

Evidence for doing diagnostic tests that guide the management of urticaria

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Definition of urticaria

- A disease characterised by fluctuating weals, angio-oedema, or both with a spectrum of clinical presentations
- New('ish) European terminology:
 - 'Urticaria' defines a heterogeneous disease as much as an eruption of weals
 - Classification should be based primarily on clinical pattern rather than aetiology. Urticaria may be spontaneous (the ordinary presentation) or inducible (physical and cholinergic urticarias). The qualifier 'idiopathic' should only be used if an underlying aetiology has been actively sought and excluded.

What should be included as a clinical presentation of urticaria?

Spontaneous urticaria

Inducible urticaria

Physical urticaria

- Mechanical
- Cold and heat contact

Other urticaria types

- Cholinergic
- Contact

Diseases related to urticaria

- Urticarial vasculitis
- Non-histaminergic angioedema (e.g. HAE)

Syndromes associated with urticaria

Ordinary urticaria

Physical urticarias

- Mechanical
- Thermal
- Other

Angio-oedema without weals

Contact urticaria

Urticarial vasculitis

Autoinflammatory syndromes

Diseases with an urticarial component

	Clinical features	Diagnostic tests
Urticarial vasculitis	Burning weals > 24 h, bruising	Lesional skin biopsy, C3 and C4
Autoinflammatory syndromes	Weals, fever, malaise, bone pain	High ESR/CRP, Monoclonal IgM, <i>CIAS1</i> mutations
Hereditary angio-oedema, Type I	Skin or mouth swellings +/- colic	Low C4 and C1 inh, <i>SERPING1</i> mutations
HAE, Type II	As above	Low C4, normal C1 inh, low functional inh <i>SERPING1</i> mutations
HAE Type III	As above, mainly women	Normal C4 and C1 inh. <i>F12</i> mutations

Defining clinical features of urticaria

- Ordinary urticaria
 - Spontaneous weals lasting usually < 24 h +/- angio-oedema
 - Disease duration defined acute, chronic and episodic patterns
- Physical and cholinergic urticarias
 - Inducible weals lasting < 2 h EXCEPT delayed pressure urticaria
 - Distinct and reproducible provoking stimulus

Physical provocation tests

- Define the trigger but NOT the cause of physical and cholinergic urticarias
- Definition should help avoidance 😊 and MAY allow physical 'desensitisation'

Tests used in physical urticarias to diagnose the trigger but not the cause

TYPE	STIMULUS	DIAGNOSTIC TEST
Dermographism	Stroking	Dermographometer
Cold contact	Localized cooling	Ice or TempTest®
Delayed pressure	Vertical pressure	Dermographometer or weighted rods
Cholinergic	Overheating	Exercise <u>or</u> hot bath

Magerl et al, Consensus guidelines on physical urticaria testing. Allergy; in press

Tests used in ordinary urticaria to diagnose the cause, but not the trigger

ACUTE	Allergy Infection	SPT, ImmunoCAP 😊 Viral studies ¹
CHRONIC	Infection Autoimmune ? Coagulation	Bacterial, parasitic ² ASST, BHRA ³ 😊 APST, F ₁₊₂ , D-dimer ⁴
EPISODIC	Drug and diet	Challenge capsules ⁵

¹Zuberbier et al, Acta Derm Venereol 1996;76:295-8

²Wedi et al, Current Opinion in Allergy Clin Immunol 2004; 4:387-96

³Grattan et al, Immunology and Allergy Clinics of N America 2004; 24@163-82

⁴Asero et al, J Allergy Clin Immunol 2006; 117:1113-7

⁵Wedgeworth et al, in press

Diagnostic tests for autoimmune urticaria

- *In vivo*
 - ASST¹
- *In vitro*
 - Thyroid autoantibodies²
 - Functional autoantibodies³ including basophil histamine release assay⁴ 😊
 - Immunoassays
 - Basophil activation markers

¹Konstantinos et al, Consensus on ASST. Allergy, in press

²O'Donnell et al, Br J Dermatol 2005; 153:331-5

³Hide et al, NEJM 1993; 328:1599-1604

⁴Platzer et al, Allergy 2005; 60:1152-6

Evidence for histamine releasing autoantibodies against FcεRI

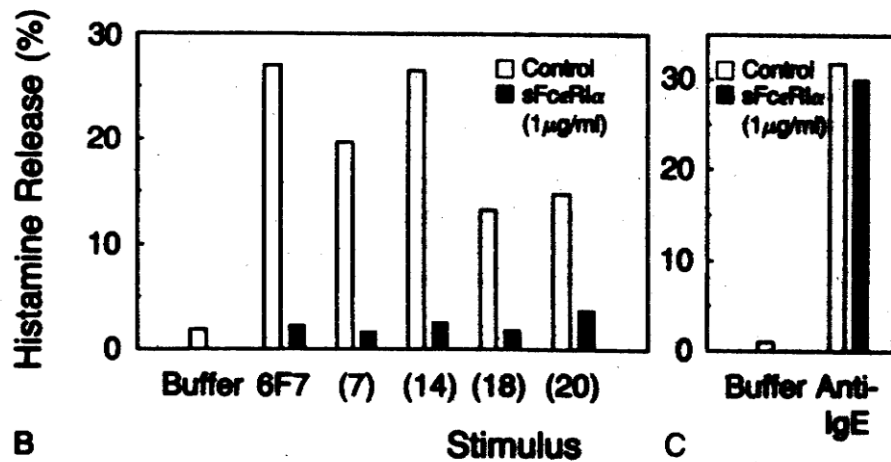


Figure 3. Concentration-Dependent Inhibition by sFcεRIα of Histamine Release from Basophils from Donor 1 Induced by Whole Serum (Panel A) and IgG Fractions (Panel B) from Four Patients with Chronic Urticaria.

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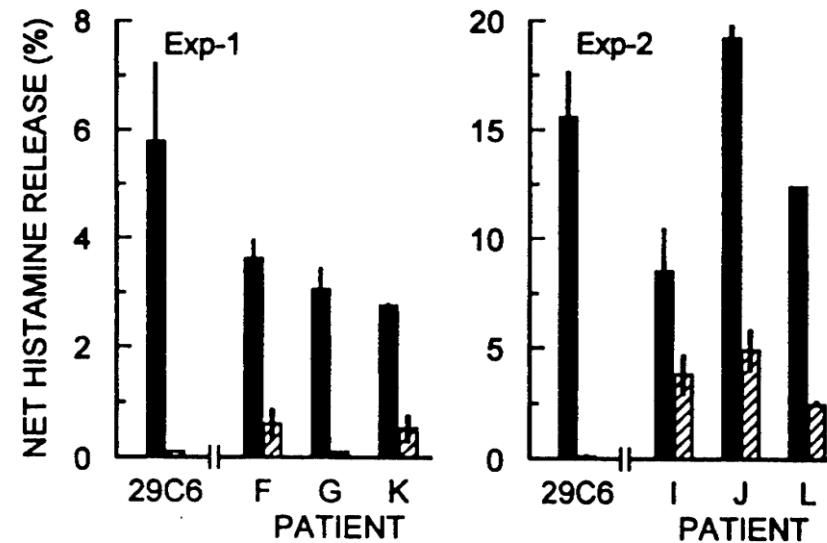


Figure 5. Serum IgG-induced histamine release from skin mast cells was inhibited by preincubation of the IgG fraction with sFcεRIα. The IgG fraction, isolated from patients' sera by protein G chromatography, was preincubated with assay buffer (solid bars) or 1 μg/ml sFcεRIα (hatched bars) prior to assay of histamine-releasing activity from

Potential criteria for definition of autoimmune urticaria

Severe spontaneous urticaria

Poorly responsive to H1 antihistamines

Associated organ-specific autoimmune disease, especially thyroid

BHRA+

ASST+

(Immunoassays)

(Basophil activation markers)

Diagnostic tests to determine management

- Infection:
 - Helicobacter ag, ab and breath test 😊
 - Streptococcal swabs and serology
 - Ova, cysts and parasites for infestation 😊
 - SPT for anisakiasis
- Pseudoallergy:
 - Food additive +/- aspirin challenge 😊
 - Low pseudoallergen diet

Diagnostic tests to define response to drugs

- Antihistamines: none
- Corticosteroids: none
- Epinephrine: 'not effective for HAE'
- Dapsone and sulphasalazine: +ve pressure test
- Ciclosporin: 13/18 ciclosporin responders had positive BHRA vs 1/9 non-responders¹
- Other immunosuppressives: not known
- Anti-IgE: not known

¹Grattan et al, Br J Derm 2000; 143:365-72

Other potential biomarkers for treatment response and remission of autoimmune urticaria

- Basopenia
- Total IgE
- Organ-specific autoantibodies
- Basophil anti-IgE responsiveness
- Expression of basophil activation markers

What blood tests should be done in CU?

- H1 antihistamine responders: none 😊
- H1 antihistamine non-responders:
 - FBC, ESR
 - Thyroid autoantibodies 😊, TFT
- Angio-oedema without weals or urticarial vasculitis: C4 😊
- Follow any lead from the history of exam
- Appropriate screening and monitoring for adverse drug effects.