World Allergy Forum Symposium:
Urticaria: Different Phenotypes and Diverse Treatments

2011 EAACI Congress
Tuesday, 14 June 2011 - 10:30 – 12:00
Lutfi Kirdar Convention and Exhibition Centre (ICEC)
Harbiye 34267
Istanbul, Turkey

Moderators:
Richard F. Lockey (USA)
Jan Lötvall (Sweden)

Phenotypes
Malcolm Greaves (United Kingdom)

New and Diverse Approaches to the Treatment of Urticaria
Marcus Maurer (Germany)

Systemic Manifestations of Atopic Urticaria
Allen Kaplan (USA)

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www.worldallergy.org/wac2011
Urticaria: Different Phenotypes and Diverse Treatments

Program

Moderators:
Richard F. Lockey
University of South Florida
Tampa, FL, USA

Jan Lötvall
Goteborg University
Goteborg, Sweden

1. Welcome to the World Allergy Forum Symposium and Introduction to “Urticaria: Different Phenotypes and Diverse Treatments”
Richard F. Lockey and Jan Lötvall

2. Phenotypes
Malcolm W. Greaves
St. John’s Institute of Dermatology, St. Thomas’ Hospital
London, United Kingdom

3. New and Diverse Approaches to the Treatment of Urticaria
Marcus Maurer
Charité - Universitätsmedizin Berlin
Berlin, Germany

4. Systemic Manifestations of Atopic Urticaria
Allen P. Kaplan
Medical University of South Carolina
Charlestown, SC, USA

Upon completion of this session, participants should be able to:
• Discuss the pathogenesis of different forms of urticaria
• Describe the systemic co-morbidities associated with urticaria
• Formulate a differential diagnosis and treatment plan for patients with urticaria

2010-2011 World Allergy Forum Advisory Board

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The World Allergy Organization (WAO) is a global federation of 89 regional and national allergy, asthma and clinical immunology societies. Through collaboration with its member societies, WAO provides a wide range of educational and outreach programs to WAO individual members around the globe. These programs, relating to the clinical practice of allergy, allergy service provision, and physician training in allergy help better understand and address the challenges facing allergists worldwide.

**Mission**

WAO’s mission is to be a global resource and advocate in the field of allergy, advancing excellence in clinical care through education, research and training as a worldwide alliance of allergy and clinical immunology societies.

**Meetings**

**World Allergy Congress™ (WAC)**

WAO hosts the World Allergy Congress™ (WAC) — its main scientific meeting — biennially in different regions of the world. Please join us in Cancún, México in 2011, Milan, Italy in 2013 and Seoul, South Korea in 2015. For more details on WAC 2011 in Cancún, please visit www.worldallergy.org/wac2011

**WAO International Scientific Conference**

WAO is excited to launch its theme-based scientific conferences alternating with and complementing WAO’s biennial Congresses.

The 1st WAO International Scientific Conference was held in Dubai, UAE from 5-8 December 2010 and was focused on Asthma and Co-morbid Conditions.

The 2nd WAO International Scientific Conference will take place from 6-9 December 2012 in Hyderabad, India.

**WAO Website**

[www.worldallergy.org](http://www.worldallergy.org)

As a leading global online destination for allergy, asthma and clinical immunology, [www.worldallergy.org](http://www.worldallergy.org) supports and enhances all WAO educational activities and provides materials specifically designed for continued medical training, and reviews of the scientific literature. Popular resources include the specially commissioned educational synopses on major topics posted in the Allergic Diseases Resource Center, interactive case studies that challenge allergists to diagnose unusual cases, an archive of webinars recorded at major meetings, and audio recordings of interviews with key opinion leaders around the world. The WAO website is now HONcode certified.

**The World Allergy Organization Journal**

[www.waojournal.org](http://www.waojournal.org)

The World Allergy Organization Journal (WAO Journal) is the official publication of WAO and underscores WAO’s commitment to raising awareness and advancing excellence in clinical care, education, research and training. This international, peer-reviewed journal covers a broad spectrum of the interdisciplinary fields of allergy and clinical immunology. As an online-only journal, the publication process of the WAO Journal is efficient and quick, with articles posted each month on schedule. All WAO members have free access to the WAO Journal.

The primary goals of the WAO Journal are:

- To be a premier journal of original scientific and clinically relevant information for practicing allergists/immunologists and other physicians concerned with the practice of allergy and clinical immunology
- To publish state-of-the-art review articles and editorials on translational and clinical medicine in the field of allergy and immunology
- To present a forum for scientific interaction between allergists and immunologists worldwide

**WAO Programs for Education, Research & Patient Care**

**Global Resources in Allergy™ (GLORIA)**

GLORIA promotes best practices in the management of allergic disease through didactic programs developed by international experts. GLORIA is presented at national and regional allergy society meetings throughout the world and also at regional, state and local society meetings within the United States. All current GLORIA modules are available for free download at [www.worldallergy.org/gloria](http://www.worldallergy.org/gloria)

**World Allergy Forum ® (WAF)**

WAF brings cutting edge symposia to major allergy meetings throughout the world. Developed by international expert advisory panels, the symposia provide up-to-the minute presentations on scientific and clinical developments in the field of allergic disease. WAF placements attract up to 1,000 attendees. WAF is supported by an unrestricted educational grant from Novartis. View presentations for free at [www.worldallergy.org/waf](http://www.worldallergy.org/waf)

**Emerging Societies Program (ESP)**

ESP advances the WAO mission by supporting developments that enable allergists to better serve patients now and in the future. ESP aims to disseminate information on and share experiences about new treatments for allergic disease and about new indications for available therapies. All ESP meetings and training schools are conducted with the help and support of WAO Member Societies. The American College of Allergy, Asthma and Immunology (ACAAI) partners with WAO on ESP. View all ESP activities at [www.worldallergy.org/esp](http://www.worldallergy.org/esp)
WAO Projects and Publications

www.worldallergy.org/publications

WAO White Book on Allergy has been published, and is available in full text on the WAO website. The White Book outlines the data which indicate that allergy is a major global public health issue, and provides “high-level” recommendation for action based on WAO member society reports on allergy education and service provision requirements. Editors: Professors Ruby Pawankar, Stephen T. Holgate, G. Walter Canonica, and Richard F. Lockey. The Executive Summary is also available.


WAO Member Society Surveys

WAO’s federal structure provides a unique network to conduct effective global surveys about allergy. A number of projects have taken place over the last two years:

- The WAO Specialty and Training Council conducted surveys on general/adult and pediatric clinical allergy services and training to obtain global information on current and future allergy service provision.

- Building on the WAO’s 2007 international survey on the availability of epinephrine auto-injectors worldwide, in 2008 the WAO Special Committee on Anaphylaxis conducted a survey of Member Societies to gather data on how anaphylaxis is diagnosed and treated in healthcare settings in their respective countries. The combined results of these surveys will form the basis of the WAO international guidelines for the assessment and management of anaphylaxis, which was introduced at WAC 2009 and was launched in 2010.

- The Asthma Special Committee conducted a survey of Member Societies to find out about the major allergens involved in exacerbations of severe and chronic asthma, and to learn whether national definitions of severe asthma exist. The information obtained will form a WAO educational program based on the 2009 World Health Organization’s definition of Severe Asthma.

- The Drug Allergy Special Committee conducted a survey on in-vivo methods used in the diagnosis of allergic reactions to major drug classes. The information obtained will be the first step to reaching a global consensus about the best way to diagnose drug hypersensitivity reactions, and to sharing expertise on this clinical problem.

- The Evidence Based Medicine and Methodology Special Committee developed a survey to establish allergists’ educational needs in evidence based medicine.

WAO Junior Members Group

www.worldallergy.org/juniormembers/

The WAO Junior Members Group aims to support and encourage young scientists and clinicians by providing the opportunity for them to contribute to the ongoing work of the WAO - and become future WAO leaders! Applicants must be working in the field of allergy/clinical immunology, be 35 years of age or under and/or within 5-years of their latest degree, and a current member of a WAO Member Society. Visit www.worldallergy.org/juniormembers/ for further information or to apply.
WAO Member Societies

All active members of dues-paying Member Societies are Individual Members of the World Allergy Organization (WAO).

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American Academy of Allergy, Asthma and Immunology
American College of Allergy, Asthma and Immunology
Argentine Association of Allergy and Clinical Immunology
Argentine Society of Allergy and Immunopathology
Australasian Society of Clinical Immunology and Allergy
Austrian Society of Allergology and Immunology
Azerbaijan Society for Asthma, Allergy and Clinical Immunology
Bangladesh Society of Allergy and Immunology
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Allergy, Asthma and Immunology Society of Thailand
Turkish National Society of Allergy and Clinical Immunology
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Uruguayan Society of Allergology
Venezuelan Society of Allergy and Immunology
Vietnam Association of Allergy, Asthma and Clinical Immunology
Zimbabwe Allergy Society

Regional Organizations

Asia Pacific Association of Allergology and Clinical Immunology
Commonwealth of Independent States (CIS Society)
European Academy of Allergy and Clinical Immunology
Latin American Society of Allergy, Asthma and Immunology

Affiliate Organizations

Global Allergy and Asthma European Network (GA2LEN)
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International Association of Asthma
Southern European Allergy Societies (SEAS)

Associate Member Societies

National Association for Private Algerian Allergists
Ecuadorian Society of Allergology and Affiliated Sciences
Ecuadorian Society of Allergy and Immunology
Jordanian Society for Allergy and Clinical Immunology
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Moroccan Society of Allergology and Clinical Immunology
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For WAO membership information please contact the Secretariat
World Allergy Organization (WAO)
555 East Wells Street, Suite 1100 • Milwaukee, WI 53202-3823 USA
Tel: +1 414 276 1791 • Fax: +1 414 276 3349
e-mail: info@worldallergy.org
Web site: www.worldallergy.org
Dear Colleagues,

Welcome to the thirty-ninth symposium in the World Allergy Forum series; “Urticaria: Different Phenotypes and Diverse Treatments.” The World Allergy Organization is delighted to bring this symposium to the Istanbul Congress of the European Academy of Allergy and Clinical Immunology (EAACI). WAO is proud and appreciative that this symposium is an annual event at the Congress, with the EAACI hosting the World Allergy Forum every year since this major educational program commenced fourteen years ago.

Urticaria ranges from a short-term, transitory rash causing a minor inconvenience to the afflicted individual, to a severe, unremitting and disabling condition, with substantial impairment of quality of life. Today’s symposium is composed of world renowned experts on this subject. Malcolm Greaves, from London, UK, opens the session with a talk on Phenotypes of Urticaria. He will describe four important physical urticarias and their clinical presentations, pathophysiology and treatment. The second speaker, Marcus Maurer from Berlin, Germany, considers New and Diverse Approaches to the Treatment of Atopic Urticaria and provides insight into the most up-to-date management strategies. Finally, Allen Kaplan, from Charleston, South Carolina, USA, discusses the Systemic Manifestations of Atopic Urticaria. The presentation looks at the systemic diseases that may involve urticaria or urticarial vasculitis, appropriate laboratory studies, and illustrative case histories.

WAO hopes that you will enjoy this symposium and glean from it information which can be used in your everyday clinical practice. The program abstracts and slides will be available on the WAO Web site shortly after the Congress, at: http://www.worldallergy.org/educational_programs/world_allergy_forum/.

WAO gratefully acknowledges the unrestricted educational grant from Novartis that supports the World Allergy Forum program series.

With our best regards,

Richard F. Lockey
President
World Allergy Organization

Prof. Jan Lötvall
President
European Academy of Allergology and Clinical Immunology
Physical urticarias are common, by definition “atopic”, frequently passively transferrable and are presumed to involve reaction of a physically evoked neoallergen with specific IgE. The diagnosis is established by physical challenge testing in the clinic, and laboratory investigations are rarely warranted. Most have a natural history of eventual spontaneous remission, and respond to H1 antihistamines. However in a minority of patients symptoms can be severe, unremitting, and disabling, with substantial impairment of quality of life.

Four important physical urticarias will be discussed with regard to clinical presentation, pathophysiology and treatment

Symptomatic dermographism needs to be distinguished from simple dermographism. In the latter there is no axon reflex flare or itch. Using a dermographometer challenge pressure of 49g/mm² about 4% of the population have symptomatic dermographism. In a modified PK reaction, dermographic reactivity can be passively transferred by IgE. Most patients respond to suppression of dermographism by low sedation H1 antihistamines though off-label dosages are often required. Spontaneous remission usually occurs in 2-3 years.

Apart from the well known acquired cold contact urticaria, there are several variant phenotypes of cold urticaria including cold reflex urticaria, cold urticaria with cryoglobulinaemia and the familial cold autoinflammatory syndromes (FCAS). Recent advances include refined technology for accurate measurement of cold sensitivity. Cold urticaria is passively transferrable by IgE and there is convincing evidence of the role of virus infections in causation of some cases. Besides H1 antihistamines, cold tolerance treatment and occasionally omalizumab have been used in selected cases.

Cholinergic urticaria is common, and is significantly associated with atopy. Classically, cholinergic urticaria has been deemed to be due to aberrations in autonomic cholinergic innervation of eccrine sweat glands and consequent dermal mast cell activation. That autologous sweat and serum skin reactions are recently reported in cholinergic urticaria, as well as in atopic eczema, provides additional evidence of a link between the two skin disorders. As with other physical urticarias no laboratory tests are indicated once the diagnosis is confirmed by challenge testing. H1 antihistamines, often in off-label dosages, are effective, although attenuated androgens or omalizumab are of utility in severely incapacitated individuals, especially those with angioedema.

Solar urticaria can be passively transferrable, and two types have been defined: type 1 in which an abnormal photoallergen is formed in sunlight exposed skin which elicits specific IgE antibodies, and type 2 in which sunlight evokes a normal chromophore antigen which also leads to formation of specific IgE antibodies. Exposure to wavelengths outside the action spectrum in individual cases causes subsensitivity to clinical sunlight exposure and this has been used with benefit in phototolerance treatment. However, most cases respond well to a combination of H1 antihistamines and sun barrier creams. Monochromator phototesting is useful in precisely defining the action spectrum in individual cases, and enabling focused selection of optimal sun barrier cream protection.

References:
Atopic urticaria: phenotypes

Malcolm W Greaves
Cutaneous Allergy Clinic,
St John’s Institute of Dermatology,
St Thomas’ Hospital,
London

Potential conflicts of interest: have received fees for services from Genentech & Novartis

Atopic urticaria: phenotypes

- Atope (Gr) = "inappropriate response to an event"
- Physical urticarias are "orphan" dermatoses
  symptomatic dermographism
  cold urticaria
  solar urticaria
  cholinergic urticaria
- Characterised by inappropriate (urticarial) responses to innocuous physical stimuli

Chronic urticaria: physical urticarias

- Urticarial vasculitis < 5%
- Physical urticaria 30%
- Chronic ordinary urticaria (autoimmune; non-autoimmune) 65%
Physical urticarias

- Occur within minutes of exposure to triggering stimulus, and resolve within an hour of its removal
- Resolve in a mean of 2 - 4 years
- Rarely associated with systemic disease
- Rarely require laboratory investigation
- Usually respond to avoidance plus H1 antihistamines

Physical urticarias: pathogenesis – a hypothetical model

Symptomatic dermographism

- Erythema, axon reflex flare, itching in response to light stroking of the skin
- Of simple dermographism in which redness and whealing occur without axon reflex or itching
- Using a pressure of 49g/mm² symptomatic dermographism occurs in 4.2% of the population
Symptomatic dermographism: pathophysiology

- Dermal mast cell population is normal, but reduction by application of potent topical steroids under occlusion reduces mast cell population and skin reactivity.

- Elevated tissue histamine levels are present in involved skin and recent evidence also implicates Substance P.


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Symptomatic dermographism: treatment

- Treatment is by low sedation H1 antihistamines, but off-label dosage is often necessary.

- H2 antihistamines are often prescribed as well, but several RCT's have shown that any benefit is statistical rather than clinically useful.

- Narrow band UVB phototherapy (311 nm UV) may also be effective, especially for pruritus (Bossova JAAD 2008, 59: 752).

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Cold urticaria

Variants include:

- Secondary acquired cold urticaria with cryoglobulinaemia

- Cold reflex urticaria: exposure to cold atmosphere causes whealing in covered as well as exposed skin, with a negative local cold challenge test

- Hereditary cold autoinflammatory syndromes (FCAS) with negative cold challenge tests and mutation in CIAS1

- Several other very rare subtypes
Acquired cold urticaria: pathophysiology

- Improved cold contact testing (0-45°C) is enabled by a new validated Peltier effect-based method

- Cold reactivity can be passively transferred by serum to primates, and IgE has been implicated, suggesting a cold-dependent allergenic skin component

- An anti-IgE autoantibody has also been implicated (Grof et al. JID 1989;90:213)

Temp Test: Mynaka, A et al. 2010 BJD 162: 196-200

Acquired cold urticaria: role of virus infections and IgE

Virus infections including EB and HIV have consistently been associated with cold urticaria, and can cause upregulation of IgE

- Low CD4, reduced TH1 and IFN γ cause increased TH2 cells

- HIV-1 protease gp 120 and Tat induce TH2 cytokines, or interact directly with specific receptors on B cells causing increased IgE mRNA

- In either case some of this IgE binds specifically to a putative cold induced antigenic determinant

Cold urticaria: management

- Off-label dosages of 2nd generation H1 antihistamines are often needed

- Omalizumab (Xolair) has been effective in selected intractable cases (Boye JACI 2006;117)

- Bathing in cool water risks anaphylactoid reactions which may be fatal

- A recently recognised hazard: anaphylactoid reaction due to systemic hypothermia (4°C) in open heart surgery, avoided by normothermic cardioplegia
Cholinergic urticaria

- Affects about 10% of young adults
- About one third are atopic
- Attacks are provoked by heat, exercise and emotion and are short-lived
- Systemic symptoms, especially flushing may occur and peak flow may be impaired

Cholinergic urticaria: pathophysiology

- Heat
- Exercise
- Stress
- Gustatory

Postganglionic sympathetic cholinergic nerves

Ach

Intermediate substance eg protease (?)

(Effah et al et al etc).

Sweat gland

Histamine and other mediators

- Atropinised skin is non-reactive
- Increased plasma histamine levels and mast cell degranulation
- Rat mast cells express acetylcholine receptors and acetylcholine degranulates rat mast cells

Cholinergic urticaria: autologous sweat and serum reactions

Recent work (Fukunaga et al JACI 2005; 116: 397-402) has suggested that cholinergic urticaria are reactive to autologous sweat and can be divided into 2 subtypes:

- Type 1 shows strong reactions to autologous sweat, satellite wheals to id acetylcholine and negative reactions to autologous serum
- Type 2 shows a weak reaction to autologous sweat, a positive reaction to autologous serum and no reaction to acetylcholine

Positive autologous sweat tests have recently been reported in atopic eczema (Hilde et al 2002) which links cholinergic urticaria and atopy and sweat from cholinergic urticaria patients releases histamine from autologous basophils
Cholinergic urticaria: pathophysiology

- Heat
- Exercise
- Stress
- Gustatory

- Postganglionic sympathetic cholinergic neurons

- Sweat gland

- Acetylcholine

- Histamine and other mediators

- ID autologous sweat causes urticarial reaction and releases histamine from autologous basophils

Cholinergic urticaria: diagnosis

- The diagnosis is clinical and based upon history and challenge testing: usually hot bath, exercise

- Intradermal acetylcholine/methacholine ID testing shows low specificity

- No laboratory investigations are warranted

Cholinergic urticaria: treatment

- H1 antihistamines, often in off-label dosages, are usually effective

- Systemic anticholinergics are usually only effective in toxic dosages

- RCT’s have shown the effectiveness and safety, especially in male patients, of attenuated androgens based upon findings of reduced serum protease inhibitors

- Omalizumab has been used successfully in selected cases
Solar urticaria

- Whealing occurs within 5 min of sun exposure, and fades within 2h
- Acton spectrum: 280 – 700nm
- Angioedema and anaphylactoid symptoms can occur
- Prognosis: 5-10y duration

Solar urticaria: pathophysiology

- Reactivity can be passively transferred
- Type 1: abnormal chromophore only occurs in skin and serum of solar urticaria patients and evokes specific IgE antibodies
- Type 2: a normal chromophore evokes specific IgE antibodies

Solar urticaria: pathogenesis
Solar urticaria: diagnosis

- Most referrals turn out to be PLE (lesions last > 48h, cf solar urticaria < 2h)
- Can be manifestation of erythropoietic protoporphyria
- Phototesting (natural sunlight, solar simulator lamp) confirms
- Monochromator testing establishes action spectrum, enables focussed photoprotection

Solar urticaria: treatment

- H1 antihistamines + photoprotection
- Inhibition spectra and tolerance treatment: wavelengths greater than the action spectra diminish solar urticaria – probably by inactivating photoallergens
- Tolerance treatment has proved effective though necessitating maintenance
- Plasmapheresis and most recently omalizumab have been used in selected cases
Urticaria is a heterogeneous group of diseases characterized by recurrent itchy wheal and flare type skin reactions and/or angioedema. Urticaria of longer than six weeks duration is classified as chronic urticaria. Urticaria with spontaneously occurring symptoms (spontaneous urticaria) is distinguished from inducible urticaria types, in which symptoms occur in response to physical or other triggers.

What is the role of atopy or allergy in urticaria? Chronic spontaneous urticaria is often thought to be an allergy because, similar to allergic diseases, the symptoms are brought about by mediators released from activated mast cells, and patients benefit from antiallergic treatment (e.g. antihistamines, anti-IgE). Sensitizations to environmental allergens, however, are very rarely the underlying cause of chronic spontaneous urticaria, whereas autoreactivity, chronic infections, and intolerance to food components are much more common reasons for chronic spontaneous urticaria. Sensitizations to environmental allergens are also largely irrelevant for the pathogenesis of most chronic inducible urticaria, with contact urticaria and exercise-induced urticaria being the exceptions. All in all, chronic urticaria is not an atopic disease and allergies are not a common cause.

Since chronic urticarias are different in phenotype and underlying cause, it is important to assess patients for the urticaria type(s) they exhibit and to personalize their treatment. The treatment strategy, among other factors, depends on the urticaria type, duration, and activity, and may be aimed at the elimination of underlying causes or the prevention of symptom reoccurrence. In any case, freedom of symptoms should be the goal.

This presentation will review the classification of urticaria with a special focus on the role of atopy and allergies. Participants will then be given an overview of the diversity of chronic urticaria phenotypes. The last part of this presentation will consist of practical tips and tricks on how to find the optimal treatment for each and every chronic urticaria patient.
Atopic urticaria:
Different phenotypes and diverse treatment

Marcus Maurer

Urticaria

Wheal and flare
Angioedema
Chronic urticaria is a disabling disease.

Treat it until it is gone!
Urticaria – Pathogenesis

Mast cells are the key effector cells in the induction of urticaria symptoms

**CAUSE**

- Activation
- Vascular
- Extravasation
- Recruitment

**PRURITUS**

**ERYTHEMA**

**WHEAL**

**INFLITRATE**
Urticaria - Therapeutic strategies

- Trigger
- Mast cell-activating signal → Mast cell activation → Mast cell mediators → Urticaria reaction

Causal symptomatic

Chronic Spontaneous Urticaria

- Identify underlying cause
- Treat underlying cause

once cause is found
Critical temperature thresholds

But:
<50% of urticaria patients show complete response to nsAHs!
Non-sedating H<sub>1</sub>-Antihistamine (nsAH)
If symptoms persist after 2 weeks
nsAH updosing (up to 4x)

Cold contact urticaria
TempTest<sup>®</sup> 3.0

Does updosing work?
Non sedating H1-Antihistamine (nsAH)

- If symptoms persist after 2 weeks
- nsAH updosing (up to 4x)
  - If symptoms persist after 1-4 weeks
  - Addition of Leukotriene antagonist, change nsAH
  - If symptoms persist after 1-4 weeks

+ H2-Antihistamine, Cyclosporine A, Dapsone, anti-IgE

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**Reduction of disease activity**

<table>
<thead>
<tr>
<th>Week</th>
<th>Anti-IgE</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>24</td>
<td>17.6</td>
<td>71.8</td>
</tr>
</tbody>
</table>

P < 0.009

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**Change in disease activity**

- **Anti-IgE**: Lower UAS values over time
- **Placebo**: Higher UAS values over time

P < 0.0002
We recommend against the long term use of systemic cortisone.

We recommend against the routine use of old sedating first generation antihistamines.
Non sedating H₁-Antihistamine (nsAH)

- If symptoms persist after 2 weeks
- nsAH up dosing (up to 4x)
  - If symptoms persist after 1-4 weeks
  - +Leukotriene antagonist, change nsAH
  - If symptoms persist after 1-4 weeks

+H₂-Antihistamine, Cyclosporine A, Dapsone, anti-IgE
Chronic urticaria is a disabling disease

Treat it until it is gone!

Clinics for Mast Cell-driven Diseases and Dermatological Allergology Lab

www.allergie-centrum-charite.de

Disclosure of Significant Relationships with Commercial Companies and Organizations

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IgE antibody is a requisite mediator of acute urticaria due to food or drug allergy, but less well appreciated is its role in physical urticarias or chronic spontaneous urticaria (idiopathic or autoimmune). A subpopulation of patients with cold urticaria and dermatographism have a disorder that can be passively transferred with plasma that contains IgE, while IgE antibody directed to an antigen in sweat has been reported in a subpopulation of patients with cholinergic urticaria and a positive methacholine skin test. Systemic symptoms can be associated with cold urticaria, particularly hypotension, due to submersion causing a temperature change involving a large surface area. Familial auto-inflammatory cold-dependent disease presents with an urticarial rash associated with fever, myalgia and arthralgia, and leucocytosis. Patients with chronic spontaneous urticaria (idiopathic or autoimmune) have a 40% incidence of accompanying angioedema, but it is rare for additional symptoms to be present. There are exceptions, however, where myalgia and arthralgia (but not true arthritis) accompany urticarial episodes. There is a 25% incidence of antithyroid antibodies; although most are euthyroid, some present with thyroid dysfunction. There is also a high incidence of low titer, positive ANA’s with a speckled pattern in the absence of other signs or symptoms of systemic lupus erythematosus. Yet systemic connective tissue disorders can have urticaria as a manifestation; these include systemic lupus erythematosus, the vasculitis associated with serum sickness, Sjogren’s syndrome, polyarteritis nodosa, Churg-Strauss syndrome, and Wegener’s granulomatosis. However it is rare to have urticaria alone as a presenting symptom of these disorders and the incidence of urticarial vasculitis diagnosed by skin biopsy of patients presenting with chronic urticaria is less than 1 percent. Thus a serologic evaluation searching for connective tissue disorders (rheumatoid factor, anti double-stranded DNA, anti Sm, anti RNP, anti Scl 70, anti Ro, anti La, etc., etc.) is not recommended for routine evaluation of patients with chronic Urticaria. For those with hives lasting over 24 hours, or with myalgia or arthralgia, a C-Reactive Protein, complement C4 and a skin biopsy to rule out vasculitis, should be performed.

References:
Systemic Manifestations of Atopic Urticaria

Allen P. Kaplan, MD

Medical University of South Carolina
Charleston, SC, USA

Urticaria

- Acute
- Physical
- Chronic

Systemic Manifestation

Anaphylaxis

Hypotension
Diarhea

1) Systemic Manifestation
2) Systemic Disease

Anaphylaxis

Skin
Respiratory
Gastrointestinal
Vascular

Urticaria
Angioedema
Stridor
Wheeze
Vomiting
Pain
Diarrhea
Hypotension

A) Typically antigen-dependent, IgE dependent thru IgE receptors
B) Skin involvement as early symptom is >90%
C) Diagnostic consideration: Find the antigen
IgE-Dependent Physical Urticaria

1) Cold Urticaria
2) Dermatographism
3) Solar Urticaria – light-inducible autoantigen
4) Cholinergic Urticaria

1.3.4 – Occasionally associated with hypotension

Cold urticaria

Histamine release in cold urticaria
Diagnostic Consideration

1) Cold Urticaria – Occasionally associated with cold agglutinins or Cryoglobulins
2) Physical Urticarias occur spontaneously and are not associated with systemic diseases
3) Solar Urticaria and photosensitive rashes in SLE are different
Serologic Abnormalities

1) CRP is elevated compared to normal
2) IL-6 levels are increased
3) Metalloproteinase 9 levels are increased
4) Prothrombin fragments 1 + 2 are increased
5) There is no fever, or thrombosis or bleeding
Search for Systemic Disease in Chronic Urticaria

A) Systemic diseases can have urticaria as a manifestation
B) Urticaria can be the presenting symptom of a systemic disease, but it's uncommon
C) What to order, and when

Systemic Diseases with Urticaria or Urticarial Vasculitis

A) Systemic Lupus Erythematosus
   a) Autoimmune
   b) Cutaneous vasculitis
B) Dermatomyositis
C) Microscopic Polyarteritis Nodosa
D) Wegener's Granulomatosis
E) Churg-Strauss Syndrome
F) Rheumatoid Vasculitis
G) Cryoglobulinemia

Cases

A) A 30 yr old male presents with urticaria on a daily basis for 3 months. There is no fever, arthralgia, or myalgia. He is somewhat tired but indicates that he is not sleeping well because of pruritus. There is no other significant history and physical exam is normal except for generalized urticaria
B) A 30 yr old female presents with chronic urticaria for 10 weeks accompanied by angioedema affecting the lips and eyes. When symptoms are prominent she complains of fatigue and joint pain. A prior evaluation by a family physician reveals a sedimentation rate of 16 and a positive ANA at 1:80 titer
Rationale for Doing the Minimum

1) With the exception of idiopathic urticarial vasculitis, the incidence of chronic urticaria being the presenting symptom of a rheumatic disease is less than 1%.
2) Patients with chronic urticaria frequently have a (+) ANA (low titer ~15-20%) and elevated CRP as part of the disorder.
3) Although arthralgia, if prominent, frequently leads to extensive testing for rheumatic diseases, it can be part of the syndrome of chronic urticaria as long as there is no true arthritis.

Rationale for Doing the Minimum

4) Drawing ANA's routinely means that a significant number of patients who have a titer that is less than 1:320 will have tests for anti ds DNA, anti SLA, s (Ro), anti SSB (La), anti Sm, anti RNP, anti SCL-70 and rheumatoid factor and typically none are positive.

Rationale for Doing the Minimum

5) If you miss a connective tissue disease that has presented with chronic urticaria, it will become obvious, and if you knew about it earlier, there is nothing you could have done.
6) Patient A- order CBC, CRP, thyroid function tests and antimyotroid antibodies, and antibody to IgE receptor.
7) Patient B- Tests for systemic disorders other than SLE are unwarranted. An ANA and anti ds DNA are reasonable, but will likely be negative.
Rationale for Doing the Minimum

A skin biopsy is indicated if the patient has fever, palpable purpura, true arthritis, hives lasting >24 hrs. that leave a bruise when they fade. Then serologies for rheumatic diseases are also indicated.
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Plenary Sessions
• Asthma: From Genetics to Treatment
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• Mastocytosis and Mast Cell Activation Syndromes
• Microbiome: A New Window to Health and Allergic Diseases?
• New Concepts in Mast Cell Mediators
• Novel Cytokines in Allergic Diseases
• Obesity and Asthma
• Specific Immunotherapy (SIT)
• WAO Presidential Session

New Horizon Sessions
• Advances in Food Allergy
• Asthma in Children
• Asthma and Co-Morbid Conditions
• Drug Allergy
• Novel Scientific Approaches in Allergic and Respiratory Diseases
• Is Your Patient Immunodeficient (ID)?
• Skin Diseases
• Specific Immunotherapy (SIT) (full day)

University Training Program Sessions
• Cleveland Clinic: An Evidence Based Approach to Diagnosis and Management of Urticaria and Angioedema
• Harvard University: Adverse Drug Reactions and Managements
• Henry Ford Hospital, Georgia Health Sciences University, University of California San Francisco and The University of Michigan: Allergy Prevention. Do Cats and Dogs Feed Infants Microbes?
• Universidad Autonoma de Nuevo Leon: Insect Allergy
• University of South Florida: Rhinolaryngoscopy Hands-on Workshop
• University of Sao Paulo: Allergy and Asthma: Risk Factors, Diagnosis and Treatment
• Wake Forest University: Translational Medicine and Personalized Asthma Management

Collaborating Partner Sessions
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• G2LEN: Severe Allergy & Asthma: A Global Problem
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• NIAID and NHLBI: Standardizing Outcomes in Asthma Clinical Research
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