6th Consensus Conference on the Update and Revision of the international EAACI/GA²LEN/EuroGuiDerm/APAACI Guideline for Urticaria

Information about this slide set

This slide set contains an overview of the key questions to be answered in the guideline. Each slide with a key question is followed by a slide that shows the recommendation(s) from 2016 as well as the suggested recommendation(s) 2020 (with pre-voting results from the panel). Please note, each recommendation will be voted on again during the conference.

We have also included a short justification and/or brief summary of the evidence.

GRADE wording

Strength	Wording	Symbols	Implications
Strong recommendation **for** the use of an intervention	'We recommend . . .'	↑↑	We believe that all or almost all informed people would make that choice. Clinicians will have to spend less time on the process of decision-making, and may devote that time to overcome barriers to implementation and adherence. In most clinical situations, the recommendation may be adopted as a policy.
Weak recommendation **for** the use of an intervention	'We suggest . . .'	↑	We believe that most informed people would make that choice, but a substantial number would not. Clinicians and health care providers will need to devote more time on the process of shared decision-making. Policy makers will have to involve many stakeholders and policy making requires substantial debate.
No recommendation with respect to an intervention	'We cannot make a recommendation with respect to . . .'	**0**	At the moment, a recommendation in favour or against an intervention cannot be made due to certain reasons (e.g. no reliable evidence data available, conflicting outcomes, etc.)
Weak recommendation **against** the use of an intervention	'We suggest against . . .'	↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
Strong recommendation **against** the use of an intervention	'We recommend against . . .'	↓↓	We believe that all or almost all informed people would make a choice against that intervention. This recommendation can be adopted as a policy in most clinical situations.

Voting cut-offs

Urticaria GL 2016 voting cut-offs

Strong consensus	Agreement of ≥90% participants
Consensus	Agreement of ≥70-89% participants
Agreement of the majority	Agreement of >50-69% participants

Part I:
Recommendations on classification and diagnosis

How should urticaria be classified?

How should urticaria be classified? (1/2)

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **recommend** that urticaria is classified based on its duration as acute (≤ 6 weeks) or chronic (> 6 weeks).	↑↑	
New: We **recommend** that urticaria is classified based on its duration as acute (≤ 6 weeks) or chronic (> 6 weeks).	↑↑	92% (46 of 50) EXPERT CONSENSUS

Justification

Urticaria is classified based on its duration and the role of definite triggers.

Acute urticaria is defined as the occurrence of wheals, angioedema or both for 6 weeks or less. Chronic urticaria is defined as the occurrence of wheals, angioedema, or both for more than six weeks. Chronic urticaria can come with daily or almost daily signs and symptoms or an intermittent / recurrent course.

How should urticaria be classified? (2/2)

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **recommend** that urticaria is classified as spontaneous (no specific eliciting factor involved) or inducible (specific eliciting factor involved).	↑↑	
New: We **recommend** that urticaria is classified as spontaneous (no definite eliciting factor involved) or inducible (specific definite factor involved).	↑↑	88% (44 of 50) EXPERT CONSENSUS

Justification

Inducible urticaria is characterized by definite and subform-specific triggers of the development of wheals, angioedema, or both. These triggers are definite because wheals, angioedema or both always and never occur when the trigger is present and absent, respectively. These triggers are specific because each subform of inducible urticaria has its relevant trigger, for example cold in cold urticaria, and this trigger is not relevant in other forms of inducible urticaria. Rare subforms of inducible urticaria exist in which the combined presence of two or more definite and specific triggers is required for the induction of wheals, angioedema or both, for example cholinergic cold urticaria.

Some patients with spontaneous urticaria experience trigger-induced wheals, angioedema, or both. These triggers are not definite, as their presence does not always induce signs and symptoms and because wheals, angioedema or both also occur spontaneously.

Should we maintain the current guideline classification of chronic urticaria?

Should we maintain the current guideline classification of chronic urticaria?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **recommend** that the current guideline classification of chronic urticaria should be maintained.	↑↑	
New: We **recommend** that the current guideline classification of chronic urticaria should be maintained.	↑↑	88% (44 of 50) EXPERT CONSENSUS

Justification

Chronic urticaria (CU) is classified as spontaneous (CSU) and inducible (CIndU; reference to table). CSU is further subclassified as CSU with known cause and CSU with unknown cause. CIndU is further subclassified as symptomatic dermographism, cold urticaria, delayed pressure urticaria, solar urticaria, heat urticaria, and vibratory angioedema (collectively referred to as chronic physical urticaria), as well as cholinergic urticaria, contact urticaria, and aquagenic urticaria. CU patients can have more than one form of CU including more than one form of CIndU and they often do.

Comment: In the table with the classification, we use superscript numbers that refer to the following information provided in the table legend. With reference to CSU of known cause: For example, type I autoimmunity (autoallergy) and type IIb autoimmunity; with reference to symptomatic dermographism: also called urticaria factitia or dermographic urticaria; with reference to cold urticaria: also called cold contact urticaria; with reference to delayed pressure urticaria: also called pressure urticaria; with reference to cholinergic urticaria: also called heat contact urticaria.

Should routine diagnostic measures be performed in acute urticaria?

Should routine diagnostic measures be performed in acute urticaria?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **recommend against** any routine diagnostic measures in acute spontaneous urticaria.	↓↓	
New: We **recommend against** any routine diagnostic measures in acute spontaneous urticaria.	↓↓	88% (44 of 50) EXPERT CONSENSUS

Justification

Acute urticaria usually does not require a diagnostic workup, as it is usually self-limiting. The only exception is the suspicion of acute urticaria due to a type I food allergy in sensitized patients or the existence of other eliciting factors such as non-steroidal anti-inflammatory drugs (NSAIDs). In this case, allergy tests as well as educating the patients may be useful to allow patients to avoid re-exposure to relevant causative factors.

Should differential diagnoses be considered in patients with chronic urticaria?

Should differential diagnoses be considered in patients with chronic urticaria?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **recommend** that differential diagnoses be considered in all patients with signs or symptoms suggestive of chronic urticaria based on the guideline algorithm.	↑↑	
New: We **recommend** that differential diagnoses be considered in all patients with signs or symptoms suggestive of chronic urticaria based on the guideline algorithm.	↑↑	94% (47 of 50) EXPERT CONSENSUS

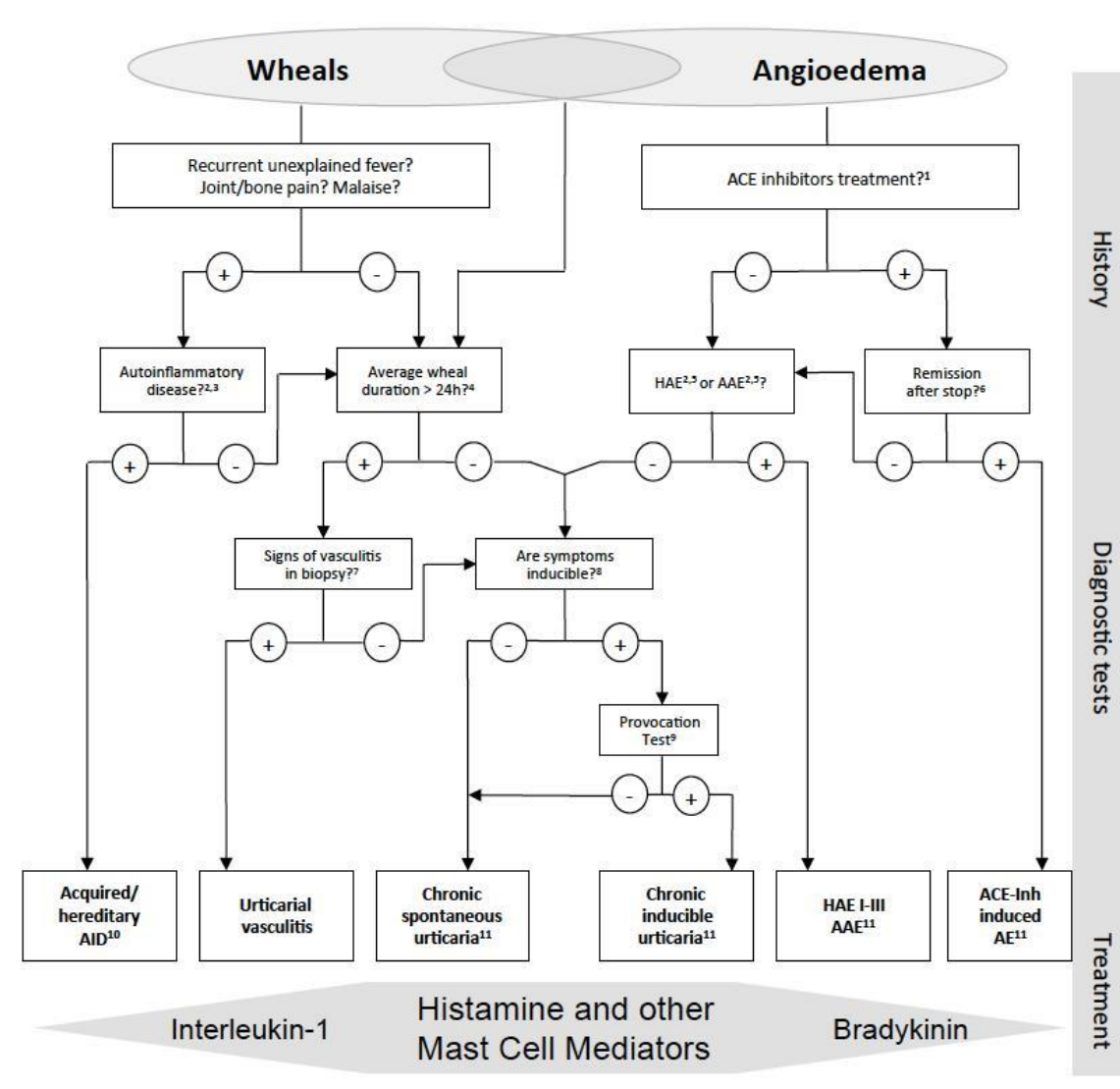
Justification

Urticarial vasculitis, maculopapular cutaneous mastocytosis (formerly called urticaria pigmentosa), auto-inflammatory syndromes (e.g. cryopyrin-associated periodic syndromes or Schnitzler's syndrome), non-mast cell mediator-mediated angioedema (e.g. bradykinin-mediated angioedema), and other diseases such as syndromes that can manifest with wheals and/or angioedema are not considered to be subtypes of urticaria, due to their distinctly different pathophysiologic mechanisms (Table 5).

The diagnostic work up of CSU has three major aims: 1) to exclude differential diagnoses, 2) to assess disease activity, impact, and control, and 3) to identify triggers of exacerbation or, where indicated, any underlying causes. Ad 1) Wheals or angioedema can be present in some other conditions, too. In patients who display only wheals (but no angioedema), urticarial vasculitis and autoinflammatory disorders such as Schnitzler syndrome or cryopyrin-associated periodic syndromes (CAPS) need to be ruled out. On the other hand, in patients who suffer only from recurrent angioedema (but not from wheals), bradykinin-mediated angioedema like angiotensin-converting-enzyme (ACE)-inhibitor induced angioedema or other non-mast cell related angioedema, i.e. HAE type 1-3, should be considered as differential diagnoses (Figure 1).

Algorithm

Algorithm



RESULTS ONLINE PRE-VOTING

90%
45 of 50 *

EXPERT CONSENSUS

* 14 of them agreed to leave as is
* 31 of them agreed, if “treatment” is replaced by “mediators” and if the bottom box with tapering edges is replaced by a rectangular box

What routine diagnostic measures should be performed in chronic spontaneous urticaria?

What routine diagnostic measures should be performed in chronic spontaneous urticaria?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **recommend** limited investigations. Basic tests include differential blood count and CRP and/or ESR. In CSU, we **recommend** performing further diagnostic measures based on the patient history and examination, especially in patients with long standing and/or uncontrolled disease.	↑↑ ↑↑	
New: We **recommend** limited investigations. Basic tests include differential blood count, CRP and/or ESR, total IgE and anti-TPO. We **recommend** performing further diagnostic measures based on the patient history and examination, especially in patients with long standing and/or uncontrolled disease.	↑↑ ↑↑	76% (38 of 50) EXPERT CONSENSUS

Justification

The first step in the diagnostic workup in CSU is a thorough history, physical examination, and review of patients' documentation of signs and symptoms (including pictures of wheals and/or angioedema). The basic set of laboratory investigations should be limited to a differential blood count, CRP and/or ESR, total IgE and anti-TPO.

COMMENT: We will explain the rationale and value of each of these tests.

Further diagnostic tests should be performed only if indicated.

Should routine diagnostic measures be performed in inducible urticaria?

Should routine diagnostic measures be performed in inducible urticaria?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **recommend** using provocation testing to diagnose chronic inducible urticaria.	↑↑	
We **recommend** to use provocation threshold measurements and the UCT to measure disease activity and control in patients with chronic inducible urticaria, respectively.	↑↑	
New: We **recommend** using provocation testing to diagnose chronic inducible urticaria.	↑↑	96% (48 of 50)
We **recommend** using provocation threshold measurements and the UCT to measure disease activity and control in patients with chronic inducible urticaria, respectively.	↑↑	EXPERT CONSENSUS

Justification

In CIndUs, the routine diagnostic work up should follow the consensus recommendations on the definition, diagnostic testing, and management of CIndUs. Diagnostics in CIndU are used to identify the subtype of CIndU and to determine trigger thresholds. The latter is important as it allows for assessing disease activity and response to treatment. For most types of CIndU, validated tools for provocation testing are available.

In addition to disease activity, it is important to assess disease control. *(Text was shortened)*. The Urticaria Control Test (UCT) is a validated and easy to administer tool to determine the level of disease control in all forms of CU including CIndU. The UCT has only four items with a clearly defined cut off for patients with “well-controlled” vs. “poorly controlled” disease, and it is thus suited for the management of patients in routine clinical practice. The cut-off value for a well-controlled disease is 12 out of 16 possible points. This helps to guide treatment decisions.

Should patients with chronic urticaria be assessed for disease activity, impact, and control?

Should patients with chronic urticaria be assessed for disease activity, impact, and control?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **recommend** that patients with CU be assessed for disease activity, impact, and control at every visit.	↑↑	
New: We **recommend** that patients with CU be assessed for disease activity, impact, and control at every visit.	↑↑	98% (49 of 50) EXPERT CONSENSUS

Justification

Patients with CU should be assessed for disease activity, impact and control at the first and every follow up visit, acknowledging that some tools, e.g. the UAS can only be used prospectively and others, e.g. the UCT, allow for retrospective assessment. Validated instruments such as the UAS7, AAS, CU-Q2oL, AE-QoL, UCT, and AECT should be used for this purpose.

Which instruments should be used to assess and monitor disease activity in chronic spontaneous urticaria patients?

Which instruments should be used to assess and monitor disease activity in chronic spontaneous urticaria patients?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **suggest** the use of the urticaria activity score, UAS7, and of the angioedema activity score, AAS, for assessing disease activity in patients with chronic spontaneous urticaria.	↑	
New: We **recommend** the use of the urticaria activity score, UAS7, and of the angioedema activity score, AAS, for assessing disease activity in patients with chronic spontaneous urticaria.	↑↑	96% (48 of 50) EXPERT CONSENSUS

Justification

Disease activity in spontaneous urticaria should be assessed both in clinical care and trials with the UAS7 (Table 7), a unified and simple scoring system. The UAS7 is based on the assessment of key urticaria signs and symptoms (wheals and pruritus), which are documented by the patient, making this score especially valuable. The use of the UAS7 facilitates comparison of study results from different centres. As urticaria activity frequently changes, the overall disease activity is best measured by advising patients to document 24-h self-evaluation scores once daily for several days. The UAS7, i.e. the sum score of 7 consecutive days, should be used in routine clinical practice to determine disease activity and response to treatment of CSU patients with wheals. For CSU patients with angioedema, with or without wheals, the Angioedema Activity Score (AAS) should be used. In CSU patients with wheals and angioedema, the UAS7 and the AAS should be used.

Which instruments should be used to assess and monitor quality of life impairment in chronic spontaneous urticaria patients?

Which instruments should be used to assess and monitor quality of life impairment in chronic spontaneous urticaria patients?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **suggest** the use of the chronic urticaria quality of life questionnaire, CU-Q2oL, and the angioedema quality of life questionnaire, AE-QoL, for assessing quality of life impairment in patients with chronic spontaneous urticaria.	↑	
New: We **recommend** the use of the chronic urticaria quality of life questionnaire, CU-Q2oL, and the angioedema quality of life questionnaire, AE-QoL, for assessing quality of life impairment in patients with chronic spontaneous urticaria.	↑↑	94% (47 of 50) EXPERT CONSENSUS

Justification

In addition to disease activity, it is important to assess the impact of disease on quality of life as well as disease control both in clinical practice and trials. The CU-Q2oL should be used to determine QoL impairment in CSU patients with wheals. For CSU patients with angioedema, with or without wheals, the AE-QoL should be used. In CSU patients with wheals and angioedema, the CU-Q2oL and the AE-QoL should be used.

Which instruments should be used to assess and monitor disease control in chronic spontaneous urticaria patients?

Which instruments should be used to assess and monitor disease control in chronic spontaneous urticaria patients?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **suggest** the use of the urticaria control test, UCT, for assessing disease control in patients with chronic spontaneous urticaria.	↑	
New: We **recommend** the use of the urticaria control test, UCT, and/or the angioedema control test, AECT, for assessing disease control in patients with CSU.	↑↑	94% (47 of 50) EXPERT CONSENSUS

Justification

It is important to assess disease control in patients with CSU. The UCT should be used to do this in CSU patients with wheals. For CSU patients with angioedema, with or without wheals, the AECT should be used. In CSU patients with wheals and angioedema, the UCT and the AECT should be used.

Part II: Recommendations on management

GRADE – quality of evidence

Symbol	Quality	Interpretation
⊕⊕⊕⊕	**High**	We are very confident that the true effect lies close to that of the estimate of the effect.
⊕⊕⊕O	**Moderate**	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
⊕⊕OO	**Low**	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
⊕OOO	**Very low**	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

**Table taken from the GRADE Handbook, available at

http://gdt.guidelinedevelopment.org/app/handbook/handbook.html#h.9rdbelsnu4iy

Should modern second generation H1-antihistamines be used as first-line treatment of urticaria?

Should modern second generation H1-antihistamines be used as first-line treatment of urticaria?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **recommend** 2nd generation H1-antihistamines as first-line treatment of chronic urticaria.	↑↑	
New: We **recommend** a 2nd generation H1-antihistamine as first-line treatment for all types of urticaria.	↑↑	98,3% (59 of 60) EVIDENCE BASED & EXPERT CONSENSUS

2ND GENERATION H1-AH 1-FOLD vs. PLACEBO

Data added in 2020 update from 3 new studies (differences to 2016 marked in purple)

Efficacy

2nd generation H1-AH 1-fold was superior to placebo based on the outcomes:

- complete suppression (⊕⊕◯◯ / ⊕⊕⊕◯)
- good or excellent response at weeks 1-2 and weeks 3-4 (⊕⊕◯◯ / ⊕⊕⊕◯)
- change in symptom score [standardized mean difference] (⊕⊕⊕◯)
- mean change in DLQI at weeks 1-2 (⊕⊕⊕⊕)
- mean change in DLQI at week 4 (⊕⊕◯◯) and mean change in DLQI at week 6 (⊕⊕⊕◯)

No difference was found for the outcomes:

- good or excellent response at week 6 (⊕◯◯◯)
- mean difference in symptom score (⊕⊕⊕◯) and mean change in SF-36' (⊕⊕◯◯)

Safety

No difference was found for the outcomes:

- withdrawal due to adverse event (⊕◯◯◯ / ⊕⊕⊕◯)
- patients with at least one adverse event (⊕⊕◯◯ / ⊕⊕⊕◯)

Are second generation H1-antihistamines to be preferred over first generation H1-antihistamines for the treatment of urticaria?

Are second generation H1-antihistamines to be preferred over first generation H1-antihistamines for the treatment of urticaria?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **suggest** 2nd generation H1-antihistamines over 1st generation H1-antihistamines for the treatment of patients with chronic urticaria.	↑	90,0% (54 of 60)
New: *<u>delete</u> recommendation*	-	EVIDENCE BASED & EXPERT CONSENSUS

2nd generation H1-AH versus 1st generation H1-AH for CSU

No new data added in 2020

Efficacy

No difference was found for 2nd generation H1-AH compared to 1st generation H1-AH based on the outcomes:

- good or excellent response (⊕⊕◯◯ / ⊕⊕⊕⊕)
- withdrawal due to adverse event at week 2 (⊕⊕◯◯)
- relapse after one week of stopping treatment (⊕⊕⊕◯)

Safety

2nd generation H1-AH were superior to 1st generation H1-AH based on the outcomes:

- withdrawal due to adverse event at week 4 (⊕⊕◯◯)
- somnolence at week 4 (⊕⊕◯◯)
- tiredness' (⊕⊕◯◯)

No difference was found for the outcomes:

- patients with at least one adverse event (⊕◯◯◯)
- somnolence at week 2 (⊕◯◯◯)
- fatigue (⊕⊕◯◯)

Is an increase in the dose to up to four-fold of modern second generation H1-antihistamines useful and to be preferred over other treatments in urticaria?

Is an increase in the dose to up to four-fold of modern second generation H1-antihistamines useful and to be preferred over other treatments in urticaria?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **suggest** updosing 2nd generation H1-antihistamines up to 4-fold in patients with chronic urticaria unresponsive to 2nd generation H1-antihistamines 1-fold.	↑	
New: We **recommend** updosing 2nd generation H1-antihistamines up to 4-fold in patients with chronic urticaria unresponsive to 2nd generation H1-antihistamines 1-fold as second line treatment before other treatments are considered.	↑↑	96.7% (58 of 60) EVIDENCE BASED & EXPERT CONSENSUS

1) COMPARISON: 2ND GENERATION H1-AH 2-FOLD vs. 2ND GENERATION H1-AH 1-FOLD

Data added in 2020 update from 2 new studies

Efficacy

No difference was found for the outcomes:

- good or excellent response (⊕⊕◯◯)
- itch+rash score/UAS7/DLQI (⊕⊕◯◯ / ⊕⊕⊕◯)
- relapse (⊕⊕◯◯)

Safety

No difference was found for the outcomes:

- withdrawal due to adverse event (⊕⊕⊕◯)
- patients with at least one adverse event (⊕◯◯◯ / ⊕⊕◯◯)

2) COMPARISON: 2ND GENERATION H1-AH 4-FOLD vs. 2ND GENERATION H1-AH 1-FOLD

No new data added in 2020

Efficacy

No difference was found for the outcome:

- mean change in UAS (⊕⊕⊕◯)

Safety

No difference was found for the outcome:

- withdrawal due to adverse event (⊕◯◯◯)

3) COMPARISON: 2ND GENERATION H1-AH 4-FOLD VS. 2ND GENERATION H1-AH 2-FOLD

No new data added in 2020

Efficacy

No difference was found for the outcome:

- mean change in UAS (⊕⊕⊕◯)

Safety

No difference was found for the outcome:

- withdrawal due to adverse event (⊕⊕⊕◯)

Should modern second generation H1-antihistamines be taken regularly or as needed?

Should modern second generation H1-antihistamines be taken regularly or as needed?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **suggest** 2nd generation H1-antihistamines to be taken regularly for the treatment of patients with chronic urticaria.	↑	
New: We **suggest** 2nd generation H1-antihistamines to be taken regularly for the treatment of patients with chronic urticaria.	↑	94,9% (56 of 59) EVIDENCE BASED & EXPERT CONSENSUS

2nd generation H1-AH taken regularly versus 2nd generation H1-AH taken as needed

No new data added in 2020

Taking 2nd generation H1-AH regularly is marginally superior to taking 2nd generation H1-AH as needed based on 'complete suppression', however the quality of evidence is very low.

No difference was found for the outcome:

- withdrawal due to AE (⊕◯◯◯)
- patients with at least one AE (⊕⊕◯◯)

Expert opinion:

Weller et al. 2013 found no difference in the reduction of wheal area size between taking H1-AH on-demand and no H1-AH.

Should different second generation H1-antihistamines be used at the same time?

Should different second generation H1-antihistamines be used at the same time?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **recommend against** using different H1-antihistamines at the same time.	↓↓	
New: We **recommend against** using different H1-antihistamines at the same time.	↓↓	88,1% (52 of 59) EVIDENCE BASED & EXPERT CONSENSUS

2ND GENERATION H1-AH + DIFFERENT 2ND GENERATION H1-AH vs. 2ND GENERATION H1-AH ALONE

New evidence summary 2020

Efficacy

No difference was found for the outcome:

- good or excellent response (⊕◯◯◯)

Safety

No difference was found for the outcomes:

- withdrawal due to adverse event (⊕◯◯◯)
- patients with at least one adverse event (⊕◯◯◯ / ⊕⊕◯◯)

If there is no improvement, should higher than fourfold doses of second generation H1-antihistamines be used?

If there is no improvement, should higher than fourfold doses of second generation H1-antihistamines be used?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **recommend against** using higher than 4-fold standard dosed H1-antihistamines in chronic urticaria. New: We **recommend against** using higher than 4-fold standard dosed H1-antihistamines in chronic urticaria.	↓↓ ↓↓	98.3% (58 of 59) EVIDENCE BASED & EXPERT CONSENSUS

If there is no improvement, should higher than fourfold doses of second generation H1-antihistamines be used?

No Evidence identified.

Is omalizumab useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines?

Is omalizumab useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **recommend** adding on omalizumab* for the treatment of patients with CU unresponsive to 2nd generation H1-antihistamines. * currently licensed for urticaria	↑↑	88,1% (52 of 59)
New: We **recommend** adding on omalizumab* for the treatment of patients with CU unresponsive to 2nd generation H1-antihistamines. * currently licensed for urticaria	↑↑	EVIDENCE BASED & EXPERT CONSENSUS

1) COMPARISON: OMALIZUMAB 300MG EVERY 4 WEEKS AS ADD-ON TREATMENT vs. PLACEBO

Data added in 2020 update from 5 new studies

Efficacy

Omalizumab 300mg every 4 weeks as add-on treatment was superior to placebo for the outcomes:

- complete suppression (⊕⊕⊕⊕)
- good or excellent response at weeks 4, 8 and 12 (⊕⊕⊕⊕)
- UAS7 (⊕⊕⊕◯)
- DLQI (⊕⊕⊕⊕)
- CU-Q2oL (⊕⊕⊕◯ / ⊕⊕⊕⊕)
- relapse: DLQI 12 weeks after last treatment (⊕⊕⊕⊕)
- relapse: percent of patients with clinical worsening (UAS7>6 for 2 weeks) from week 24-48 (⊕⊕⊕◯)

No difference was found for the outcome:

- good or excellent response at weeks 1-2 (◯◯◯⊕)

Safety

No difference was found for the outcomes

- withdrawal due to adverse events up to week 12 (⊕⊕⊕⊕)
- patients with at least one adverse event (⊕⊕⊕◯ / ⊕⊕⊕⊕)

2) COMPARISON: OMALIZUMAB 150MG EVERY 4 WEEKS AS ADD-ON TREATMENT vs. PLACEBO

Data added in 2020 update from 1 new study

Efficacy

Omalizumab 150mg every 4 weeks as add-on treatment was superior to placebo for the outcomes:

- complete suppression (⊕⊕⊕◯ / ⊕⊕⊕⊕)
- good or excellent response at weeks 4, 8 and 12 (⊕⊕⊕⊕)
- UAS7 (⊕⊕⊕⊕)
- DLQI (⊕⊕⊕◯)

Safety

No difference was found for the outcomes:

- withdrawal due to adverse event up to week 12 (⊕⊕⊕◯)
- patients with at least one adverse event (⊕⊕⊕◯)

Is ciclosporin A useful as add-on treatment in patients unresponsive to high doses of H1-antihistamine?

Is ciclosporin A useful as add-on treatment in patients unresponsive to high doses of H1-antihistamine?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **suggest** adding on ciclosporin A for the treatment of patients with CU unresponsive to 2nd generation H1-antihistamines.	↑	
New: We **suggest** adding on ciclosporin A for the treatment of patients with CU unresponsive to 2nd generation H1-antihistamines. *Treatment algorithm (Figure 2) 2016: it was decided that omalizumab should be tried before ciclosporin A since the latter is not licensed for urticaria and has an inferior profile of adverse effects.*	↑	88,1% (52 of 59) EVIDENCE BASED & EXPERT CONSENSUS

Ciclosporin versus placebo

No difference was found for:

- complete suppression (⊕◯◯◯)
- good or excellent response - w4 (⊕⊕◯◯)
- withdrawal due to AE (⊕⊕⊕⊕)

Add-on CSA was superior to no add-on treatment based on:

- good or excellent response - w1-2 (⊕⊕◯◯)
- mean change UAS7 (⊕⊕⊕◯)

No evidence was found for CSA as add-on treatment versus other interventions as add-on.

Are leukotriene antagonists useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines?

Are leukotriene antagonists useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **cannot make a recommendation** with respect to montelukast as add-on treatment to H1-antihistamines in patients with chronic urticaria unresponsive to H1-antihistamines.	**0**	89,8% (53 of 59)
New: We **cannot make a recommendation** with respect to montelukast as add-on treatment to H1-antihistamines in patients with chronic urticaria unresponsive to H1-antihistamines.	**0**	EVIDENCE BASED & EXPERT CONSENSUS

1) COMPARISON: MONTELUKAST + 2ND GENERATION H1-AH 1-FOLD vs. PLACEBO

No new data added in 2020

Efficacy

No difference was found for the outcomes:

- mean difference in total symptom score (⊕⊕◯◯)
- good or excellent response (⊕◯◯◯)

Safety

No safety data were available.

2) COMPARISON: MONTELUKAST + 2ND GENERATION H1-AH 1-FOLD vs. 2ND GENERATION H1-AH 1-FOLD

No new data added in 2020

Efficacy

Montelukast + 2nd generation H1-AH 1-fold was superior to 2nd generation H1-AH 1-fold for the outcome*:*

- excellent response' (⊕⊕◯◯)

No difference was found for the outcome:

- mean difference in TSS (⊕⊕◯◯)

Safety

No difference was found for:

- withdrawal due to adverse event (⊕⊕⊕◯)
- patients with at least one adverse event' (⊕⊕◯◯)

3) COMPARISON: MONTELUKAST + LEVOCETIRIZIN 1-FOLD vs. LEVOCETIRIZIN 2-FOLD

Data added in 2020 update from 1 new study

Efficacy

Montelukast + levocetirizine 1-fold was superior to levocetirizine 2-fold for the outcome:

- DLQI (⊕◯◯◯)

No difference was found for the outcome:

- good or excellent response (⊕⊕◯◯)
- UAS (⊕◯◯◯ / ⊕⊕◯◯)

Safety

No safety data were available.

Should oral corticosteroids be used as add-on treatment in the treatment of urticaria?

Should oral corticosteroids be used as add-on treatment in the treatment of urticaria?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **recommend against** the long-term use of systemic glucocorticosteroids in CU. We **suggest** considering a short course of systemic glucocorticosteroids in patients with an acute exacerbation of CU.	↓↓ ↑	
New: We **recommend against** the long-term use of systemic glucocorticosteroids in CU. We **suggest** considering a short course of systemic glucocorticosteroids in patients with an acute exacerbation of CU.	↓↓ ↑	91,5% (54 of 59) EVIDENCE BASED & EXPERT CONSENSUS

Should oral corticosteroids be used as add-on treatment in the treatment of urticaria?

No Evidence identified.

Are H2-antihistamines useful as add-on treatment in patients unresponsive to low or high doses of H1-antihistamines?

Are H2-antihistamines useful as add-on treatment in patients unresponsive to low or high doses of H1-antihistamines?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **cannot make a recommendation** for or against the combined use of H1-and H2-antagonists in patients with chronic urticaria.	**0**	
New: We **cannot make a recommendation** for or against the combined use of H1-and H2-antagonists in patients with chronic urticaria.	**0**	96,6% (57 of 59) EXPERT CONSENSUS

Could any other treatment options be recommended for the treatment of urticaria?

Could any other treatment options be recommended for the treatment of urticaria?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION	RESULTS ONLINE PRE-VOTING
Old: We **cannot make a recommendation** with respect to further treatment options.	**0**	
New: We **cannot make a recommendation** with respect to further treatment options for a standard therapy to be included in the algorithm but acknowledge that some alternative treatment have a better level of evidence than others (mentioned in table XX) and may be considered in special cases which also include those where financial or legal limitations for the recommended algorithm treatment exist.	**0**	93,2% (55 of 59) EVIDENCE BASED & EXPERT CONSENSUS

COMPARISON: MONTELUKAST + PLACEBO vs. MONTELUKAST + DESLORATIDINE

No new data added in 2020

Efficacy

Montelukast + desloratadine was superior to montelukast + placebo based on the outcome:

- mean difference/mean change in total symptom score (⊕⊕⊕◯)

No further evidence could be identified.

COMPARISON: NB-UVB vs. PUVA

Data added in 2020 update from 1 new study

Efficacy

NB-UVB was superior to PUVA for the outcome:

- UAS7 (⊕⊕◯◯)

No difference was found for the outcomes:

- complete supression (⊕⊕◯◯)
- good/excellent response (⊕⊕⊕◯)
- mean change in TSS (⊕⊕◯◯) and relapse ⊕⊕⊕◯)

Safety

No difference was found for the outcomes:

- withdrawal due to adverse event (⊕⊕⊕◯)
- patients with at least one adverse event (⊕⊕◯◯)

COMPARISON: NB-UVB BIW + LORATADINE 10MG QD vs. LORATADINE 10MG QD

Data added in 2020 update from 1 new study

Efficacy

NB UVB BIW + loratadine 10mg was superior to loratadine 10mg alone for the outcomes:

- UAS (⊕◯◯◯)
- relapse defined as UAS7 4 weeks after treatment finished (⊕◯◯◯)

Safety

No difference was found for the outcome:

- patients with at least one adverse event (⊕◯◯◯)

COMPARISON: NB-UVB TIW + LEVOCETIRIZINE 10MG (2-FOLD) QD vs. LEVOCETIRIZINE 10MG (2-FOLD) QD

No new data added in 2020

NB-UVB TIW + levocetirizine 10mg (2-fold) QD was superior to levocetirizine 10mg (2-fold) for the outcome:

- mean change in USS7 (⊕⊕⊕◯, but of uncertain clinical importance)

No further evidence could be identified.

COMPARISON: NB-UVB TIW + MIZOLASTINE 10MG QD vs. MIZOLASTINE 10MG QD

No new data added in 2020

Efficacy

NB-UVB TIW + mizolastine 10mg QD was superior to mizolastine 10mg alone for the outcome:

- mean change in total symptom score (⊕⊕⊕◯)

Safety

No difference was found for the outcome:

- withdrawal due to adverse event (⊕⊕⊕◯)

COMPARISON: AUTOLOGOUS WHOLE BLOOD INJECTIONS vs. PLACEBO

Data added in 2020 update from 1 new study

Efficacy

No difference was found for the outcome:

- clear (⊕⊕◯◯)
- good or excellent response (⊕⊕◯◯ / ⊕⊕⊕◯)
- total symptom score (⊕⊕◯◯)

No further evidence could be identified.

COMPARISON: HYDROXYCHLOROQUINE AS ADD-ON TO H1-AH vs. PLACEBO + H1-AH

Data added in 2020 update from 1 new study (an extension of study included in 2016)

Efficacy

Hydroxychloroquine as add-on to H1-AH was superior to placebo + H1-AH for the outcome:

- mean change in USS (⊕◯◯◯)

No difference was found for:

- mean change in DLQI (⊕◯◯◯)

Safety

No difference was found for:

- patients with at least one AE (⊕◯◯◯)

COMPARISON: METHOTREXATE AS ADD-ON TO H1-AH vs. PLACEBO + H1-AH

Data added in 2020 update from 1 new study

Efficacy

No difference was found for the outcome:

- median change in DLQI (⊕◯◯◯)

Data on other relevant outcomes were not available.

Should the same treatment algorithm be used in children?

Should the same treatment algorithm be used in children?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION
Old: We **suggest** using the same treatment algorithm with caution in children with chronic urticaria.	↑
New: We **suggest** using the same treatment algorithm with caution in children with chronic urticaria.	↑

Should the same treatment algorithm be used in children? No new Data since 2016

2nd gen H1-AH 1-fold compared to placebo for children with CSU

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with 2nd gen H1-AH (1 fold)
good or excellent response (by patient) - rupatadine 2.5/5mg QD vs placebo (w6)	135 (1 RCT)	⨁⨁⨁◯ MODERATE[1]	**RR 2.38** (1.27 to 4.43)	159 per 1.000	**220 more per 1.000** (43 more to 547 more)
good or excellent response (by patient) - desloratadine 0.5mg/ml QD vs placebo (w6)	140 (1 RCT)	⨁⨁◯◯ LOW[1,2]	**RR 2.03** (1.07 to 3.84)	159 per 1.000	**164 more per 1.000** (11 more to 453 more)
mean change in C-DLQI - desloratadine 0.5mg QD vs placebo (w6)	136 (1 RCT)	⨁⨁◯◯ LOW[1,2]	-	The mean mean change in C-DLQI - desloratadine 0.5mg QD vs placebo (w6) was **0**	MD **2.9 lower** (4.62 lower to 1.18 lower)
mean change in C-DLQI - rupatadine 2.5/5mg QD vs placebo (w6)	130 (1 RCT)	⨁⨁◯◯ LOW[1,2]	-	The mean mean change in C-DLQI - rupatadine 2.5/5mg QD vs placebo (w6) was **0**	MD **3.6 lower** (5.49 lower to 1.71 lower)
patients with at least 1 AE - rupatadine 2.5/5mg QD vs placebo (w6)	130 (1 RCT)	⨁⨁◯◯ LOW[1,3]	**RR 1.15** (0.86 to 1.53)	552 per 1.000	**83 more per 1.000** (77 fewer to 293 more)
patients with at least 1 AE - desloratadine 0.5mg/ml QD vs placebo (w6)	136 (1 RCT)	⨁⨁◯◯ LOW[1,3]	**RR 1.21** (0.92 to 1.59)	552 per 1.000	**116 more per 1.000** (44 fewer to 326 more)

Should the same treatment algorithm be used in pregnant women and during lactation?

Should the same treatment algorithm be used in pregnant women and during lactation?

RECOMMENDATION	STRENGTH OF RECOMMEN-DATION
Old: We **suggest** using the same treatment algorithm with caution both in pregnant and lactating women after risk-benefit assessment. Drugs contraindicated in pregnancy should not be used.	↑
New: We **suggest** using the same treatment algorithm with caution both in pregnant and lactating women after risk-benefit assessment. Drugs contraindicated in pregnancy should not be used.	↑


The End