Urticaria
An Evidence-Based Approach to Diagnosis & Management

April 8, 2015 | Anaheim Convention Center
Session 4: Urticaria: An Evidence-Based Approach to Diagnosis and Management

Learning Objectives

1. Formulate an appropriate diagnostic workup for symptomatology suggestive of chronic urticaria taking into account the potential differential diagnosis.
2. Incorporate into practice evidence-based treatment options and guidelines for managing chronic urticaria that maximize efficacy, minimize adverse effects, and take into account patient quality of life.

Faculty

Richard G. Gower, MD, FACAAI, FAAAAI, FACP
Clinical Associate Professor of Medicine
University of Washington School of Medicine
Principal Investigator
Marycliff Clinical Research
Spokane, Washington

Dr Richard Gower is clinical associate professor of medicine at the University of Washington School of Medicine and on the staff of Sacred Heart Medical Center and Deaconess Medical Center in Spokane.

After receiving his medical degree from the University of Colorado School of Medicine, Denver, Dr Gower completed a residency in internal medicine at the University of Miami Affiliated Hospitals, Miami, Florida. He then completed a fellowship in allergy/clinical immunology and vasculitis at the University of Colorado Medical Center.

Dr Gower is a fellow of the American College of Allergy, Asthma and Immunology (ACAAI), the American Academy of Allergy, Asthma and Immunology, and the American College of Physicians. In 2013, Dr Gower was awarded the ACAAI distinguished fellow award. He is also past president of the ACAAI, Intermountain West Allergy Association Western Society of Allergy, Asthma and Immunology, and Washington State Society of Internal Medicine.

Recently, Dr Gower has been an author of several publications regarding hereditary angioedema and urticaria.

Michael E. Manning, MD
President/Medical Director
Medical Research of Arizona
Allergy, Asthma & Immunology Associates, Ltd.
Scottsdale, Arizona

Dr Michael Manning is president of Allergy, Asthma and Immunology Associates, Ltd., and medical director of the clinical research division, Medical Research of Arizona.

Dr Manning is a graduate of Baylor University, Waco, Texas, and he received his medical degree from the University of Texas Medical School at Houston. He completed an internship and subsequent residency in internal medicine at St. Joseph's Hospital and Medical Center, Phoenix, Arizona, and an allergy and immunology fellowship at Scripps Clinic and Research Foundation, La Jolla, California.

Dr Manning has served as president of the Greater Phoenix Allergy Society, the Arizona State Allergy and Asthma Society, and the Western Society of Allergy, Asthma and Immunology. He is a fellow of the American Academy of Allergy, Asthma and Immunology, and the American College of Allergy, Asthma and Immunology, and a member of the American Thoracic Society and the American College of Physicians.

Dr. Manning has been published in many peer reviewed journals and presented at meetings, conventions, and conferences around the country.
**Faculty Financial Disclosure Statements**

The presenting faculty reported the following:

Dr Gower has affiliations with Genentech (*Advisory Board*); Genentech, Novartis, Roche (*Research*).

Dr Manning has affiliations with Genentech, Dyax, Shire, CSL Behring, Merck (*Speakers Bureau*); Shire (*Advisory Board*); Shire, CSL Behring, Dyax, BioCryst, Teva, Novartis (*Research*).

**Education Partner Financial Disclosure Statements**

The content collaborators at RMEI, LLC have reported the following:

Jacqui Brooks, MBBCh, MRCPsych, has no affiliations with commercial interests to disclose.

Title: Vice President, Medical Strategy
Role: Medical Review

Boris Rozenfeld, MD, has no affiliations with commercial interests to disclose.

Title: Manager, Medical Content and Educational Development
Role: Medical Review

**Suggested Reading List**


SESSION 4
12:30 – 1:45pm
Urticaria: An Evidence-Based Approach to Diagnosis and Management

SPEAKERS
Richard G. Gower, MD, FACAAI, FAAAAI, FACP
Michael E. Manning, MD

Presenter Disclosure Information
The following relationships exist related to this presentation:
► Richard G. Gower, MD, FACAAI, FAAAAI, FACP, has affiliations with Genentech (Advisory Board); Genentech, Novartis, Roche (Research).
► Michael E. Manning, MD, has affiliations with Genentech, Dyax, Shire, CSL Behring, Merck (Speakers’ Bureau); Shire (Advisory Board); Shire, CSL Behring, Dyax, BioCryst, Teva, Novartis (Research).

Off-Label/Investigational Discussion
► In accordance with pmICME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Learning Objectives
• Formulate an appropriate diagnostic workup for symptomatology suggestive of chronic urticaria taking into account the potential differential diagnosis.
• Incorporate into practice evidence-based treatment options and guidelines for managing chronic urticaria that maximize efficacy, minimize adverse effects, and take into account patient quality of life.

Drug List
• Amoxicillin
• Azathioprine
• Cetirizine
• Cimetidine
• Clarithromycin
• Colchicine
• Cylophosphamide
• Cyclosporine
• Dapone
• Diphenhydramine
• Doxapin
• Ephedrine
• Fexofenadine
• Hydroxychloroquine
• Hydroxyzine
• Lansoprazole
• Levocetirizine
• Loratadine
• Methotrexate
• Montelukast
• Mycophenolate mofetil
• Omalizumab
• Prednisolone
• Prednisone
• Ranitidine
• Sulfasalazine

Differential Diagnosis and Diagnostic Workup in CIU
Richard G. Gower, MD, FACAAI, FAAAAI, FACP
Clinical Associate Professor of Medicine
University of Washington
Principal Investigator
Marycliff Clinical Research
Spokane, Washington
Introduction

- Approximately 20% of people experience acute urticaria (AU) during their lifetime
- AU is more common than chronic idiopathic urticaria (CIU)
  - Associated with rapid recovery
  - Identification of etiology helps prevent recurrence
- CIU tremendously impacts quality of life

Definition of Urticaria/Angioedema

- "Urticaria" is umbrella term inclusive of diverse clinical entities
  - **Urticaria**
    - Characterized by wheals, or cutaneous swelling of variable size, surrounding erythema, itching and burning
    - Evanescent over 24 hours without scarring
    - Worsened by scratching
    - Skin usually returns to normal in 1 to 24 hours
  - **Angioedema**
    - Sudden pronounced painful swelling of deep tissue or mucous membrane
    - Slower resolution than wheals – up to 72 hours
- Any area of body may be involved in urticarial angioedema (UA)
  - Common areas are perioral, periorbital regions, tongue, genitalia, and extremities

MW – Case Study

- 57-year-old Caucasian female presents with a 15-year history of chronic persistent hives
- Laboratory evaluation not significant
- Refractory to H1 and H2 antihistamines
- Disruption in quality of life
  - Frequently awakened with hives and pruritus
  - Frustrated
  - Medications caused undesirable side effects

Prevalence of Urticaria

- 10–20% of population experience an episode in lifetime and ~0.1% will develop CIU
- Angioedema presents in 40–50% of CIU cases
  - 10–20% of patients experience only angioedema without wheals
  - 40% exhibit wheals alone
- Up to 40% with CIU lasting longer than 6 months still have urticaria 10 years later
- Autoimmune disturbances present in 40–45% of CIU patients
- Most cases of CIU are idiopathic

Pathophysiology of Urticaria

- Most due to activation of dermal mast cells and basophils
- Release of histamine and other mediators cause local vasodilation, vasopermeability, fibrin deposition, pruritus, and perivascular infiltration by lymphocytes, neutrophils, and eosinophils
- Mediators of wheal formation when injected into the skin:
  - Histamine
  - Leukotrienes C and D
  - Platelet activating factor
  - Bradykinin
  - Substance P
- Minimal endothelial swelling without leukocytoclasia

Some Skin Rashes Mimic Urticaria: “Pseudourticaria”

- Maculopapular exanthems (viral, drug rashes)
- Urticarial dermatitis
- Erythema multiforme
- Insect bite reactions (“papular urticaria”)
- Leukocytoclastic vasculitis (including urticarial vasculitis)
- Polymorphic light eruption
- Some autoinflammatory syndromes (eg, Muckle-Wells)

Algorithm of CIU

CIU

- Cryopyrin-mediated disorders
- Physical urticaria
- Ordinary chronic urticaria
- Contact urticaria
- Schnitzler syndrome

Classification of CIU

- Classification based on:
  - Duration
  - Inducing factors (induced vs spontaneous) – presence or absence

- Duration
  - Acute <6 weeks
    - Cause identified in 15–20% of patients
    - >90% chance of remission
  - Chronic >6 weeks
    - Cause identified in <5% of cases
    - ≤50% chance of remission

Classification of Urticaria Subtypes Based on Different Inducing Factors

<table>
<thead>
<tr>
<th>Types</th>
<th>Subtypes</th>
<th>Definition / Inducing factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous urticarias</td>
<td>Acute spontaneous urticaria</td>
<td>Spontaneous wheals and/or angioedema &lt;6 weeks</td>
</tr>
<tr>
<td></td>
<td>Chronic spontaneous urticaria</td>
<td>Spontaneous wheals and/or angioedema &gt;6 weeks</td>
</tr>
<tr>
<td>Physical urticarias</td>
<td>Cold contact urticaria</td>
<td>Cold exposure</td>
</tr>
<tr>
<td></td>
<td>Delayed pressure urticaria</td>
<td>Delayed pressure (wheals arising with 2–12 h latency)</td>
</tr>
<tr>
<td></td>
<td>Heat contact urticaria</td>
<td>Induced heat</td>
</tr>
<tr>
<td></td>
<td>Solar urticaria</td>
<td>Solar heat exposure</td>
</tr>
<tr>
<td></td>
<td>Contact urticaria</td>
<td>Contact with substance (latex, animal dander, etc.)</td>
</tr>
<tr>
<td>Physical urticarias</td>
<td>Aquagenic urticaria</td>
<td>Skin reaction to water</td>
</tr>
<tr>
<td></td>
<td>Cholinergic urticaria</td>
<td>Increased body core temperature due to physical exercise, spicy food</td>
</tr>
<tr>
<td>Other Inducible urticarias</td>
<td>Aquagenic urticaria</td>
<td>Physical exercise</td>
</tr>
</tbody>
</table>

Exacerbants of Urticaria

- Exacerbants
  - Non-steroidal anti-inflammatory drugs (NSAIDs)
  - Certain “pseudoallergens” in foods (controversial)
  - Alcohol consumption
  - Viral infections
  - Stress / fatigue
  - Heat / pressure

- Causes of many cases of CIU still remain unclear, but weight of evidence indicates these are NOT causes:
  - “Stress”
  - Food allergy
  - Chronic infections including Helicobacter pylori
  - Drug allergy
  - Environmental pollution

Autoimmune Urticaria

- Clinically and histologically indistinguishable from non-autoimmune CIU
- 40–45% of CIU is autoimmune
- Frequently more aggressive, treatment-resistant course
- Histologically, activated eosinophils more prominent in older lesions of non-autoimmune patients

Autoantibody-Associated CIU

- 25–50% of CIU patients have C’ activating IgG1 and IgG3 autoantibodies with histamine-releasing functional activity vs high-affinity IgE receptor FcεR1 or less commonly to IgE
- IgG antibody to α subunit of FcεR1 (35–40%)
- IgG antibody to α subunit of IgE (5–10%)
Characteristics of Dermographism

- Common physical urticaria
- Frequently overlooked
- Generalized pruritus and wheals, aggravated by scratching, rubbing, or tight clothing
- Mucous membranes unaffected, no angioedema
- Evaluation – none indicated
- Treatment – non-sedating antihistamines

Cholinergic Urticaria

- Wheals begin on neck, trunk; spread to face and extremities
- Triggered by:
  - Exercise, sweating, hot showers, strong emotion
  - Exercise induction is reproducible; requires increase in core body temperature
- Small punctate urticarial lesions few millimetres in diameter with erythema
- Occasional confluence of lesions and associated angioedema
- Histamine released within circulation after exercise challenge
- Evaluation – none indicated

Delayed Pressure Urticaria

- Concurrent with CIU in ~ 40% of cases
- Common distribution sites – shoulders, waist, soles, palms
- Swellings frequently last >24h, often tender and painful; arthralgia common
- Diagnosis – firm application of rod tip to uninvolved skin for 2 min
  - (+) result = red papule in 3–5 hours
- Evaluation – none indicated
- Treatment
  - Antihistamines disappointing
  - Dapsone*, hydroxychloroquine* may be tried
  - High-dose prednisone* effective but condition is chronic

Cold Contact Urticaria

- Wheals due to contact with cold stimulus
- Predominance on unclothed areas – hands, face
- Can be generalized with anaphylactic-like symptoms (hypotension) with swimming
- A sub-group is IgE-mediated and can be passively transferred
- Evaluation – cryoglobulins and cold agglutinins sought but rarely found

Contact Urticaria

- Eliciting substance causes local wheal and flare within minutes of application to skin
- May be associated with systemic symptoms – rhinitis, conjunctivitis, bronchospasm, angioedema, anaphylaxis
- Classified as immunological, non-immunological
- Due to release of histamine and eicosanoids, especially prostaglandin D2 from dermal mast cells

Drug Reactions and Urticaria

- Penicillin allergy
  - Drug or metabolite causes wheals by interaction with IgE on cutaneous mast cells
- NSAID reactions
  - Non-IgE mediated reactions that depend on drug metabolism with resultant mast cell activation
- Opiates
  - Direct mast cell degranulation by drugs
- Radiocontrast reactions
  - Osmotic cell degranulation and alternative C' pathway activation
Diagnostic Approach in Urticaria

- **Goals**
  - Identify underlying cause / trigger
  - Identify type and subtype
  - Improve outcomes and prevent recurrence
- **Limited initial evaluation indicated**
  - Unless history or exam dictate otherwise
  - R/O systemic disease by specific tests if indicated
  - Individualize and evaluate when chronic, severe, and/or persistent

Diagnostic Approach: Acute Urticaria

- Detailed history and exam essentials
  - URI/viral infections most common etiology in children
  - Foods, drugs (ie, antibiotics and NSAIDs) in adults and children
  - Immunologic and provocation tests to identify causative food or drug
- Many cases require no evaluation – cause evident
- Skin prick / serum IgE tests may support diagnosis

Diagnostic Approach: CIU

- Exclude comorbid disorders and physical urticaria (ie, dermographism)
- Overall duration of CIU longer in patients with an ↑ disease severity, angioedema, (+) ASST, or comorbidity with physical urticaria
- Identify underlying cause
  - Most either autoimmune or chronic spontaneous type
  - ~1/3 of CIU patients have NSAID-exacerbated UA
- ACE inhibitors/ARB medications account for an increasing % of cases
- Disease severity evaluated by Urticaria Severity Score (UAS)
- Targeted evaluation – consensus*

Diagnostic Approach: CIU/Angioedema

- Blood tests
  - CIU/A: CBC, liver function tests, ESR/CRP, cryoglobulins, TSH
  - Angioedema only: C4 and C1 INH quantitative and functional
- ASST test to screen for autoantibodies to IgE receptor/IgE
- Physical stimulation tests for suspected physical urticaria (ie, ice cubes/cold H2O, exercise challenge test for cholinergic/exercise-induced urticaria)
- Skin biopsy – confirm urticarial vasculitis or Schnitzler syndrome in patients with poor response to antihistamines
- Quality of life and evidence-based assessment tools

Diagnosis of Autoimmune Urticaria

- Autoimmune urticaria suspected if response to regular antihistamine treatment is poor
- Serum thyroid antibodies suggest autoimmune urticaria
- In-vitro testing
  - Consists of demonstrating the ability of patient’s serum to activate donor basophils* by release of mediators such as histamine
- ASST helpful
  - (-) result effectively rules out autoimmune urticaria
  - (+) result requires confirmation by in-vitro testing

* This test is now commercially available at National Jewish Laboratories (ARUP)

Autologous Serum Skin Test

- **Significance of negative ASST**
  - Essentially R/O autoimmune urticaria
- **Significance of positive ASST**
  - Indicates presence of autoreactivity in serum
  - In-vitro confirmation required before identified as due to functional autoantibodies
Quality of Life and Patient Reported Outcomes

“CIU is more than an annoying disease”

• Progress made in the last 20 years on CIU impact
  – Classical symptoms affect sleep, concentration, and life activities, and cause embarrassment
  – Exacerbations change habits and lifestyle

• Patient Reported Outcome questionnaires measured in literature – HRQoL and UAS
  – Quality of life due to CIU shown equal to that experienced by patients with triple CAD awaiting bypass surgery

• CIU – source of economic cost due to absenteeism and cost of medications


Management Approaches in Chronic Idiopathic Urticaria

Michael E. Manning, MD
President/Medical Director
Medical Research of Arizona
Allergy, Asthma & Immunology Associates, Ltd.
Scottsdale, Arizona

Jon – Case Study

• History of Present Illness
  – Jon is a 34-year-old male with an 18-month history of hives
  – He describes hives daily or every other day
  – He will awaken at night due to itching
  – Denies angioedema
  – He has tried OTC antihistamines and has been on prednisone about every 3 months
  – Denies the use of combination of medications

• Past Medical History
  – Seasonal allergic rhinitis
  – Oral itching due to melons

• Review of Systems
  – Itchy skin
  – Otherwise, unremarkable

• Current Medications
  – Ibuprofen 400 mg QOD on average

• Family History
  – No family history of hives

• Physical Exam
  – Generalized urticarial lesions

Jon – Case Study (cont.)

• Initial Treatment
  – Started on a combination, as he states that he “is at his wits’ end”

• Tx combination
  – Fexofenadine 180 mg every morning
  – Ranitidine 150 mg twice a day
  – Cetirizine 10 mg at bedtime
  – Diphenhydramine as needed

Jon – Case Study (cont.)

• 2-week Follow-up
  – Jon notes that he is about 50% better
  – Using diphenhydramine about 4 times a week
  – He is more positive but is still not satisfied
  – Treatment
    • Fexofenadine and cetirizine both doubled
    • Montelukast* 10 mg twice a day is added to his current routine
  – Follow-up in 2 weeks

* Not FDA-approved for CIU
Jon – Case Study (cont.)

• 2-week Follow-up
  – No significant improvement
  – Feels like he is getting worse
  – He is near tears and states that his hives are interfering with work and his social and family life
• Treatment
  – After discussing the risks and benefits of alternative options, he agrees to proceed with omalizumab 300 mg every 4 weeks

Jon – Case Study (cont.)

• 4-week Follow-up
  – Returns for his second injection
  – Reports that he has been hive-free for the last 3 weeks
• Treatment
  – Omalizumab is continued at 300 mg every 4 weeks and all of his other medications are weaned and discontinued

Management of CIU

• Guidelines and practice parameters are available to help in the management of CIU
• Many of the therapies mentioned are either not FDA-approved for CIU or are used at non-FDA approved doses

Management of Urticaria

Basic Considerations

• Goals of Care
  – Elimination/avoidance of the causes/triggers/stimulus
  – Symptomatic pharmacologic treatment by reducing mast cell mediator release and/or effect of these mediators
  – Induction of tolerance
  – Complete symptomatic control

Potential Triggers or Exacerbating Agents

• NSAIDs • Tobacco • Alcohol • Spicy foods
• Overheating with strenuous physical exercise
• Increasing body/skin temperature
• Hot showers • Saunas • Jacuzzi • ↑ Ambient temperatures
• Tight-fitting clothing or shoes • Pressure on the skin

Management of Urticaria

Identification & Elimination/Avoidance of the Stimulus Based on Recent EAACI Guidelines

• Drugs
  – Eliminate or substitute, stop NSAIDs
• Physical Stimuli
  – Delayed pressure, cold, heat
• Eradication of Infectious Agents
  – H. pylori
  – Bowel parasites
• Treatment of Inflammatory Process
  – Gastritis/reflux esophagitis
• Reduction of Functional Autoantibodies
• Dietary Management
  – Food allergies/ pseudoallergens
• Induce Tolerance
  – Daily cold shower/UV-A
Symptomatic Pharmacologic Treatment

• **2nd generation H_{1} antihistamines**
  – Preferred as first-line treatment
  – Taken continuously, **NOT** as needed
  – Recommend increase to 4 times the FDA-approved dosage vs mixing different H_{1} antihistamines
  – Do **NOT** recommend more than 4 times the dose
  – Strongly recommend **NOT** using 1st generation H_{1} antihistamines, especially in children

American Academy of Allergy Asthma & Immunology

**Antihistamine Refractory Urticaria**

• **First line**
  – Modern 2nd generation antihistamines
  – If symptoms persist after 2 weeks →

• **Second line**
  – Increase dosage up to fourfold of modern 2nd generation antihistamines
  – If symptoms persist after 1–4 further weeks →

• **Third line**
  – Add on to second line
  – Omalizumab or cyclosporine* or montelukast*
  – Short course (max 10 days) of corticosteroids* may also be used at times if exacerbations demand this

*Not FDA-approved for CIU


**Antihistamine Refractory Urticaria**

– Recommend trial of **omalizumab** as add-on therapy
– Recommend trial of **cyclosporine*** as add-on therapy
– Suggest trial of **montelukast***
– Recommend against long-term use of systemic steroids
– Suggest trial of short course of corticosteroids* as third-line therapy of option for acute exacerbation
– Suggest same treatment algorithm for children, and pregnant/lactating women

*Not FDA-approved for CIU

**American Academy of Allergy Asthma & Immunology**

**Joint Task Force on Practice Parameters: 2014 Update**

- **Step 1**
  - Monotherapy with 2nd generation H1 antihistamine
  - Avoid identified triggers and physical factors (if physical urticaria is present)
- **Step 2**
  - Increase dose of antihistamine (step 1)
  - Add another 2nd generation antihistamine
  - Add H2 antihistamine
  - Add leukotriene receptor antagonist
  - 1st generation antihistamine at night
- **Step 3**
  - Initiate and advance the dose of a potent antihistamine such as hydroxyzine or doxepin* as tolerated
- **Step 4**
  - Add an alternative agent
    - Omalizumab
    - Cyclosporine*
    - Other anti-inflammatory, immunosuppressive, or biologic agents

* Not FDA-approved for CIU

---

**Treatment Protocol Step 1**

- Initiate monotherapy with 2nd generation H1 antihistamine
- Avoidance of any triggers identified and any relevant physical factors if physical urticarial syndrome is present

---

**Treatment Protocol Step 2**

- Proceed with one or more of the following:
  - Increase the dose of the 2nd generation antihistamine used in step 1
  - Add another 2nd generation antihistamine
  - Add an H2 antihistamine
  - Add a leukotriene receptor antagonist
  - Add a 1st generation H1 antihistamine to be used at night

---

**Treatment Protocol Step 3**

- Initiate and advance the dose of a potent antihistamine such as hydroxyzine or doxepin* as tolerated

---

**Treatment Protocol Step 4**

- Add an alternative agent
  - Omalizumab
  - Cyclosporine*
  - Other anti-inflammatory, immunosuppressive, or biologic agents

---

**Treatment Considerations**

- Have the patient return every 2 weeks while adjusting the treatment approach
- Multiple factors are involved when selecting an alternative agent for the treatment of refractory CIU
- Many of the alternative or fourth step treatment options require close monitoring

* Not FDA-approved for CIU
Treatment of Chronic Urticaria

H1 Antihistamines

- 2nd generation H1 antihistamines are the mainstay for urticaria
- Comparative efficacy of 2nd generation H1 antihistamines (limited studies)
  - Cetirizine 10 mg vs fexofenadine 180 mg
  - Cetirizine and levocetirizine vs other non-sedating antihistamines for efficacy
- Sedation
  - No relevant difference in sedative and impaired psychomotor function among cetirizine, levocetirizine, and loratadine. Fexofenadine has none.
- 1st generation H1 antihistamines
  - Clearer efficacy similar to 2nd generation H1 antihistamines
  - Sedation and significant psychomotor impairment occurs
  - Not recommended as first-line agents since 2nd generation H1 antihistamines are safe, effective, cost-effective, and accessible
  - Cetirizine and levocetirizine contraindicated in end-stage renal disease. Doses adjusted based on creatinine clearance. Fexofenadine also requires renal dose adjustment (OCO + 60)
- Limited-dose QOD in liver failure or CrCl < 30 ml/min
- Autimmune urticaria responds poorly to H1 antihistamines

Treatment of Chronic Urticaria

H2 Antihistamines

- Most studies done with cimetidine
  - Effectiveness believed to due to ability to inhibit some cytochrome p450 isoenzymes involving metabolism of 1st generation antihistamines
  - Higher plasma concentration of antihistamine results
- Low quality of evidence for use of H2 and H1 antihistamines
  - No real advantage over H1 antihistamine alone
- No significant side effects with H2 antihistamines
- There are a variety of drug interactions with H2 antihistamines, more prominent with cimetidine
  - May need to adjust dose of concomitant medications

Management of Chronic Urticaria

What If Antihistamines Don’t Work?

- Add montelukast 10 mg daily
  - It helps some but not all patients and adverse effects are rarely a problem
- Add doxepin 25 mg at night
  - This tricyclic is best known as an antidepressant but is a very potent H1 and H2 antihistamine, causing sedation
  - It should not be given with other antihistamines
- Prednisolone
  - Short tapering courses commencing 30 mg daily
  - Useful to deal with the occasional temporary flare-up
- Cyclosporine
  - Best known for its effectiveness in autoimmune urticaria
  - Also effective in non-autoimmune chronic urticaria
- Intolerance or ineffectiveness of cyclosporine
  - Methotrexate 10-25 mg orally once weekly
  - Mycophenolate mofetil 1–2 g daily
- Corticosteroids
  - Oral corticosteroids (OC) clinically effective for H1 antihistamine-resistant urticaria – controlled studies lacking
  - Side effects associated with long-term treatment
    - OC should be used for short periods at minimal dose
    - No consensus on dose/duration
  - One protocol suggests prednisone 10–5 mg once a day with a gradual decrease of 1 mg/week
  - Attempt to find alternative agents to control urticaria
  - Should only be used intermittently
  - Monitor for adverse effects

Treatment of Chronic Urticaria

Corticosteroids

- Oral corticosteroids (OC) clinically effective for H1 antihistamine-resistant urticaria – controlled studies lacking
- Side effects associated with long-term treatment
  - OC should be used for short periods at minimal dose
  - No consensus on dose/duration
- One protocol suggests prednisone 10–5 mg once a day with a gradual decrease of 1 mg/week
- Attempt to find alternative agents to control urticaria
- Should only be used intermittently
- Monitor for adverse effects

The treatment of chronic urticaria often involves a combination of medications to control symptoms. H1 antihistamines are typically the first-line therapy, with some patients requiring additional treatment. H2 antihistamines may be used when H1 antihistamines are ineffective or have adverse effects. Corticosteroids can be effective in severe cases, but they should be used cautiously due to the risk of side effects. Other options include leukotriene receptor antagonists and immunosuppressive agents, such as cyclosporine, which may be effective in autoimmune urticaria. It is important to monitor patients closely for adverse effects and adjust treatment as needed.
Treatment of Chronic Urticaria

Immunosuppressive Agents

- **Other immunosuppressive agents**
  - Methotrexate*, cyclophosphamide*, azathioprine*, mycophenolate mofetil*, dapsone*, hydroxychloroquine*
  - Used to treat H₁ antihistamine-resistant CIU
  - Experience limited to case reports / uncontrolled single-center trials
  - Need to monitor laboratory parameters/vision depending on the medication
  - Must weigh risk-benefit with the patient

* Not FDA-approved for CIU


Biological Agents

- **Omalizumab**
  - Recent studies indicate efficacy in antihistamine-unresponsive CIU
  - Efficacy and side effect profiles suggest omalizumab has a role in refractory CIU
  - Has the most published data on efficacy in CIU
  - Limitations include high cost and potential anaphylaxis


Omalizumab and Chronic Urticaria

- Mechanism of action not understood
- Indicated for adults and adolescents (≥12 years of age) with CIU who remain symptomatic despite H₁ antihistamine treatment (FDA approved March 2014)
- Dose 150 or 300 mg every 4 weeks
- Maximum suppression of free IgE was observed 3 days following the first subcutaneous dose
- Best studied agent for treatment of refractory CIU
- Duration of therapy not known at this time


Omalizumab Safety

- Boxed warning re: anaphylaxis
- Local injection site reactions
- Possible malignancy association in initial studies for another indication. Recent 5 year safety study shows no association
- Discontinue if the constellation of fever, arthralgia, and rash is present

Alternative Agents

Treatment Considerations

- Have the patient return every 2 weeks while adjusting the treatment approach
- Multiple factors are involved when selecting an alternative agent for the treatment of refractory CIU
- Many of the alternative or fourth step treatment options require close monitoring

Leukotriene receptor antagonist (montelukast)*
Doxapram*
Corticosteroids*
Cyclosporine*
Methotrexate*
Mycophenolate mofetil*
Omalizumab
Dapsone*
Sulfasalazine*
Hydroxychloroquine*
Colchicine*
Cyclophosphamide*
IVIG*
Vitamin D*

* Not FDA-approved for CIU
### CIU Diagnosis Summary

- **Differential diagnosis**
  - Exclude comorbid conditions and physical urticarias
- **Diagnostic workup**
  - CBC with differential
  - ESR and CRP
  - Cryoglobulins
  - TSH
- **Quality of life assessment**

### CIU Therapy Summary

- **2nd generation H<sub>1</sub> antihistamine**
  - Used with dose escalation to 4x/day as needed
- **Addition of H<sub>2</sub> antihistamine or leukotriene antagonists**
  - Evidence to recommend next
  - European guidelines eliminated H<sub>2</sub> antihistamines
  - Retained in American guidelines
- **Anti-inflammatory, immune suppressants, & modulators**
  - Consider when resistance to above agents (~50% of patients)
- **Omalizumab and cyclosporine**
  - Greatest degree of efficacy
  - Omalizumab – much better safety profile; more costly
- **Dapsone**
  - Efficacious when neutrophil dominant skin biopsy
  - Routine biopsy – NOT RECOMMENDED

*Not FDA-approved for CIU*