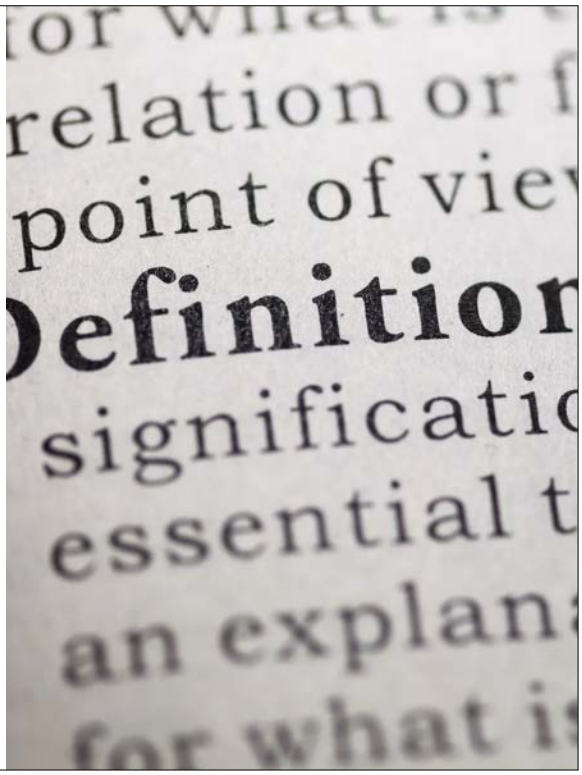
URTICARIA

Dr Daniel Micallef
Consultant Dermatologist

BASIC DEFINITIONS

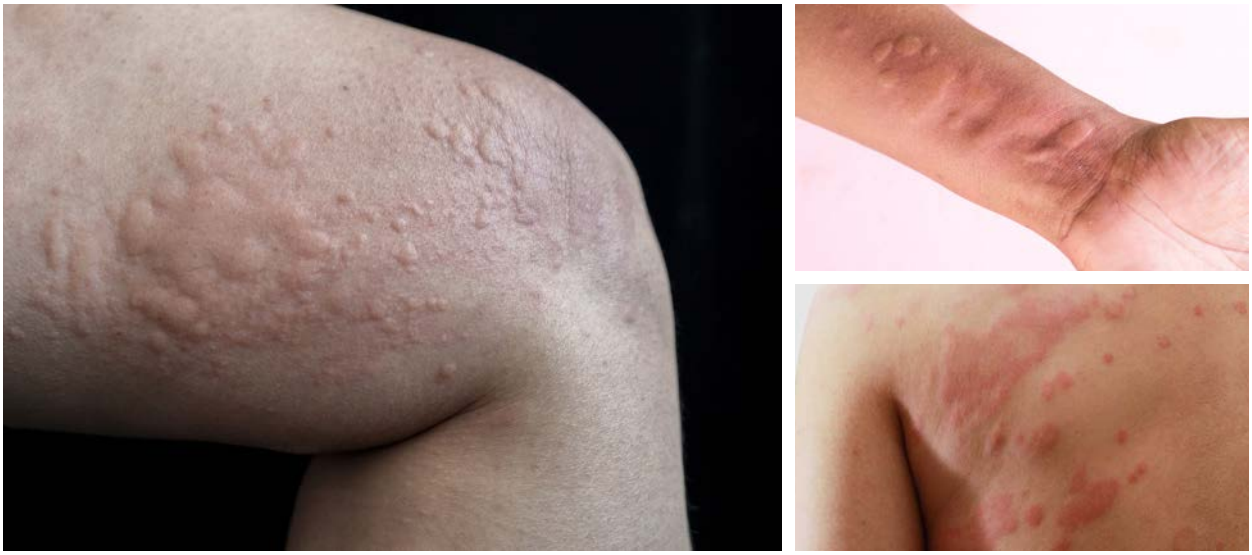
Urticaria



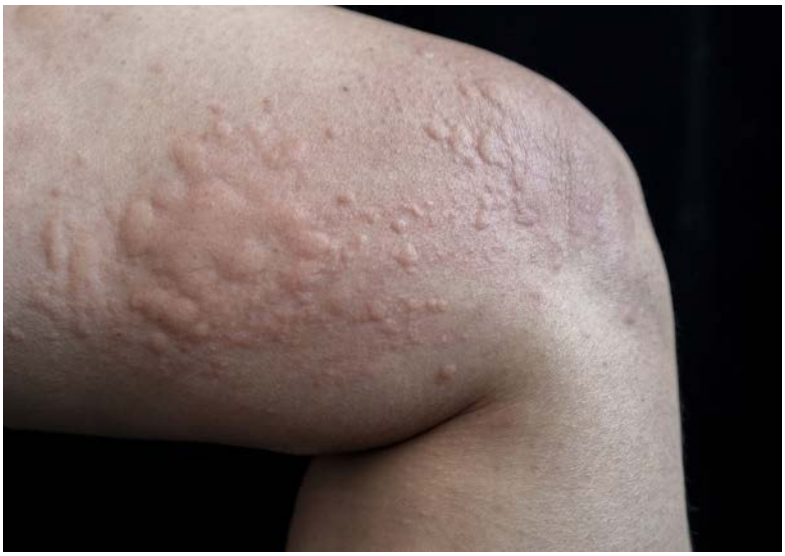
“

A mast cell-driven condition characterised by **wheals**, **angioedema** or **both**.

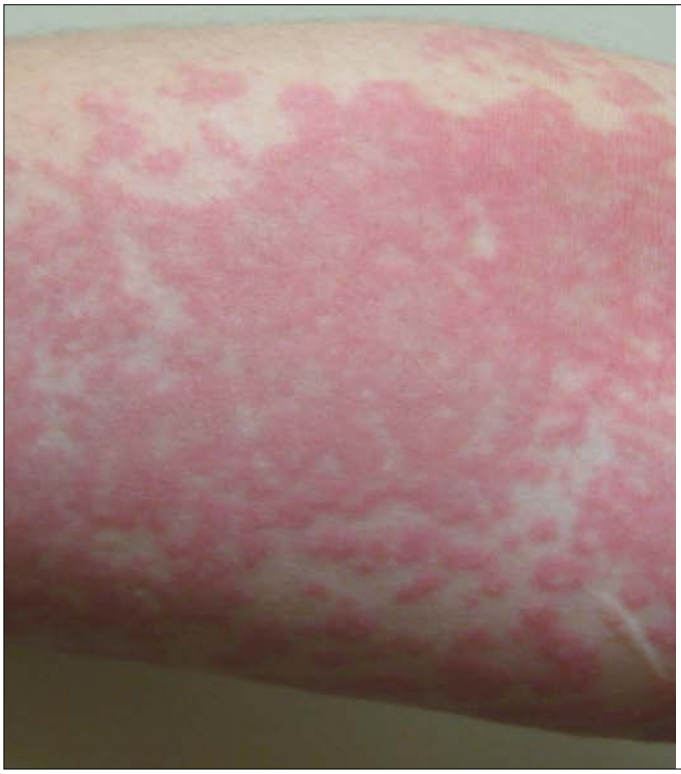
Rook’s Textbook of Dermatology



Wheals

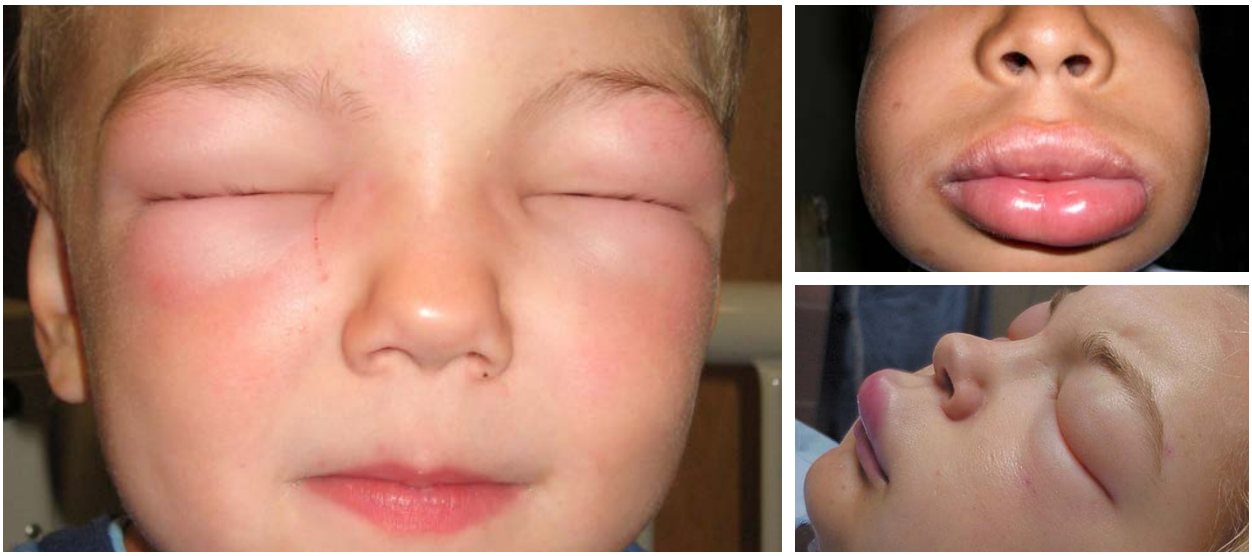


"Bezzun" - "Ħobż ħobż" - "Ħruq…" - "Ifferoċjat"

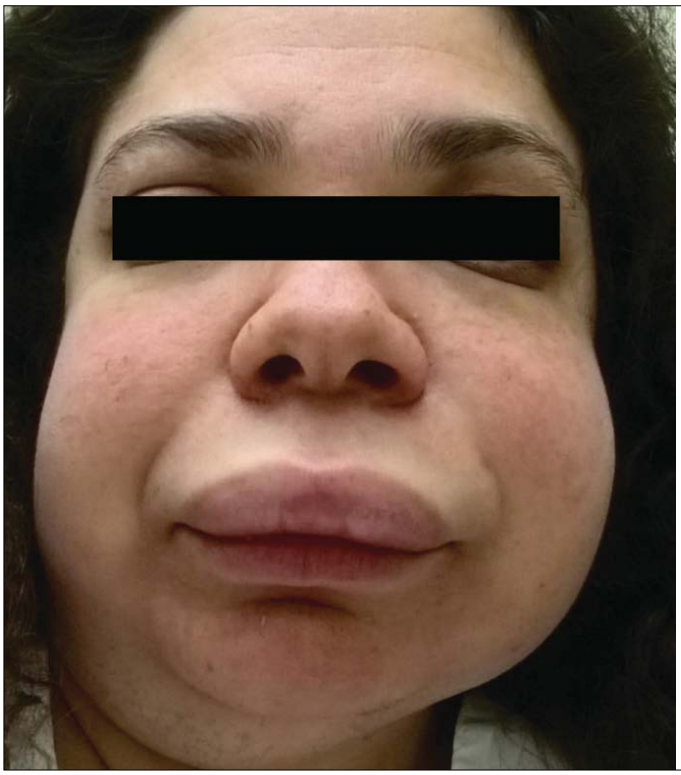


WHEAL

- Central **swelling**, almost invariably surrounded by **erythema** (flare)
- **Pruritic**, sometimes **burning** sensation
- **Fleeting** nature: 30 minutes to 24 hours



Angioedema



ANGIOEDEMA

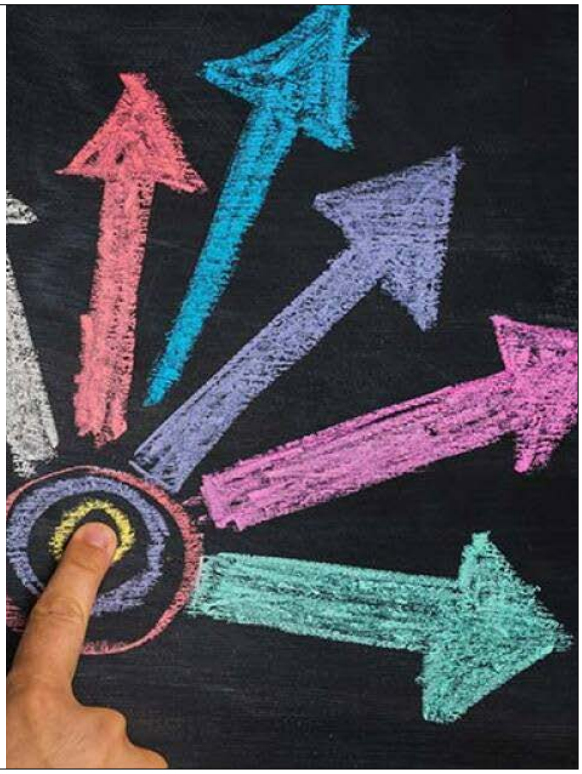
- Sudden, pronounced erythematous or skin-coloured **swelling of the lower dermis, subcutis or mucous membranes**.
- **Sometimes painful** (rather than itchy)
- Resolution slower than wheals (**up to 72 hours**)

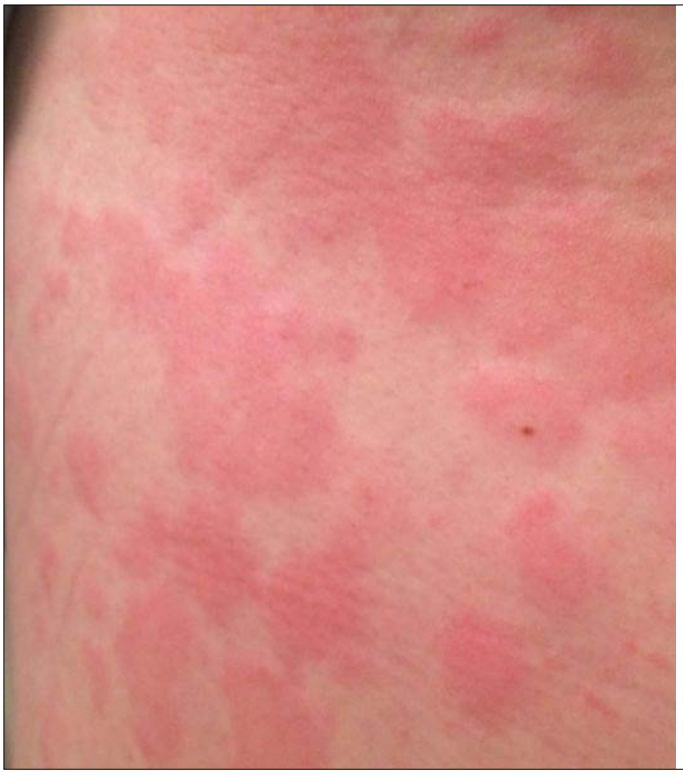
ANGIOEDEMA VS. ANAPHYLAXIS

Feature	Angioedema	Anaphylaxis
Definition	Localised swelling in deeper skin layers	Severe, systemic allergic reaction
Causes	Idiopathic, allergy, stress, infection	Allergens (e.g., food, medications) but not always
Symptoms	Rapid swelling, burning	Difficulty breathing, drop in blood pressure, hives, nausea
Severity	Typically localised, rarely life-threatening	Potentially life-threatening, widespread
Treatment	Antihistamines, corticosteroids, adrenaline (severe cases)	Adrenaline, antihistamines, corticosteroids, emergency medical care

DIFFERENTIALS AND CLASSIFICATION

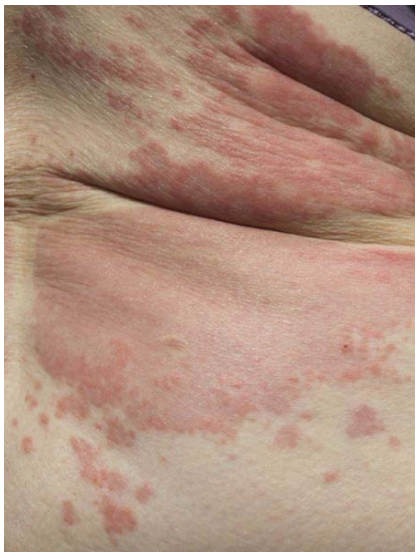
Urticaria



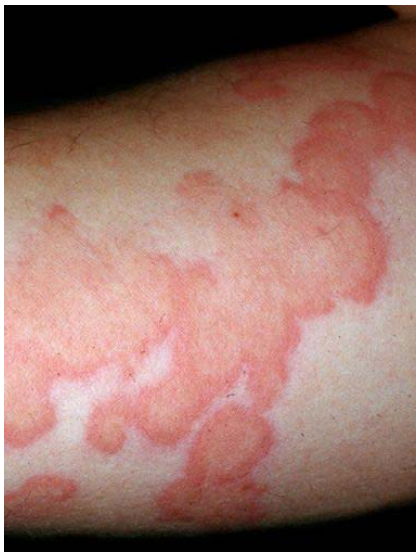


DIFFERENTIALS...

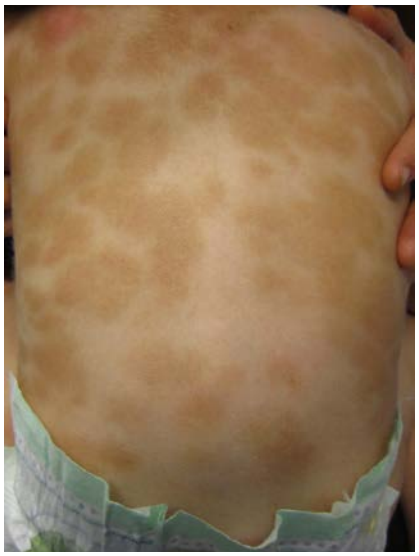
- **Bullous pemphigoid**
- **Urticarial vasculitis**
- **Maculopapular cutaneous mastocytosis (urticaria pigmentosa)**
- Mast cell activation syndrome
- Bradykinin-mediated angioedema
- Exercise-induced anaphylaxis
- Cryopyrin-associated periodic syndromes
- Schnitzler syndrome
- Gleitch syndrome
- Wells syndrome
- Adult-onst Still disease



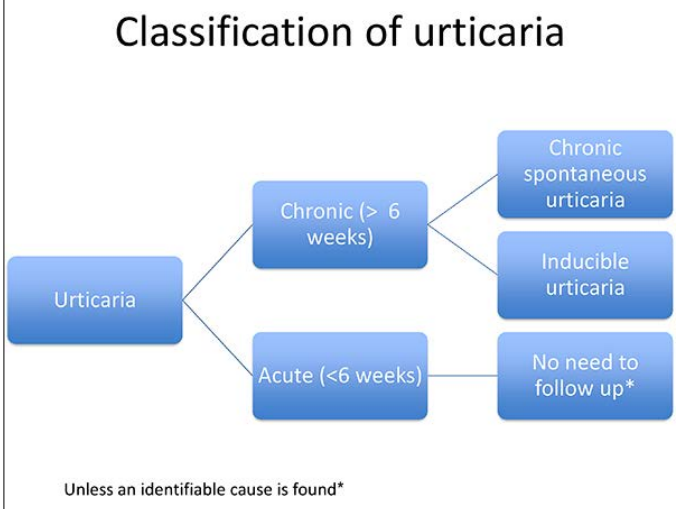
Bullous pemphigoid



Urticarial vasculitis



Urticaria pigmentosa (Maculopapular cutaneous mastocytosis)

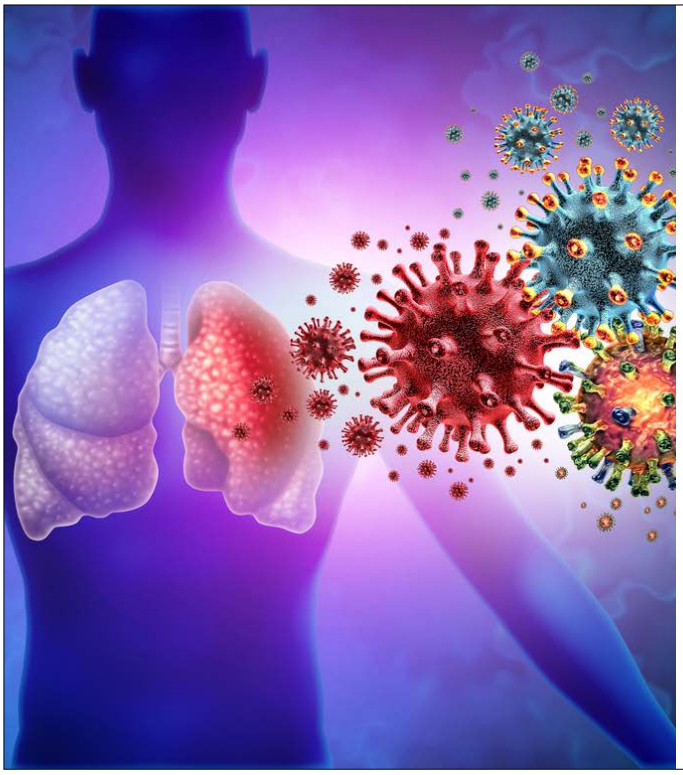


CLASSIFICATION

- Urticaria:
  - **Acute** urticaria (≤6 weeks)
  - **Chronic** urticaria (>6 weeks)
    - **Spontaneous** ("Idiopathic")
    - **Inducible**

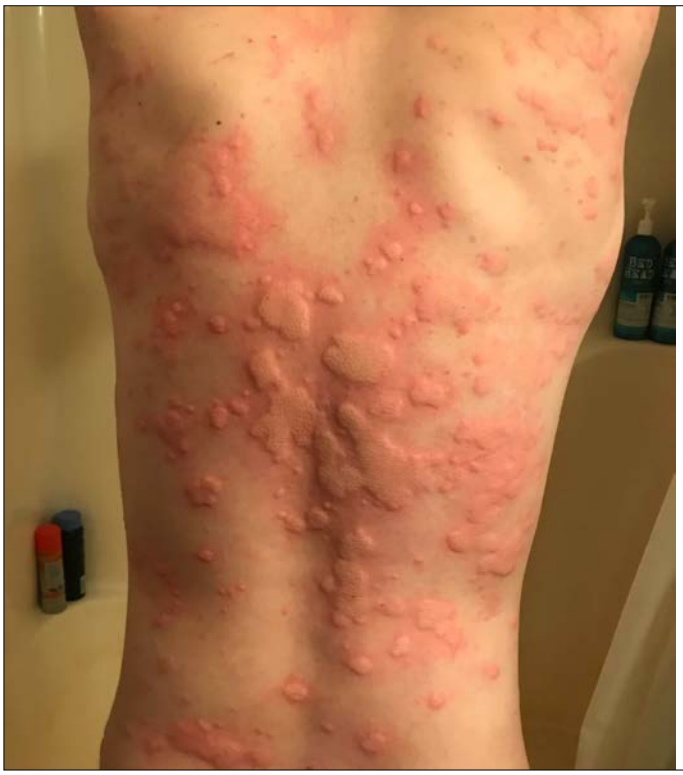
ACUTE URTICARIA

- Usually **sudden-onset** and lasts **hours to days**
- 1 in 5 people get at least one episode in their lifetime
- **More likely** than chronic urticaria to be **linked to a recent 'insult'** or 'event' (but cause remains unknown in >50%)



ACUTE URTICARIA: CAUSES

- Viral infection
- Bacterial infection
- Food allergy (IgE-mediated): usually milk, egg, peanut, shellfish
- Drug-induced (IgE-mediated): usually an antibiotic
- Drug-induced (pseudoallergy): aspirin, NSAID, contrast media…
- Vaccination
- Bee or wasp sting

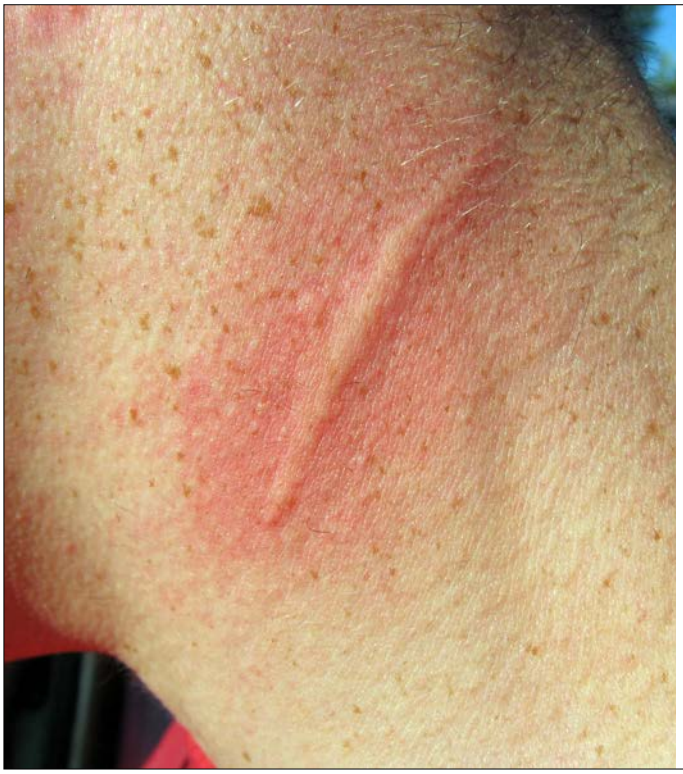


CHRONIC URTICARIA

- Symptoms daily or almost daily OR can run an intermittent course
- Can recur after months or years of remission
- **Common**: affects around 2% of the population
- Twice as common in **females**
  - c. **80% spontaneous**
  - c. **20% are inducible**

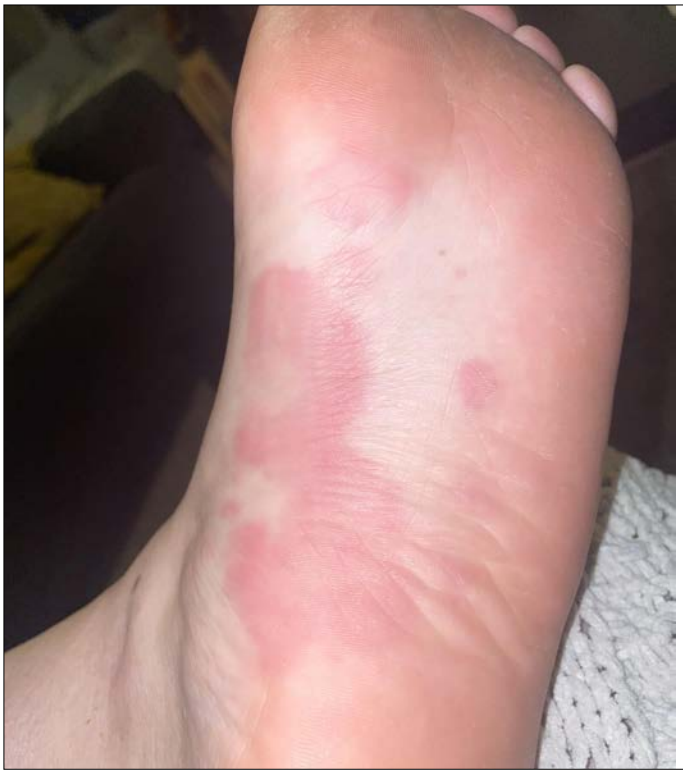
“

Chronic Inducible Urticaria (CIndU) is characterised by wheals and/or angioedema in response to specific triggers or stimuli.



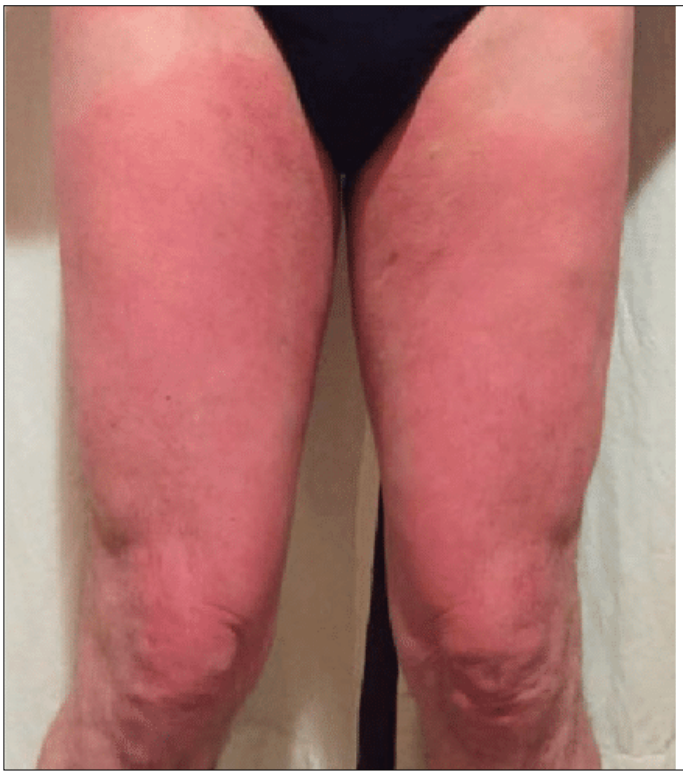
SYMPTOMATIC DERMOGRAPHISM

- **Dermographism** (erythema, oedema and flare) at **sites of trauma or friction**
- Usually in young adults
  - Test with a smooth blunt object on the upper back -> read in 10 minutes



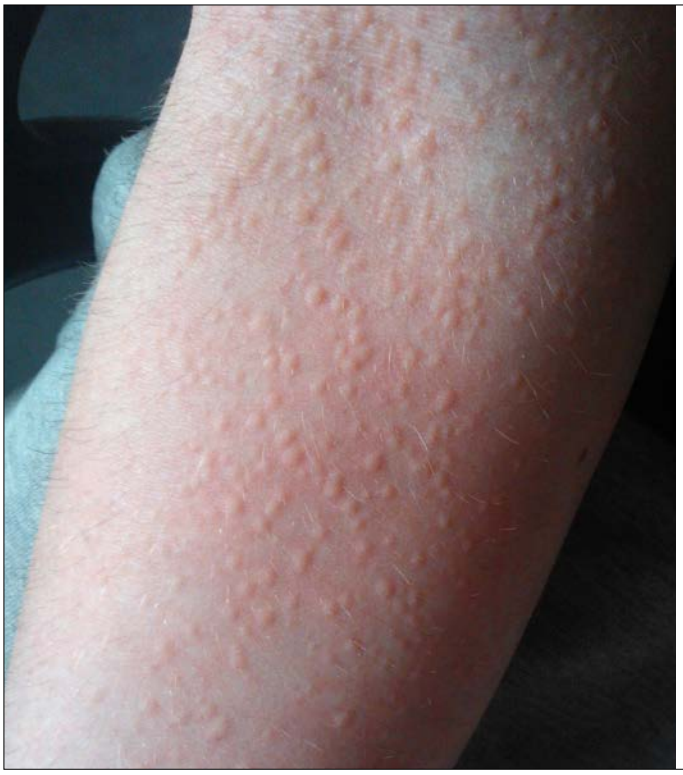
DELAYED PRESSURE URTICARIA

- Wheals at **sites of sustained pressure** with a **delay** of 30 minutes to 9 hours
- Can persist **up to 72 hours**
- Commonly under tight clothing, hands after manual work or soles after walking
- May be itchy but **often tender**
  - Calibrated dermographometer on the upper back -> read after 6 hours



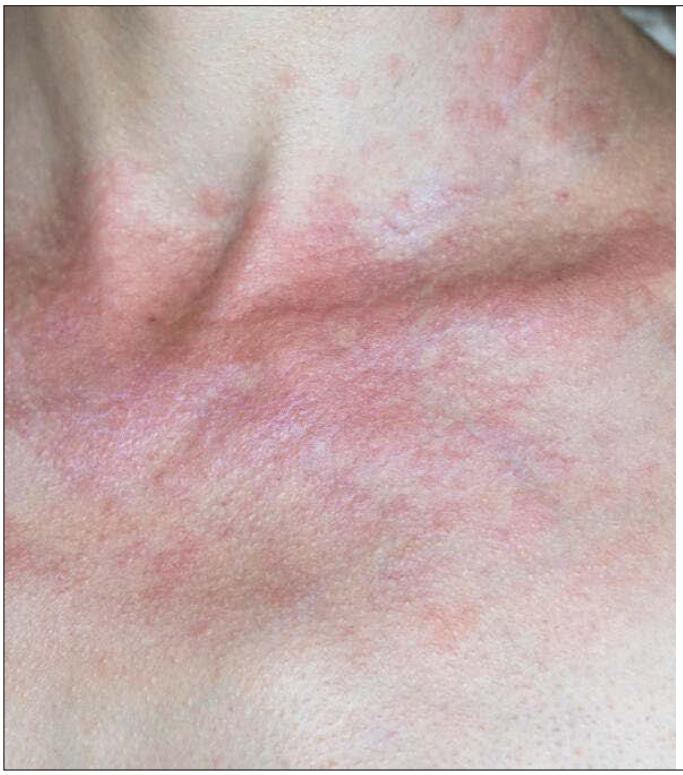
COLD URTICARIA

- Itching and wheals within minutes on **cold exposure** (especially cold winds and rain).
- Lasts **around 1 hour**
- Beware of **possible oropharyngeal swelling** with cold drinks and **systemic symptoms** after a cold bath or swimming
  - Apply a melting ice cube in a thin plastic bag on the volar forearm -> read in 10 minutes



CHOLINERGIC URTICARIA

- **Small (1-3 mm) wheals** in response to **sweating or stress** within minutes of exertion
- Lasts **≤2 hours**
- **Some** have cholinergic **pruritus only**
  - Passive heating in a bath or shower (≤42C) or exercise to the point of sweating -> read in 10 minutes

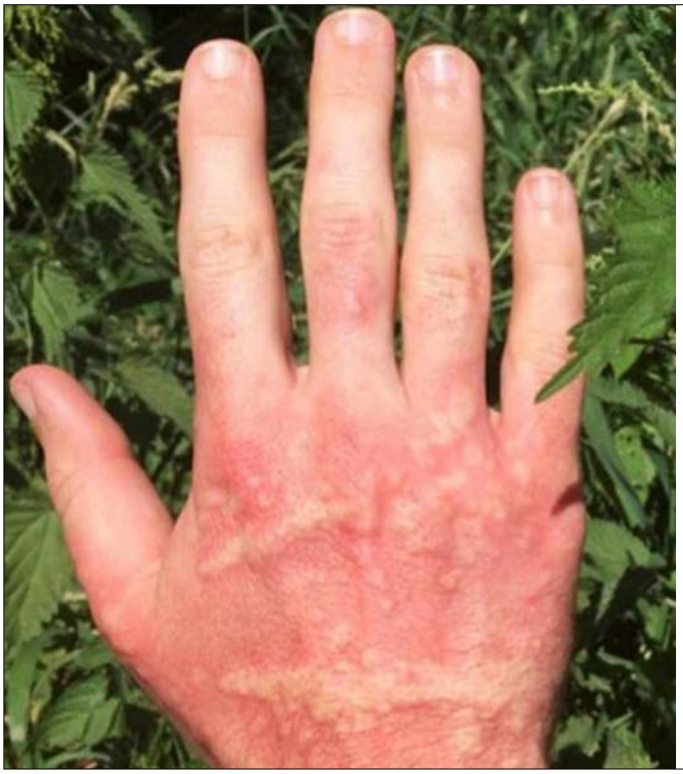


SOLAR URTICARIA

- Wheals at **sites of UV exposure** within minutes, lasting **≤2 hours**
- Mainly affects **sites which are normally shielded from sunlight**
  - Exposure to sunlight -> read in 10 minutes

AQUAGENIC URTICARIA

- Wheals on **contact with water at any temperature**
- **Some** have aquagenic **pruritus only**
  - Wet towel for 5 minutes -> read in 5-10 minutes

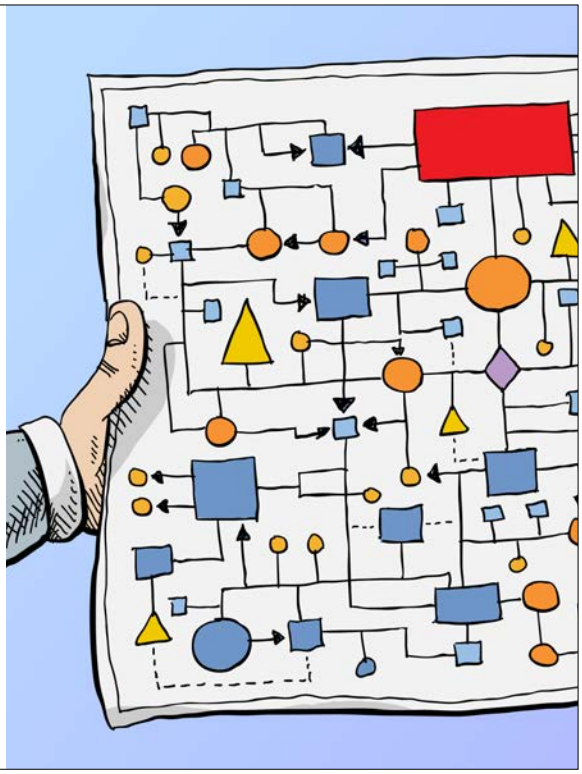


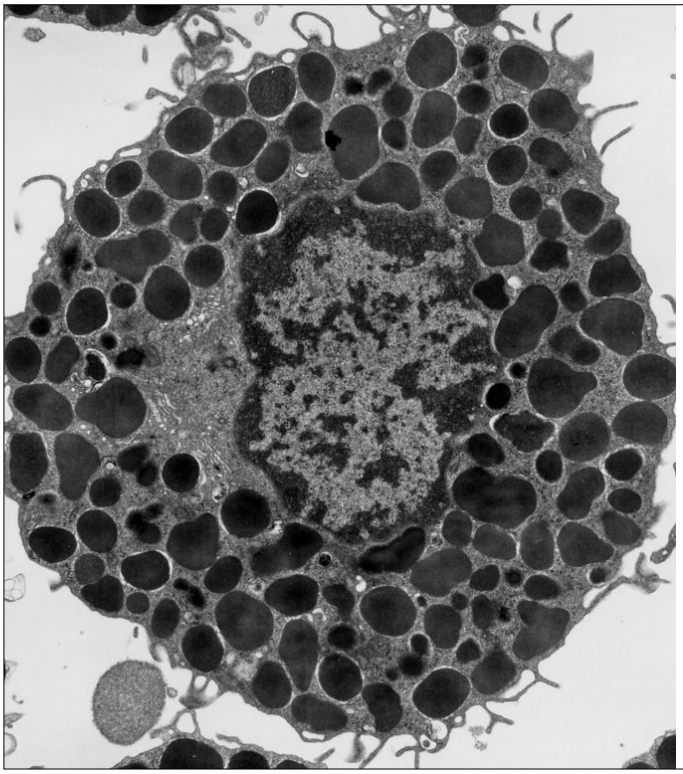
CONTACT URTICARIA

- **Immediate urticarial rash** at the site of **contact with causative agent** ex. nettles, bee stings, jellyfish, latex
- Can **occasionally** give **extracutaneous reactions** (wheezing, runny nose, lip swelling, diarrhoea, cramps, anaphylactic shock)

PATHOGENESIS

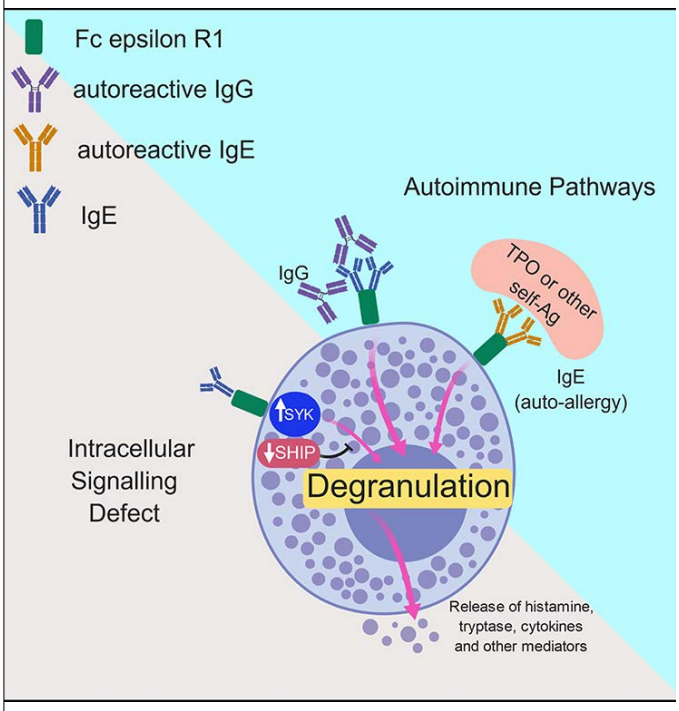
Urticaria





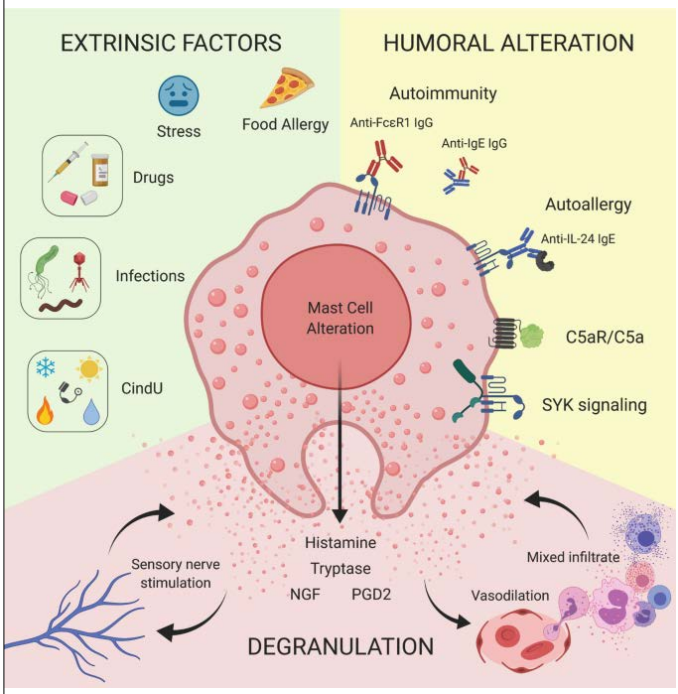
BASIC MECHANISM

- **Mast cells** release **histamine**
  - **Postcapillary venules dilate** become more permeable to plasma (wheal and flare)
  - **C-fibre nerve endings** are **stimulated** (itch)
- **Basophils** may contribute too



WHY MAST CELLS DEGRANULATE…

- **Cross-linking of IgE** (through binding with an antigen) which **binds to FcεRi** (type I)
- **Binding of autoreactive IgG to FcεRi** (type IIb)
  - These lead to **mast cell degranulaton**

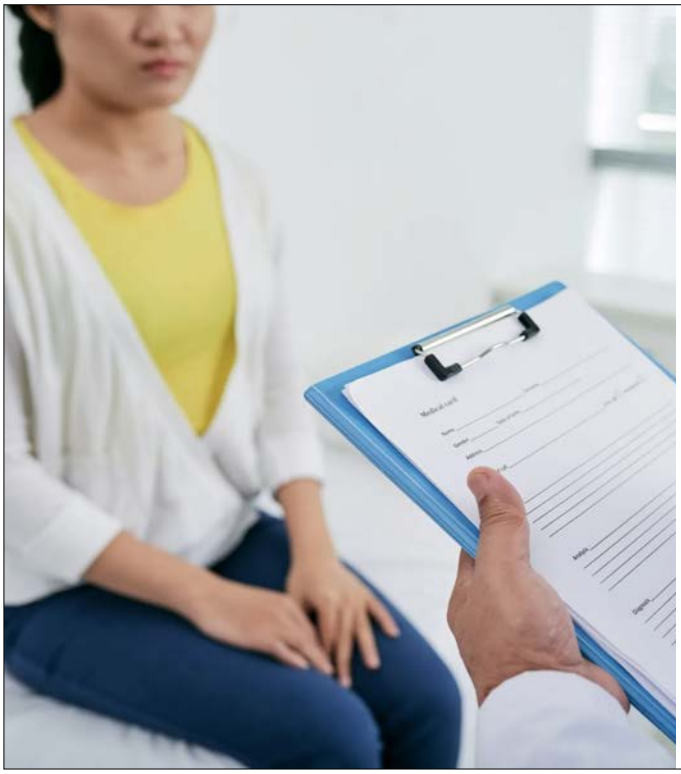


WHY MAST CELLS DEGRANULATE…

- **Sometimes, the trigger is not immunological - substances** (drugs, foods, infections, physical triggers) can **directly stimulate mast cells**.

INVESTGIATION

Urticaria



WORKUP OF ACUTE URTICARIA

- **History** is almost always enough
- If type I food allergy (to a specific ingredient) or drug hypersensitivity (especially to NSAIDs) is suspected, consider:
  - Skin prick testing
  - RAST testing

ACUTE URTICARIA

748 WILEY Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI

Should routine diagnostic measures be performed in acute urticaria?

We **recommend against** any routine diagnostic measures in acute spontaneous urticaria.	↓↓	Strong consensus[1] Expert consensus

[1]≥90% agreement

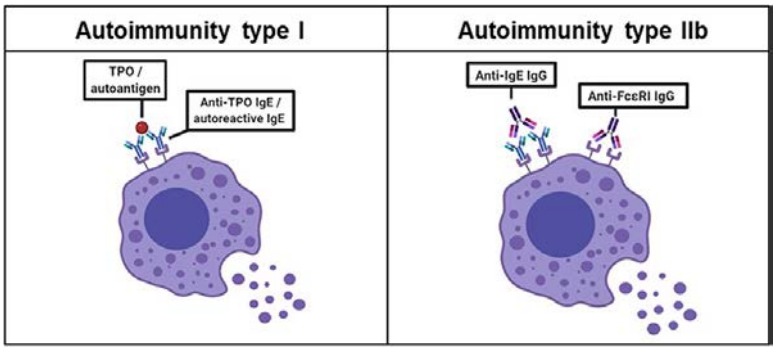
WORKUP OF CHRONIC URTICARIA

- **History** is most important
- In primary care, perform:
  - **CBC**
  - **ESR** and/or **CRP**

WORKUP OF CHRONIC URTICARIA

- In secondary care, consider the following (especially if refractory to antihistamines):
  - Total IgE
  - Anti-thyroid peroxidase (IgG) antibody

IgE ≥40 IU/mL
anti-TPO -ve
(omalizumab)



IgE <40 IU/mL
anti-TPO +ve
(less response
to omalizumab)

MANAGEMENT

Urticaria

BASIC ADVICE

- In inducible urticaria, **avoid situations which induce the urticaria**
- Otherwise, the underlying cause will often remain unknown.
- **Avoid**:
  - **Heat**
  - Tight clothing

Antihistamine	Dose
Bilastine	20mg
Cetirizine	10mg
Levocetirizine	5mg
Desloratadine	5mg
Loratadine	10mg
Fexofenadine	180mg
Rupatadine	20mg

STEP 1: ANTIHISTAMINES

- **Standard dose, non-sedating antihistamine**:
  - (wait up to 2-4 weeks)
- If control suboptimal, **increase up to four times the standard dose**
  - **Consider referral** at this stage

WHICH ANTIHISTAMINE?

Original Article

Comparative Efficacy and Acceptability of Licensed Dose Second-Generation Antihistamines in Chronic Spontaneous Urticaria: A Network Meta-Analysis

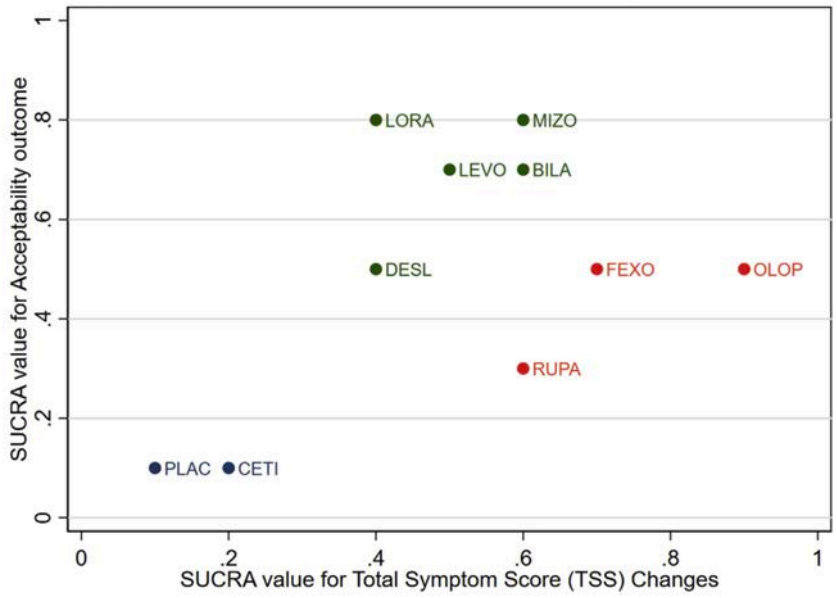
Phichayut Phinyo, MD[a,b,*], Pattaraporn Koompawichit, MD[c,*], Surapon Nochaiwong, PharmD[d,e], Napatra Tovanabutra, MD[f], Siri Chiewchanvit, MD[f], and Mati Chuamanochan, MD[f] *Chiang Mai and Phayao, Thailand*

What is already known about this topic? Licensed dose second-generation H1-antihistamines (sgAHs) are the first-line treatment in chronic spontaneous urticaria (CSU). However, the available evidence up to the present is insufficient to rank sgAHs in terms of their efficacy.

What does this article add to our knowledge? Among sgAHs included in this network meta-analysis focusing on the comparative efficacy of licensed dose sgAHs in CSU treatment, olopatadine, fexofenadine, bilastine, rupatadine, and levocetirizine demonstrate superior therapeutic efficacy to placebo.

How does this study impact current management guidelines? The findings from our study may help to guide physicians who take care of patients with CSU in their choice of sgAHs.

WHICH ANTIHISTAMINE?



> Olopatadine, fexofenadine, bilastine, rupatadine, and levocetirizine were superior placebo in clinical outcome. Other considerations including safety, cost, patient preference, and drug availability, should be taken into account in real-world practice.

WHICH ANTIHISTAMINE?

Clinical, Cosmetic and Investigational Dermatology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

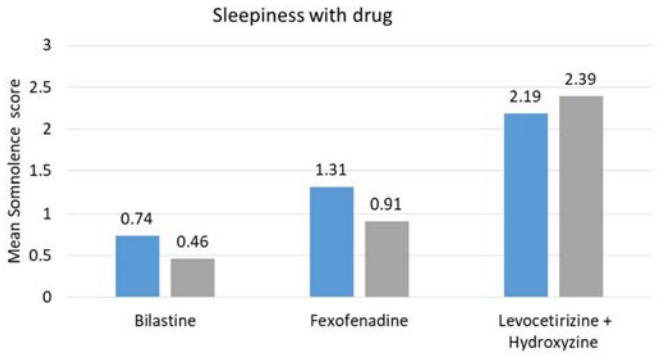
A Comparative, Three-Arm, Randomized Clinical Trial to Evaluate the Effectiveness and Tolerability of Bilastine vs Fexofenadine vs Levocetirizine at the Standard Dose and Bilastine vs Fexofenadine at Higher Than the Standard Dose (Up-Dosing) vs Levocetirizine and Hydroxyzine (in Combination) in Patients with Chronic Spontaneous Urticaria

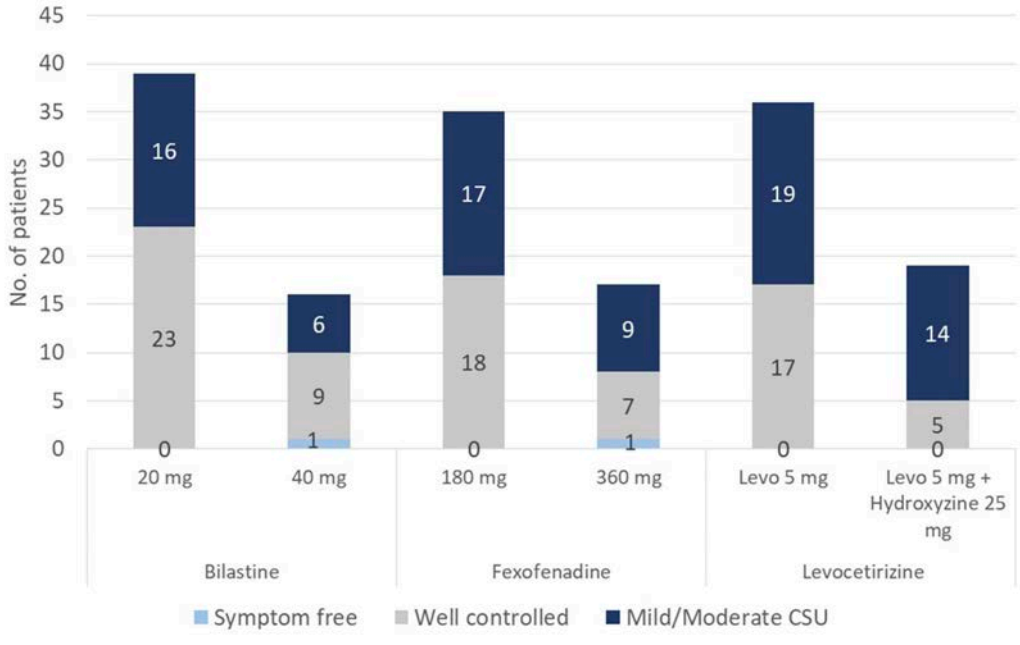
Bela Shah[1], Dhiraj Dhoot[2], Ankita Choudhary[1], Neha Jangid[1], Deval Mistry[1], Shikha Shah[1], Shruti Kamat[1], Hanmant Barkate[3]

[1]Department of Dermatology, Venereology and Leprosy, B.J.Medical College, Civil Hospital, Ahmedabad, India; [2]DGM, Department of Global Medical Affairs, Glenmark Pharmaceuticals Ltd, Mumbai, India; [3]Department of Global Medical Affairs, Glenmark Pharmaceuticals Ltd, Mumbai, India

Correspondence: Dhiraj Dhoot, DGM, Department of Global Medical Affairs, Glenmark Pharmaceuticals Ltd, Mumbai, Maharashtra, 400099, India, Tel +91 9619811219, Email dddhoot@gmail.com


Improvement in quality of life
Percentage of patients
80
70
60
50
40
30
20
10
0
46.15
68.75
14.28
47
22.2
26.3
Bilastine
Fexofenadine
Levocetirizine + Hydroxyzine
week 2
week 4


Sleepiness with drug
Mean Somnolence score
3
2.5
2
1.5
1
0.5
0
0.74
0.46
1.31
0.91
2.19
2.39
Bilastine
Fexofenadine
Levocetirizine + Hydroxyzine


No. of patients
45
40
35
30
25
20
15
10
5
0
16
23
0
6
9
1
17
18
0
9
7
1
19
17
0
14
5
0
20 mg
40 mg
180 mg
360 mg
Levo 5 mg
Levo 5 mg + Hydroxyzine 25 mg
Bilastine
Fexofenadine
Levocetirizine
Symptom free
Well controlled
Mild/Moderate CSU

WHICH ANTIHISTAMINE?

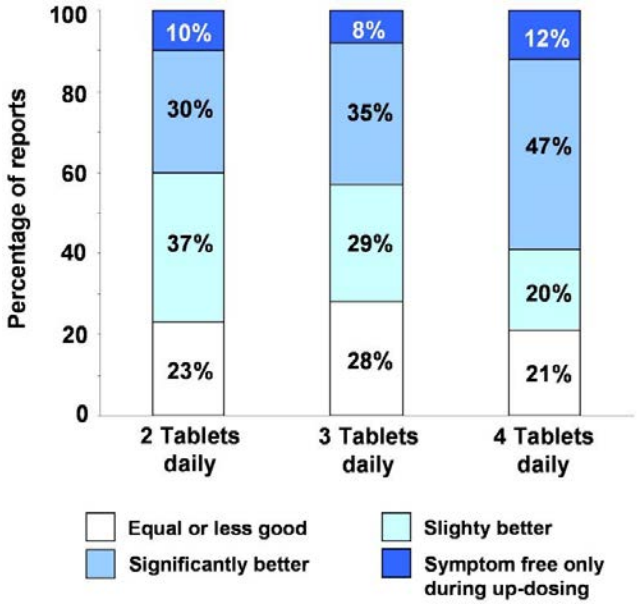
Study	Patients	Treatment	Results
Zuberbier et al. 2010[11]	CSU (*n*=525)	Bilastine 20 mg OD (*n*=173), levocetirizine 5 mg OD (*n*=165) or placebo OD (*n*=184) for 28 days	• Bilastine improved TSS, DLQI, general discomfort and sleep disruption compared with placebo ($p<0.001$ for all) • Bilastine had comparable efficacy to levocetirizine • Bilastine and levocetirizine were safe and well tolerated
Podder et al. 2020[12]	Moderate to severe CSU (*n*=58)	Bilastine 20 mg OD (*n*=31) or levocetirizine 5 mg OD (*n*=27) for 42 days	• Both bilastine and levocetirizine significantly improved changes from baseline in UAS7, DLQI and Urticaria-Induced Global Discomfort at day 42 ($p<0.001$ for all) • UAS7 at day 42 was significantly lower with bilastine compared with levocetirizine ($p=0.03$) • Somnolence was more common with levocetirizine than bilastine (63% *versus* 12.9%, $p=0.002$)
Hide et al. 2017[13]	CSU (*n*=304)	Patients randomized to receive bilastine 20 mg OD (*n*=101), bilastine 10 mg OD (*n*=100) or placebo OD (*n*=103) for 2 weeks	• Bilastine 20 mg and 10 mg improved TSS, rash score, itch score and DLQI compared with placebo ($p<0.001$ for all) • Bilastine was safe and well tolerated

CSU, chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index; OD, once daily; TSS, total symptom score; UAS7, 7-day Urticaria Activity Score.

“

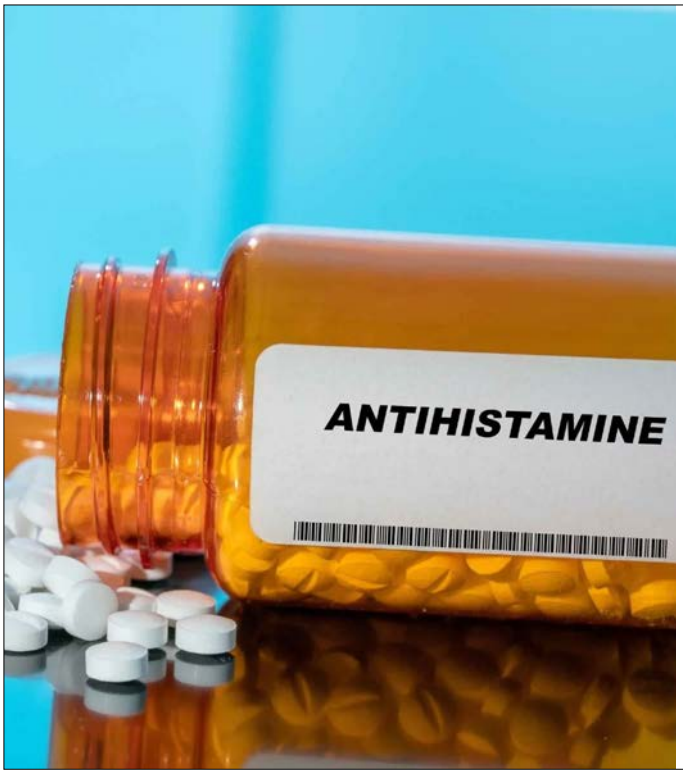
As a summary, based on the reviewed studies, **no definitive conclusion can be drawn regarding the superiority of any specific second generation antihistamine.**

EFFICACY OF UPDOSING...



HOW SHOULD I UPDOSE ANTIHISTAMINES?

Antihistamine	Time to max. plasma concentration (h)	Elimination half-life (h)	Duration of action (h)
Bilastine	1.2	14.5	≥24
Cetrizine	1.0±0.5	6.5–10	≥24
Desloratidine	1.0–3.0	27	≥24
Fexofenadine	1.0–3.0	11.0–15.0	24
Levocetirizine	0.8±0.5	7±1.5	>24
Loratadine	1.2±0.3	7.8±4.2 (24±9.8)	24
Rupatadine	0.75–1.0	6 (4.3–14.3)	24



HOW SHOULD I UPDOSE?

- Overall **duration of action and half-life are long** - technically, **can be given once daily**.
- However, **BD dosing is usually convenient and more effective** especially with those antihistamines with a shorter half-life.

SHOULD DIFFERENT ANTIHISTAMINES BE COMBINED?

Should different 2nd generation H_1-antihistamines be used at the same time?		
We **suggest against** using different H_1-antihistamines at the same time.	↓	Consensus[1] Evidence- and consensus-based (see Evidence Report)

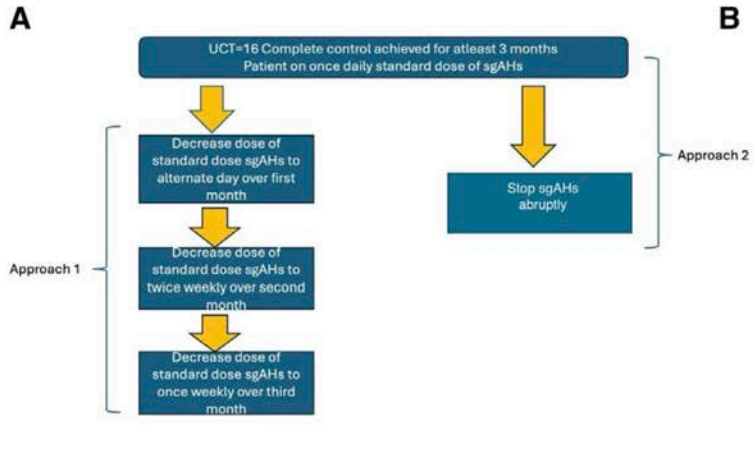
[1] ≥70% agreement

> Studies suggest that **updosing** a single antihistamine is **better than combining** different second-generation antihistamines.

HOW LONG SHOULD I TREAT?

- Generally treat **continuously, not intermittently**
- **Do not rush to tail off:**
  - Remove one tablet monthly until taking one tablet daily
  - Continue one tablet daily for 3 months
  - Then stop or tail-off gradually

FOR HOW LONG TO TAKE AND HOW TO TAIL-OFF?



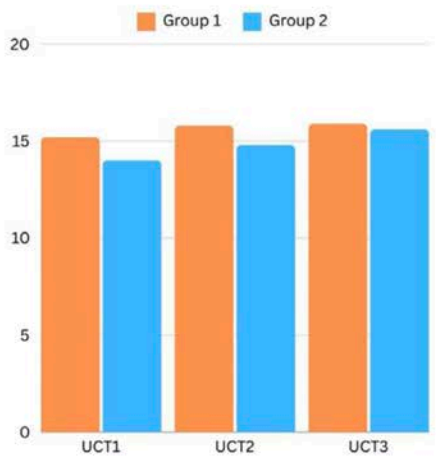


Figure 1. (A) Stepping-down approaches proposed for patients of CSU. Study was done in patients who were uniformly on standard dose of sgAHs. Approach 1- tapering of antihistamines, Approach 2- abrupt discontinuation of antihistamines. (B) Comparison of UCT at 1, 2, and 3 months of follow-up in 2 groups (orange panel, group 1—tapering of antihistamines) (blue panel, group 2—antihistamines abruptly stopped). CSU, chronic spontaneous urticarial; sgAH, second-generation antihistamines; UCT, urticaria control test.

WHAT ABOUT CHILDREN?

- Second-generation H1-antihistamines are unlicensed in children <6 months
- First-generation H1-antihistamines have an inferior safety profile
- Studies support **using the same algorithm with caution**, taking into consideration the **available formulations**

STANDARD LICENSED DOSES IN PAEDIATRICS

Antihistamine	Licensed age	Standard dose
Bilastine 2.5mg/mL or 10mg tab	>6 years (>20kg)	10mg
Cetrizine 10mg/mL	2-5 years	2.5mg BD
	6-12 years	5mg BD
Desloratadine 0.5mg/mL	1-5 years	1.25mg DLY
	6-11 years	2.5mg DLY

WHAT ABOUT PREGNANCY?

- **If possible**, **avoid** systemic treatment in the **first trimester**
- Otherwise, follow the same guidelines, using minimum dose to achieve control
- As a precaution, **loratadine** and **cetirizine** are preferred (most supported by literature)

WHAT ABOUT SEDATION?

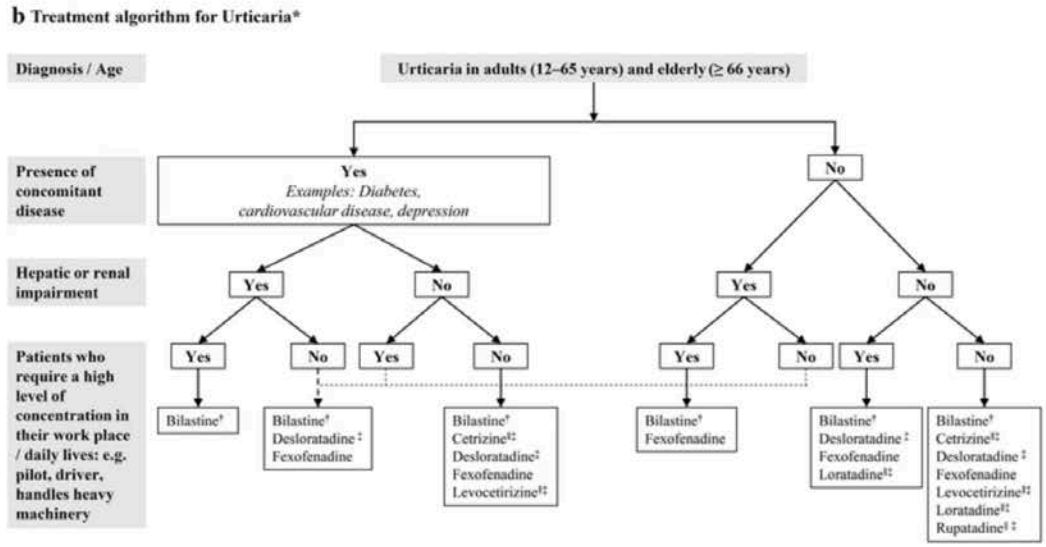
- **First-generation antihistamines should not be used** due to their anticholinergic and sedative effects.
- At **high doses**, **sedation** has been reported with second-generation antihistamines, especially with **cetirizine**.

WHAT ABOUT INTERACTIONS?

- Some antihistamines are **absorbed better** when **not taken with food**.
- **Fruit juices** (graprefruit, apple, orange…) can **slow absorption**.
- Overall, **no significant interaction with alcohol at standard doses**.
- At high doses, with alcohol, some studies report psychomotor impairment.

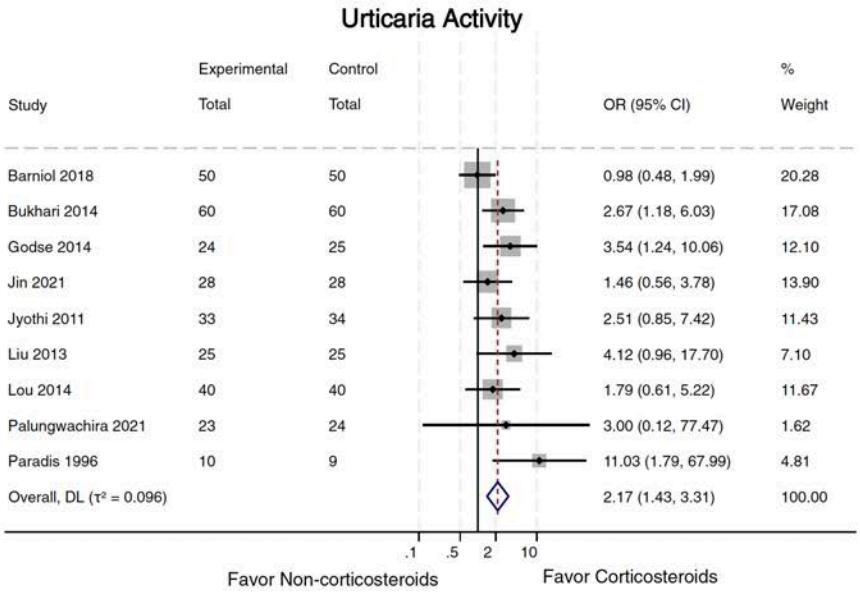
WHAT ABOUT INTERACTIONS?

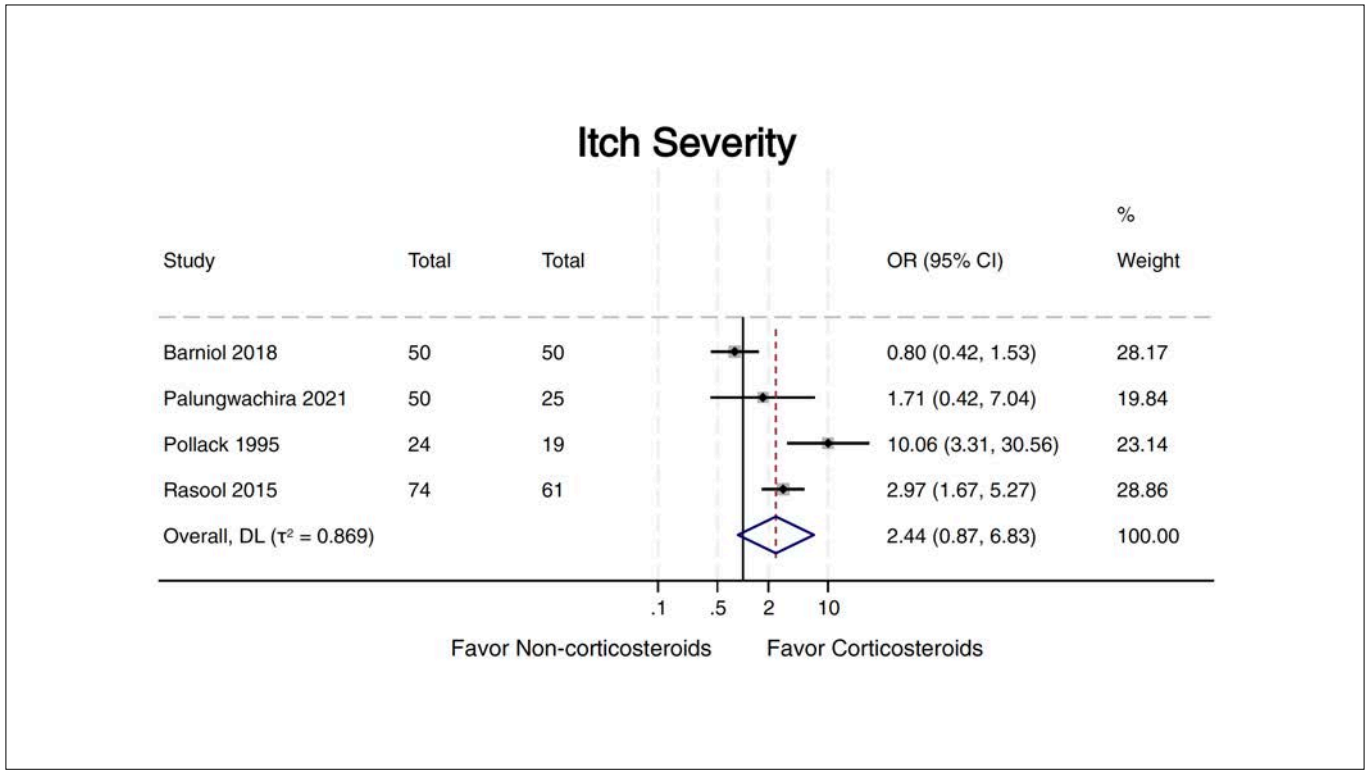
- Drug-drug interactions: co-administration of **ciclosporin**, **erythromycin**, **diltiazem** with **bilastine**, **rupatadine** and possibly **loratadine** can lead to **increased antihistamine concentration** (this does not appear to affect safety)

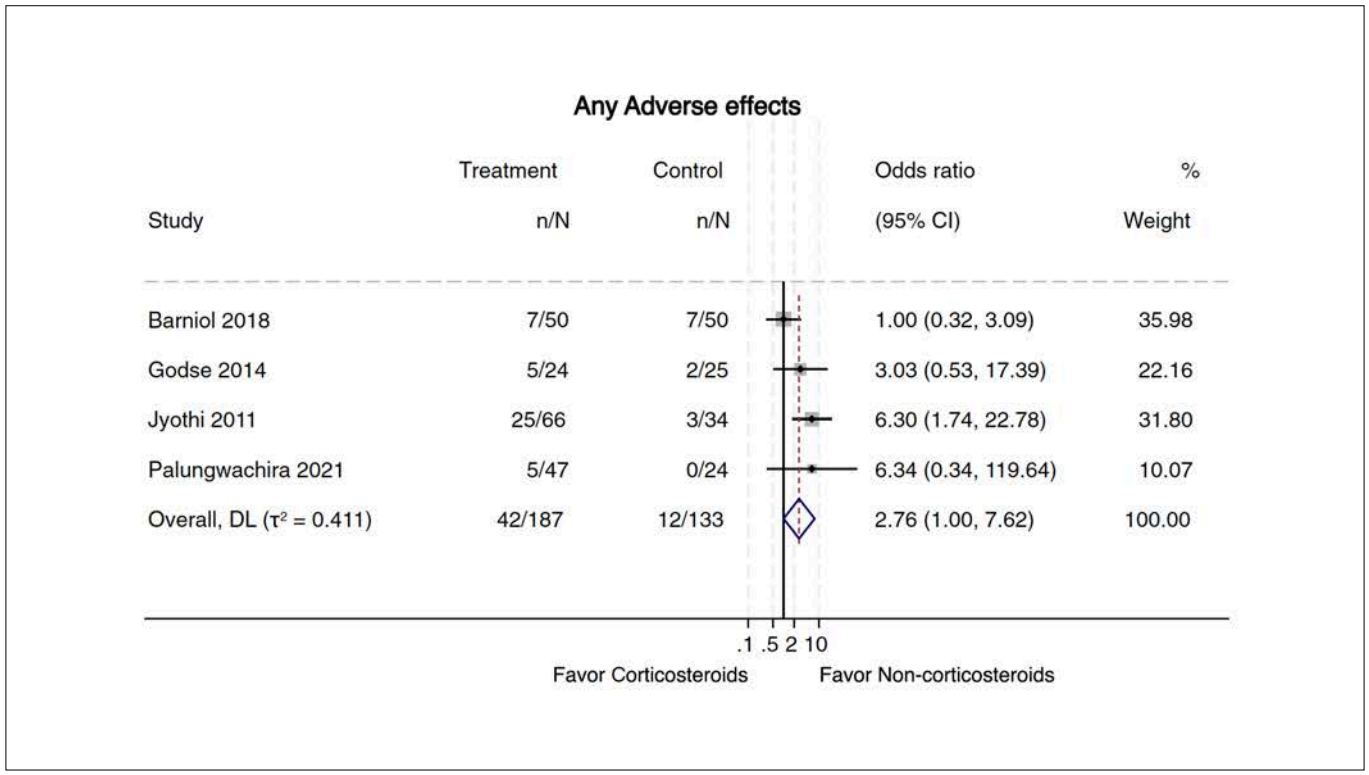


IS THERE A ROLE FOR STEROIDS?

- **Most do not need** prednisolone.
- In **severe or acute urticaria** with **poor response to antihistamine**, a short course of **prednisolone** (**40-60mg for 5 days**) can help (14-15% improvement).
- In milder urticaria, the benefit is much less pronounced (2.2%).
- Several **adverse effects** are reported with prednisolone.




Itch Severity
Study
Total
Total
OR (95% CI)
%
Weight
Barniol 2018 50 50 0.80 (0.42, 1.53) 28.17
Palungwachira 2021 50 25 1.71 (0.42, 7.04) 19.84
Pollack 1995 24 19 10.06 (3.31, 30.56) 23.14
Rasool 2015 74 61 2.97 (1.67, 5.27) 28.86
Overall, DL (τ² = 0.869) 2.44 (0.87, 6.83) 100.00
.1
.5
2
10
Favor Non-corticosteroids
Favor Corticosteroids


Any Adverse effects
Study
Treatment
n/N
Control
n/N
Odds ratio
(95% CI)
%
Weight
Barniol 2018 7/50 7/50 1.00 (0.32, 3.09) 35.98
Godse 2014 5/24 2/25 3.03 (0.53, 17.39) 22.16
Jyothi 2011 25/66 3/34 6.30 (1.74, 22.78) 31.80
Palungwachira 2021 5/47 0/24 6.34 (0.34, 119.64) 10.07
Overall, DL (τ² = 0.411) 42/187 12/133 2.76 (1.00, 7.62) 100.00
.1
.5
2
10
Favor Corticosteroids
Favor Non-corticosteroids

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

We **recommend against** the long-term use of systemic glucocorticosteroids in CU.	↓↓	Strong consensus[1]
We **suggest** considering a short course of rescue systemic glucocorticosteroids in patients with an acute exacerbation of CU.	↑	Evidence- and consensus-based (see Evidence Report)

[1] ≥90% agreement

STEP 2: REFER TO SECONDARY CARE

- In secondary care, if fourfold doses of antihistamines are not effective, other drugs may be offered:
  - **Omalizumab**
  - **Ciclosporin**
  - (Dapsone)

TAKE-HOME MESSAGES

Urticaria

“

Urticaria is usually spontaneous and allergy testing is not generally recommended. Patch testing is useless.

“

No need for many blood tests. In chronic urticaria, take CBC and CRP/ESR.

“

Standard dose, second-generation antihistamines are first-line. Dose can be increased fourfold.

“

Treat continuously, not intermittently. Take it easy when tailing off.

“

5-day courses of prednisolone can be useful, especially in acute urticaria and urticaria refractory to antihistamines BUT avoid long or repeated courses. Better to refer to secondary care.

URTICARIA

Dr Daniel Micallef
Consultant Dermatologist