Lesion of G6PD Deficient RBCs in Response to Dapsone Hydroxylamine in a Humanized Mouse Model. *J Pharmacol Exp Ther.* 2023;386:323-330.

60. Pamba A, Richardson ND, Carter N, Duparc S, Premji Z, Tiono AB, et al. Clinical spectrum and severity of hemolytic anemia in glucose 6-phosphate dehydrogenase-deficient children receiving dapsone. *Blood.* 2012;120:4123-4133.

61. Byrd SR, Gelber RH. Effect of dapsone on haemoglobin concentration in patients with leprosy. *Lepr Rev.* 1991;62:171-178.

62. Grindulis KA, McConkey B. Rheumatoid arthritis: the effects of treatment with dapsone on hemoglobin. *J Rheumatol.* 1984;11:776-778.

63. Hu Y, Geere M, Awan M, Leavitt AD, Brown LE, Pearson HJ, et al. Dapsone-induced methemoglobinemia and hemolysis in a woman without G6PD deficiency presenting with idiopathic urticaria. *Hematology.* 2022;27:1253-1258.

64. Colella MP, Orsi FA, Alves ECF, Delmoro GF, Yamaguti-Hayakawa GG, de Paula EV, et al. A retrospective analysis of 122 immune thrombocytopenia patients treated with dapsone: Efficacy, safety and factors associated with treatment response. *J Thromb Haemost.* 2021;19:2275-2286.

65. Morris A, Bain BJ, Atta M, Layton DM. A puzzling case of methemoglobinemia. *Am J Hematol.* 2017;92:1103-1104.

66. Mitsides N, Green D, Middleton R, New D, Lamerton E, Allen J, et al. Dapsone-induced methemoglobinemia in renal transplant recipients: more prevalent than previously thought. *Transpl Infect Dis.* 2014;16:37-43.

67. Olteanu H, Harrington AM, George B, Hari PN, Bredeson C, Kroft SH. High prevalence of Dapsone-induced oxidant hemolysis in North American SCT recipients without glucose-6-phosphate-dehydrogenase deficiency. *Bone Marrow Transplant.* 2012;47:399-403.

68. Kabra NS, Nanavati RN, Srinivasan G. Neonatal methemoglobinemia due to transplacental transfer of dapsone. *Indian Pediatr.* 1998;35:553-555.

69. Hocking DR. Neonatal haemolytic disease due to dapsone. *Med J Aust.* 1968;1:1130-1131.

70. Brabin BJ, Eggelte TA, Parise M, Verhoeff F. Dapsone therapy for malaria during pregnancy: maternal and fetal outcomes. *Drug Saf.* 2004;27:633-648.

71. Sanders SW, Zone JJ, Foltz RL, Tolman KG, Rollins DE. Hemolytic anemia induced by dapsone transmitted through breast milk. *Ann Intern Med.* 1982;96:465-466.

72. Dreisbach JA. Sulphone levels in breast milk of mothers on sulphone therapy. *Lepr Rev.* 1952;23:101-106.

73. Phillips-Howard PA, Wood D. The safety of antimalarial drugs in pregnancy. *Drug Saf.* 1996;14:131-145.

74. Drugs and Lactation Database (LactMed®) [Internet]. Bethesda (MD): National Institute of Child Health and Human Development; 2006-. Dapsone. [Updated 2024 Sep 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK501589/.

75. DAPSONE- dapsone tablet 25 mg & 100 mg2025.

76. Webster GF. Is topical dapsone safe in glucose-6-phosphate dehydrogenase-deficient and sulfonamide-allergic patients? *J Drugs Dermatol.* 2010;9:532-536.

77. Wozel G, Blasum C. Dapsone in dermatology and beyond. *Arch Dermatol Res.* 2014;306:103-124.

78. Burke P, Jahangir K, Kolber MR. Dapsone-induced methemoglobinemia: case of the blue lady. *Can Fam Physician.* 2013;59:958-961.

79. Bradberry SM, Vale JA. Multiple-dose activated charcoal: a review of relevant clinical studies. *J Toxicol Clin Toxicol.* 1995;33:407-416.

80. Edstein MD, Veenendaal JR, Newman K, Hyslop R. Excretion of chloroquine, dapsone and pyrimethamine in human milk. *Br J Clin Pharmacol.* 1986;22:733-735.

81. Kahn G. Dapsone is safe during pregnancy. *J Am Acad Dermatol.* 1985;13:838-839.

82. Smith CI, Islam TC, Mattsson PT, Mohamed AJ, Nore BF, Vihinen M. The Tec family of cytoplasmic tyrosine kinases: mammalian Btk, Bmx, Itk, Tec, Txk and homologs in other species. *Bioessays.* 2001;23:436-446.

83. Lin EV, Suresh RV, Dispenza MC. Bruton's tyrosine kinase inhibition for the treatment of allergic disorders. *Ann Allergy Asthma Immunol.* 2024;133:33-42.

84. Maurer M, Berger W, Gimenez-Arnau A, et al. Remibrutinib, a novel BTK inhibitor, demonstrates promising efficacy and safety in chronic spontaneous urticaria. *J Allergy Clin Immunol.* 2022;150:1498-1506.

85. Jain V, Gimenez-Arnau A, Hayama K, et al. Remibrutinib demonstrates favorable safety profile and sustained efficacy in chronic spontaneous urticaria over 52 weeks. *J Allergy Clin Immunol.* 2024;153:479-486.

86. Langrish CL, Bradshaw JM, Francesco MR, et al. Preclinical Efficacy and Anti-Inflammatory Mechanisms of Action of the Bruton Tyrosine Kinase Inhibitor Rilzabrutinib for Immune-Mediated Disease. *J Immunol.* 2021;206:1454-1468.

87. Lai X, Liu J, Li W, Qiao M, Qiu M, Lu L. Metabolite profiling of remibrutinib in rat and human liver microsomes using liquid chromatography combined with benchtop orbitrap high-resolution mass spectrometry. *Biomed Chromatogr.* 2023;37:e5737.

88. Schiller H, Huth F, Schuhler C, et al. Novel Bruton's tyrosine kinase inhibitor remibrutinib: Assessment of drug-drug interaction potential as a perpetrator of cytochrome P450 enzymes and drug transporters and the impact of covalent binding on possible drug interactions. *Eur J Pharm Sci.* 2022;172:106155.

89. Kaul M, End P, Cabanski M, et al. Remibrutinib (LOU064): A selective potent oral BTK inhibitor with promising clinical safety and pharmacodynamics in a randomized phase I trial. *Clin Transl Sci.* 2021;14:1756-1768.

90. Le Floc'h A, Allinne J, Nagashima K, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Ralpha antibody, is required to broadly inhibit type 2 inflammation. *Allergy.* 2020;75:1188-1204.

91. Maurer M, Casale TB, Saini SS, et al. Dupilumab in patients with chronic spontaneous urticaria (LIBERTY-CSU CUPID): Two randomized, double-blind, placebo-controlled, phase 3 trials. *J Allergy Clin Immunol.* 2024;154:184-194.

92. Zhu C, BinJadeed H, Gabrielli S, et al. Prevalence of omalizumab resistant chronic urticaria and real world effectiveness of dupilumab in omalizumab refractory chronic urticaria patients: a single center experience. *Clin Exp Dermatol.* 2024.

93. Maurer M, Casale TB, Saini SS, et al. Dupilumab Reduces Urticaria Activity, Itch, and Hives in Patients with Chronic Spontaneous Urticaria Regardless of Baseline Serum Immunoglobulin E Levels. *Dermatol Ther (Heidelb)*. 2024.

94. In Brief: Dupilumab (Dupixent) for Chronic Spontaneous Urticaria | The Medical Letter Inc. Vol 2025: The Medical Letter on Drugs and Therapeutics; 2025.

95. PRODUCT MONOGRAPH INCLUDING PATIENT MEDICATION INFORMATION. 2020.

96. Blauvelt A, Simpson EL, Tyring SK, et al. Dupilumab does not affect correlates of vaccine-induced immunity: A randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. *J Am Acad Dermatol*. 2019;80:158-167.

97. Lieberman JA, Chu DK, Ahmed T, Dribin TE, Abrams EM, Anagnostou A, et al. A systematic review and expert Delphi Consensus recommendation on the use of vaccines in patients receiving dupilumab: A position paper of the American College of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol*. 2024;133:286-294.

98. Siegfried EC, Wine Lee L, Spergel JM, et al. A case series of live attenuated vaccine administration in dupilumab-treated children with atopic dermatitis. *Pediatr Dermatol*. 2024;41:204-209.

99. Khamisy-Farah R, Damiani G, Kong JD, Wu JH, Bragazzi NL. Safety profile of Dupilumab during pregnancy: a data mining and disproportionality analysis of over 37,000 reports from the WHO individual case safety reporting database (VigiBase). *Eur Rev Med Pharmacol Sci*. 2021;25:5448-5451.

100. Avallone G, Cavallo F, Tancredi A, et al. Association between maternal dupilumab exposure and pregnancy outcomes in patients with moderate-to-severe atopic dermatitis: A nationwide retrospective cohort study. *J Eur Acad Dermatol Venereol*. 2024.

101. Chen J, Zeng X, et al. Efficacy of NB-UVB as Add-on Therapy to Antihistamine in the Treatment of Chronic Urticaria: A Systematic Review and Meta-analysis. *Dermatol Ther (Heidelb)*. 2021;11:681-694.

102. Sheikh G, Latif I, et al. Role of Adjuvant Narrow Band Ultraviolet B Phototherapy in the Treatment of Chronic Urticaria. *Indian J Dermatol*. 2019;64:250.

103. Engin B, Ozdemir M, et al. Treatment of Chronic Urticaria with Narrowband Ultraviolet B Phototherapy: a Randomized Controlled Trial. *Acta Derm Venereol*. 2008;88:247-251.

Acknowledgements

We are grateful for the immense support by our patients and caregivers' partners, McMaster Health Science Library interlibrary loan team, the CLARITY research group, Madeline Fraser, Tachlima Sunna, Keerthana Pasamurthi, Jason Chen, the AAAAI and ACAAI, Asthma and Allergy Foundation of America, Allergy & Asthma Network, Global Allergy & Airways Patient Platform and peer-reviewers and public commentators.

Members of the Evidence in Allergy Group evidence synthesis team: Aaron Wen; Alexandro Chu; Ananya Pathak; Andy Zhu; Angela Wang; Anish Samanthapudi; Anja Fog Heen; Anna Whalen-Browne; Antonio Bognanni; Archita Srivastava; Arnav Agarwal; Clement Lin; Daniel Cao; Devyani Bakshi; Dhruv Dhall; Dimitrios Deris; Dorota Borovsky; Ella Rival; Eric McMullen; Erica Aranha Suzumura; Falana Sheriff; Haseeb Faisal; Heather Le; Irene Zhao; Jared Dookie; Jeremy Steen; Karl Maxemous; Keon Maleki-Yazdi; Kiki Wang; Layla Bakaa; Leonardo Ologundudu; Lina Chen; Margaret MacDonald; Melanie Wong; Ming Liu; Nazmul Islam; Nima Makhdami; Niveditha Devasenapathy; Omar Almatrafi; Paul Oykhman; Rachel Asiniwasis; Raquel Ocvirk; Rayirth Sivakumar; Renata Ceccacci; Roshan Dinparastisaleh; Sam Al-Rammahy; Shakil Popatia; Sonia Brar; Tasnuva Ahmed; Vineeth Jarabana; Xiajing Chu; Yunli Zhao.

We express our deepest gratitude to Dr. Joseph Moellman in the development of reviews, the guideline, and in improving the care of patients with urticaria and angioedema worldwide. We are also grateful to Dr. Marcus Maurer, a pioneer and trailblazer in urticaria, who sadly passed away during the development of this guideline. We dedicate this guideline in both their memory.

DKC is an AAAAI Foundation Faculty Development Awardee and holds a Canadian Institutes of Health Research inclusive research excellence award in patient engagement, an E.J. Moran Campbell Career Award, and a CIHR Implementation Science Chair.

Fingertip image displaying fingertip units adapted from rocketpixel on Freepik.

2010

Disclosure forms details

Name	David M Lang	Lisa A Beck	Javed Sheikh	Diane R Baker
Specialty (eg. 'Patient Partner', 'Primary care', 'General Pediatrics', 'Dermatology', 'Allergy/Immunology', 'Psychotherapy', 'Pharmacy', etc.)	Allergy / Immunology	Dermatology	Dermatology	Dermatology
Primary affiliation/institution	Cleveland Clinic	University of Rochester Medical Center	Southern California Permanente Medical Group	None
Country	USA	USA	USA	USA
Job Title	Emeritus Chair	Professor	Physician	None (retired)
In the previous calendar year, did you, or a member of your household or immediate family, have competing relationships?	Yes	Yes	No	No
In the previous 12 months, did you, or any member of your household or immediate family, receive less than $5,000 in salary support, income, or other assets?	No	Yes	No	No
What is the name and role of the organization(s)?	NA	Consultant for Amgen, Zai Laboratories, UCB, Belharra Therapeutics, Bambusa, Apogee, Triveni Bio, TrexBio, Lilly, Gilead, and Abbvie; Advisory Board Member for Galderma and DMC member for Novartis.	NA	NA
In the previous 12 months, did you, or any member of your household or immediate family, receive $5,000 -	Yes	Yes	No	No

$25,000 in salary support, income, or other assets?				
What is the name of the organization(s)/topic of Testimony or Consultation?	Celldex Genentech Sanofi-Regeneron	Rapt Therapeutics, Regeneron; Dermavent; AstraZeneca	NA	NA
What is the nature of relationship?	Consultant for Celldex and Genentech, Consultant/Speaker for Sanofi-Regeneron	Consultant for Rapt Therapeutics, Regeneron, and Dermavent; recipient of a Research Grant from AstraZeneca	NA	NA
Whether is the relationship ongoing?	All relationship is ongoing	All relationship is ongoing	NA	NA
In the previous 12 months, did you, or any member of your household or immediate family, receive >$25,000 but less than $50,000 in salary support, income, or other assets?	Yes	No	No	No
What is the name of the organization(s)/topic of Testimony or Consultation?	Novartis	NA	NA	NA
What is the nature of relationship?	Consultant/Speaker for Novartis	NA	NA	NA
Whether is the relationship ongoing?	Yes	NA	NA	NA
In the previous 12 months, did you, or any member of your household or immediate family, receive $50,000 or more in salary support, income, or other assets?	No	Yes	No	No
What is the name of the organization(s)/topic of Testimony or Consultation?	NA	NIAID/NIH	NA	NA
What is the nature of relationship?	NA	Research Grant from NIAID/NIH	NA	NA
Whether is the relationship ongoing?	NA	Yes	NA	NA
During the previous 12 months, did you hold volunteer positions, including organizations, published	Yes	Yes	No	Yes

works, competing interests or academic commitments that may create or be perceived as a conflict of interest?				
What is the name of organization, competing interest, academic commitment, or nature of published work (recent or planned)?	World Allergy Organization; Allergy & Asthma Proceedings; Journal of Allergy and Clinical Immunology: In Practice	ADCARE Steering Committee; Chair of SID Nominations Committee	NA	Oregon Health & Science University
What is the nature of relationship?	Member, Board of Directors of the World Allergy Organization; Member, Editorial Board of Allergy & Asthma Proceedings; Guest Editor for Journal of Allergy and Clinical Immunology: In Practice	Member of the ADCARE Steering Committee; Chair of the SID Nominations Committee.	NA	Clinical professor on dermatology
Whether is the relationship ongoing?	Relationship with World Allergy Organization and Allergy & Asthma Proceedings is ongoing	Relationship with ADCARE Steering Committee is ongoing.	NA	Yes
What competing interests most likely to represent real or perceived conflict?	Consulting/speaking for Novartis, Genentech, Sanofi-Regeneron, and Celldex	No	No	No

2011

Name	Eric Tyrell Oliver	Sarbjit S Saini	David Khan	Sameer K. Mathur
Specialty (eg. 'Patient Partner', 'Primary	Dermatology	Dermatology	Dermatology	Dermatology

care', 'General Pediatrics', 'Dermatology', 'Allergy/Immunology', 'Psychotherapy', 'Pharmacy', etc.)				
Primary affiliation/institution	Johns Hopkins University	Johns Hopkins University	UT Southwestern	University of Wisconsin School of Medicine and Public Health
Country	USA	USA	USA	USA
Job Title	Assistant Professor of Medicine	Assistant Professor of Medicine	Professor of Medicine	Associate Professor of Medicine
In the previous calendar year, did you, or a member of your household or immediate family, have competing relationships?	Yes	Yes	Yes	Yes
In the previous 12 months, did you, or any member of your household or immediate family, receive less than $5,000 in salary support, income, or other assets?	Yes	Yes	Yes	No
What is the name and role of the organization(s)?	Advisory Board for Novartis Pharmaceuticals	Consultant for Evommune, Allakos, Seppterna, and Incyte; Consultant and Advisory Board Member for Celldex; Speaker for Regeneron.	UptoDate (Honorarium/Gift)	NA
In the previous 12 months, did you, or any member of your household or immediate family, receive $5,000 - $25,000 in salary support, income, or other assets?	No	Yes	Yes	Yes

What is the name of the organization(s) /topic of Testimony or Consultation?	NA	Celltrion and Novartis	MJH LIfe Sciences	Novartis and Sanofi-Regeneron, AstraZeneca and GSK
What is the nature of relationship?	NA	Consultant and Advisory Board Member for Celltrion and Novartis	Moderator for webinar on urticaria: MJH LIfe Sciences	Advisory Board Member for Novartis and Sanofi-Regeneron; Advisory Board Member and Speaker for AstraZeneca and GSK.
Whether is the relationship ongoing?	NA	Yes	No	Yes
In the previous 12 months, did you, or any member of your household or immediate family, receive >$25,000 but less than $50,000 in salary support, income, or other assets?	No	Yes	No	No
What is the name of the organization(s) /topic of Testimony or Consultation?	NA	Granular	NA	NA
What is the nature of relationship?	NA	Advisor for Granular	NA	NA
Whether is the relationship ongoing?	NA	Yes	NA	NA
In the previous 12 months, did you, or any member of your household or immediate family, receive $50,000 or more in salary support, income, or other assets?	Yes	Yes	No	No

What is the name of the organization(s) /topic of Testimony or Consultation?	Allakos, Blueprint Medicines, Celldex, Escient (Acquired by Incyte), Evommune, Jasper Therapeutics, and Novartis Pharmaceuticals (all ongoing); Career development award paid to institution from Bristol Myers Squibb Foundation	Allakos, Celldex, Evommune, Jasper, Novartis and Blueprint	NA	NA
What is the nature of relationship?	Grant to institution to conduct clinical trials from Allakos, Blueprint Medicines, Celldex, Escient (Acquired by Incyte), Evommune, Jasper Therapeutics, and Novartis Pharmaceuticals (all ongoing); Career development award paid to institution from Bristol Myers Squibb Foundation	Grant to institution to conduct clinical trials from Allakos, Celldex, Evommune, Jasper, Novartis and Blueprint	NA	NA
Whether is the relationship ongoing?	Yes	Yes	NA	NA
During the previous 12 months, did you hold volunteer positions, including organizations, published works, competing interests or academic commitments that	No	Yes	No	No

may create or be perceived as a conflict of interest?				
What is the name of organization, co mpeting interest, academic commitment, or nature of published work (recent or planned)?	NA	UptoDate	NA	NA
What is the nature of relationship?	NA	Section editor Uticaria and Angioad ema section	NA	NA
Whether is the relationship ongoing?	NA	Yes	NA	NA
What competing interests most likel y to represent real or perceived conflict?	No	No	Chapters on Up to Date on Therapy for Urticaria	No

2012

Name	Susan Waserman	Moshe Ben-Shoshan	Jonathan A Bernstein	Lauren Runyon
Specialty (eg. 'Patient Partner', 'Primary care', 'General Pediatrics', 'Dermatolog y', 'Allergy/Immunology', 'P sychotherapy', 'Pharmacy', etc.)	Allergy / Imm unology	Allergy / Imm unology	Dermatology	Nurse
Primary affiliation/institution	McMaster University	Montreal Children's Hospital	University of Cincinnati College of Medicine, Advanced Allergy Services, LLC, Bernstein Clinical Research Center, LLC	The University of Texas Southwestern Medical Center and The University of Texas at Arlington
Country	Canada	Canada	USA	USA
Job Title	Professor of Medicine, Allergist Clinical Immunologist	Assistant Professor (Clinical) of Pediatrics and associate member, Dep	Professor of Clinical Medicine	Nurse Practitioner at UTSW Clinical Faculty- nuring-UT Arlington

		artment of Epidemiology, Biostatistics and Occupational Health, McGill University		
In the previous calendar year, did you, or a member of your household or immediate family, have competing relationships?	Yes	Yes	Yes	No
In the previous 12 months, did you, or any member of your household or immediate family, receive less than $5,000 in salary support, income, or other assets?	Yes	Yes	Yes	No
What is the name and role of the organization(s)?	Consultant, Advisory Board Member, and Speaker for AZ, GSK, ALK, AbbVie, Viatris, CSL, Takeda, Sanofi, and Novartis. Consultant and Advisory Board Member for BioCryst and Celltrion.	Consultant for Novartis, Sanofi, ALK and Viatris and Site investigator for studies by Novartis, Sanofi and ALK	Research grant: Amgen, Astra Zeneca, GSK, Blueprint Medicine, Celldex, Cogent, Escient, Evommune, Neffy, Telios Honorarium/Gift: Teledoc	NA
In the previous 12 months, did you, or any member of your household or immediate family, receive $5,000 - $25,000 in salary support, income, or other assets?	No	No	Yes	No
What is the name of the organization(s)/topic	NA	NA	Yuhan Pharmaceuticals, Novartis, Genentech,	NA

of Testimony or Consultation?			Sanofi- Regeneron, Opella	
What is the nature of relationship?	NA	NA	Consultant and Investigator	NA
Whether is the relationship ongoing?	NA	NA	Yes	NA
In the previous 12 months, did you, or any member of your household or immediate family, receive >$25,000 but less than $50,000 in salary support, income, or other assets?	No	No	No	No
What is the name of the organization(s)/topic of Testimony or Consultation?	NA	NA	NA	NA
What is the nature of relationship?	NA	NA	NA	NA
Whether is the relationship ongoing?	NA	NA	NA	NA
In the previous 12 months, did you, or any member of your household or immediate family, receive $50,000 or more in salary support, income, or other assets?	No	No	No	No
What is the name of the organization(s)/topic of Testimony or Consultation?	NA	NA	NA	NA
What is the nature of relationship?	NA	NA	NA	NA
Whether is the relationship ongoing?	NA	NA	NA	NA
During the previous 12 months, did you hold volunteer positions, including organizations, published works, competing interests or academic commitments that may create or be perceived as a conflict of interest?	Yes	No	Yes	No
What is the name of organization, competi	Canadian Allergy	NA	UCARE/ACARE Center of Excellence; AIM Center of	NA

ng interest, academic commitment, or nature of published work (recent or planned)?	Asthma and Immunology Foundation; Canadian Hereditary Angioedema Network; Asthma Canada; Food Allergy Canada		Excellence; WAO Center of Excellence; AAAAI Foundation; JTF Member; CSU Guideline Work Group; AFI	
What is the nature of relationship?	President of Canadian Allergy Asthma and Immunology Foundation, Board of Directors Canadian Hereditary Angioedema Network, Board of Directors Asthma Canada, Medical Advisor for Food Allergy Canada	NA	Director for UCARE/ACARE Center of Excellence; Co-Director for AIM Center of Excellence; Co-Director for WAO Center of Excellence; Chairman for AAAAI Foundation; Member for JTF; Co-Chair for CSU Guideline Work Group; Executive Vice Chairman for AFI.	NA
Whether is the relationship ongoing?	Yes	NA	Yes	NA
What competing interests most likely to represent real or perceived conflict?	Served in an advisory capacity to pharmaceutical companies that produce medications for urticaria or have medications in development not yet approved	No	No	No

2013

Name	Rachel Asiniwasis	Emily Fahrig Cole	Jeffrey Chan	Kathryn E Wheeler
Specialty (eg. 'Patient Partner', 'Primary care', 'General Pediatrics', 'Dermatology', 'Allergy/Immunology', 'Psychotherapy', 'Pharmacy', etc.)	Dermatology	Dermatology	Emergency	General Pediatrics
Primary affiliation/institution	Dr. Rachel Asiniwasis Medical Prof. Corp./Origins Dermatology Centre	Washington University School of Medicine; St. Louis Department of Veteran's Affairs	Southlake Health	University of Florida
Country	USA	USA	USA	USA
Job Title	Dermatologist MD MSHS FRCPC FAAD	Assistant Professor; Staff Physician (Dermatologist)	Emergency Physician	Associate Professor of Pediatrics
In the previous calendar year, did you, or a member of your household or immediate family, have competing relationships?	Yes	No	No	No
In the previous 12 months, did you, or any member of your household or immediate family, receive less than $5,000 in salary support, income, or other assets?	Novartis	No	No	No
What is the name and role of the organization(s)?	Free Dinner while Allergist colleague presented on urticaria	NA	NA	NA
In the previous 12 months, did you, or any member of your household or immediate family, receive $5,000 - $25,000 in salary support, income, or other assets?	No	No	No	No
What is the name of the organization(s)/topic of Testimony or Consultation?	NA	NA	NA	NA
What is the nature of relationship?	NA	NA	NA	NA

Whether is the relationship ongoing?	NA	NA	NA	NA
In the previous 12 months, did you, or any member of your household or immediate family, receive >$25,000 but less than $50,000 in salary support, income, or other assets?	No	No	No	No
What is the name of the organization(s)/topic of Testimony or Consultation?	NA	NA	NA	NA
What is the nature of relationship?	NA	NA	NA	NA
Whether is the relationship ongoing?	NA	NA	NA	NA
In the previous 12 months, did you, or any member of your household or immediate family, receive $50,000 or more in salary support, income, or other assets?	Yes	No	No	No
What is the name of the organization(s)/topic of Testimony or Consultation?	Sanofi	NA	NA	NA
What is the nature of relationship?	Advisory Board Member and Consultant for atopic dermatitis, involved in clinical trials; Advisory Board Member for urticaria	NA	NA	NA
Whether is the relationship ongoing?	Yes	NA	NA	NA
During the previous 12 months, did you hold volunteer positions, including organizations, published works, competing interests or academic commitments that may create or be perceived as a conflict of interest?	No	No	No	No
What is the name of organization, competing interes t, academic commitment, or nature of published work (recent or planned)?	NA	NA	NA	NA
What is the nature of relationship?	NA	NA	NA	NA
Whether is the relationship ongoing?	NA	NA	NA	NA
What competing interests most likely	No	No	No	No

to represent real or perceived conflict?				

2014

Name	Kathryn Trayes	Paul Tran	Maisie Flindall	Jamie Tattrie
Specialty (eg. 'Patient Partner', 'Primary care', 'General Pediatrics', 'Dermatology', 'Allergy/Immunology', 'Psychotherapy', 'Pharmacy', etc.)	Family medicine	Pharmacy	Patient Partner	Patient Partner
Primary affiliation/institution	Thomas Jefferson University Hospital	Parkland Health	Town of Aurora (part-time)	BC Public Service, Ministry of Social Development and Poverty Reduction
Country	USA	USA	Canada	Canada
Job Title	Associate Professor, Department of Family and Community Medicine	Allergy and Asthma Clinical Pharmacist	Life guard, swim instructor	Service Delivery Manager
In the previous calendar year, did you, or a member of your household or immediate family, have competing relationships?	No	No	No	No
In the previous 12 months, did you, or any member of your household or immediate family, receive less than $5,000 in salary support, income, or other assets?	No	No	No	No
What is the name and role of the organization(s)?	NA	NA	NA	NA
In the previous 12 months, did you, or any member of your household or immediate family, receive $5,000 - $25,000 in salary support, income, or other assets?	No	No	No	No
What is the name of the organization(s)/topic of Testimony or Consultation?	NA	NA	NA	NA
What is the nature of relationship?	NA	NA	NA	NA
Whether is the relationship ongoing?	NA	NA	NA	NA
In the previous 12 months, did you, or any member of your household or immediate family, receive >$25,000 but less than $50,000 in salary support, income, or other assets?	No	No	No	No

What is the name of the organization(s)/topic of Testimony or Consultation?	NA	NA	NA	NA
What is the nature of relationship?	NA	NA	NA	NA
Whether is the relationship ongoing?	NA	NA	NA	NA
In the previous 12 months, did you, or any member of your household or immediate family, receive $50,000 or more in salary support, income, or other assets?	No	No	No	No
What is the name of the organization(s)/topic of Testimony or Consultation?	NA	NA	NA	NA
What is the nature of relationship?	NA	NA	NA	NA
Whether is the relationship ongoing?	NA	NA	NA	NA
During the previous 12 months, did you hold volunteer positions, including organizations, published works, competing interests or academic commitments that may create or be perceived as a conflict of interest?	No	No	No	No
What is the name of organization, competing interest, academic commitment, or nature of published work (recent or planned)?	NA	NA	NA	NA
What is the nature of relationship?	NA	NA	NA	NA
Whether is the relationship ongoing?	NA	NA	NA	NA
What competing interests most likely to represent real or perceived conflict?	No	No	No	No

2015

Name	Zena Jun
Specialty (eg. 'Patient Partner', 'Primary care', 'General Pediatrics', 'Dermatology', 'Allergy/Immunology', 'Psychotherapy', 'Pharmacy', etc.)	Patient Partner
Primary affiliation/institution	Royal bank
Country	Canada
Job Title	Software developer
In the previous calendar year, did you, or a member of your household or immediate family, have competing relationships?	No
In the previous 12 months, did you, or any member of your household or immediate family, receive less than	No

$5,000 in salary support, income, or other assets?	
What is the name and role of the organization(s)?	NA
In the previous 12 months, did you, or any member of your household or immediate family, receive $5,000 - $25,000 in salary support, income, or other assets?	No
What is the name of the organization(s)/topic of Testimony or Consultation?	NA
What is the nature of relationship?	NA
Whether is the relationship ongoing?	NA
In the previous 12 months, did you, or any member of your household or immediate family, receive >$25,000 but less than $50,000 in salary support, income, or other assets?	No
What is the name of the organization(s)/topic of Testimony or Consultation?	NA
What is the nature of relationship?	NA
Whether is the relationship ongoing?	NA
In the previous 12 months, did you, or any member of your household or immediate family, receive $50,000 or more in salary support, income, or other assets?	No
What is the name of the organization(s)/topic of Testimony or Consultation?	NA
What is the nature of relationship?	NA
Whether is the relationship ongoing?	NA
During the previous 12 months, did you hold volunteer positions, including organizations, published works, competing interests or academic commitments that may create or be perceived as a conflict of interest?	No
What is the name of organization, competing interest, academic commitment, or nature of published work (recent or planned)?	NA
What is the nature of relationship?	NA
Whether is the relationship ongoing?	NA

What competing interests most likely to represent real or perceived conflict?	No

2016
2017