The Management of Atopic Dermatitis & Urticaria

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• Dr. Gupta has provided no disclosures.

Lecture Objectives
• Discuss epidemiology & background
• Review the pathophysiology
• Describe the clinical presentation
• Review the differential diagnosis & work-up
• Discuss the basics of management
Atopic Dermatitis

Epidemiology
- Prevalence is 10-30% in children and 2-10% in adults
  - 2-3 fold increase over the last 3 decades
- Highest prevalence
  - High-income
  - Urban populations

Pathogenesis

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Pathogenesis

- Genetics
  - Two major gene sets:
    - Genes encoding epidermal proteins
      - Filaggrin
    - Genes encoding proteins with immunologic functions not specific to skin
      - High-affinity IgE receptor
      - Toll-like receptor-2

- Epidermal barrier impairment
  - Filaggrin
    - Filaggrin mutations lead to disruption of epidermal homeostasis
    - Filaggrin expression downregulated
      - Th2 cytokines
      - pH
      - Bacterial infections
  - Intrinsic inflammation
    - Underlying immunologic dysfunction
    - Scratching

- Environmental factors
  - Allergens
  - Bacterial colonization/infections
  - Irritants
    - Soaps, detergents
Environmental Factors

• Allergens
  – Role in atopic dermatitis is debated
  – Likely not causative but allergic sensitization occurs
• Barrier impairment → Penetration of allergens → Immune response → IgE mediated skin allergies

Environmental Factors

• Microbial Colonization
  – S. aureus colonization in >90% of AD patients
  • Down-regulation of antimicrobial peptides
  • Increased bacterial adherence
  – Stimulates inflammation
  – Leads to IgE-mediated sensitization
  – Secondary infections

Environmental Factors

• Irritants
  – Soap/detergents
  • Increase the skin pH
  – Down-regulates filaggrin
  – Worsening epidermal impairment
  – Increase in transepidermal water loss
  – Over drying of the skin
  – Itch → Scratching → Increased inflammation
Clinical Presentation

- “Itch that rashes”
- Hallmark of AD is intense pruritus
  - Worse in evening
- Scratching and rubbing lead to:
  - Worsening of the rash
  - Excoriations
  - Thickening of plaques
  - Secondary infections

Clinical Presentation

- Classic Triad
  - Allergies
  - Atopic Dermatitis
  - Asthma
Clinical Presentation

- Varies with age of patient
  - Infantile
    - <2 years of age
  - Childhood
    - 2-12 years of age
  - Adolescent/Adulthood
    - >12 years of age
  - Senile
    - >60 years of age

Clinical Presentation

- Infantile
  - Usually within the second month of life
  - Edematous papules and vesicles located on:
    - Cheeks
    - Scalp
    - Neck
    - Extensor surfaces of extremities
    - Trunk
  - Spares diaper area

Clinical Presentation

- Infantile
  - Edematous papules and vesicles located on:
    - Cheeks
    - Scalp
    - Neck
    - Extensor surfaces of extremities
    - Trunk
  - Spares diaper area
Clinical Presentation

- Childhood
  - Thickened pink plaques with accentuation of skin lines (lichenification) without exudate located on:
    - Antecubital fossae
    - Popliteal fossae
    - Head
    - Neck
    - Wrists
    - Ankles
  - Diffuse xerosis is pronounced in childhood AD

Clinical Presentation

- Childhood

Clinical Presentation

- Childhood

Clinical Presentation

- Childhood
Clinical Presentation

- Adult/Adolescent
  - Similar to childhood AD with lichenified plaques affecting flexural sites.
  - Adults may present with “site specific” involvement:
    - Eyelid dermatitis
    - Hand dermatitis
    - Dyshidrotic eczema
    - Nummular eczema
    - Nipple eczema
Clinical Presentation

- Adulthood/Adolescent

Clinical Presentation

- Senile
  - Characterized by diffuse xerosis
  - Typically do not have “classic” AD lesions
  - Pruritus is hallmark feature

Diagnostic Criteria

- Must have:
  - A history of atopic dermatitis
  - History of atopic dermatitis in a first-degree relative
  - History of atopic dermatitis in a first-degree relative

*Original 1991 guidelines also included the cheeks in young children.*
**Associated Features**

- Xerosis
- Ichthyosis vulgaris
- Keratosis pilaris
- Palmar and plantar hyperlinearity
- Dennie-Morgan lines
- Periorbital darkening
- Follicular prominence
- White dermographism

**Complications**

- Infections
  - Impetiginization
  - S. aureus colonization
  - Eczema herpeticum
    - Dissemination of HSV infection in eczematous skin
    - Associated with fever, malaise, and lymphadenopathy
    - Bacterial superinfections
  - Molluscum contagiosum
    - AD predisposes to widespread

[Link to clinical guidance: http://www.pcds.org.uk/clinical-guidance/eczema-eczema-herpeticum]
Complication

- Ocular complications
  - Acute conjunctivitis
  - Allergic conjunctivitis
  - Atopic keratoconjunctivitis
    - Ocular itching, burning, discharge with blepharitis
  - Vernal keratoconjunctivitis
    - Cobblestone-like papillae on upper palpebral conjunctiva
  - Subcapsular cataracts
  - Keratoconus

Histopathology

- Acute
  - Marked spongiosis
  - Vesicles
  - Perivascular lymphocytes
- Chronic
  - Irregular or regular acanthosis
  - Less inflammation and spongiosis

Differential Diagnosis

<table>
<thead>
<tr>
<th>Chronic Dermatoses</th>
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<tbody>
<tr>
<td>Seborrheic dermatitis</td>
<td>Common</td>
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<tr>
<td>Contact dermatitis (allergic or irritant)</td>
<td>Common</td>
</tr>
<tr>
<td>Psoriasis (especially palmoplantar)</td>
<td>Common</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Infections and Infestations</th>
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<tbody>
<tr>
<td>Scabies</td>
<td>Common</td>
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<tr>
<td>Dermatophytosis*</td>
<td>Common</td>
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<tr>
<th>Malignancies</th>
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<tr>
<td>Mycosis fungoides and Sézary syndrome</td>
<td>Uncommon</td>
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</table>
**Treatment**

- Management components:
  - **Avoidance** of irritants, allergens, trigger factors and microbial agents
  - **Repair epidermal barrier**
    - Emollients
    - Anti-inflammatory therapy
    - Adjunctive therapies

**Avoidance of Triggers**

- Patch test: Avoid exposure to allergens
  - Avoid harsh soaps
    - Recommend Dove unscented, Cetaphil, CeraVe wash
  - Wool and other rough clothing
  - Cigarette smoke
  - Emotional stress

**Treatment**

- Repair skin barrier
  - Ointments: Vaseline and Aquaphor
    - Burn less when applied to dry skin
  - Ceramide-Containing creams
    - CeraVe
  - Soak and Smear: 10-20 minute lukewarm baths, pat dry with immediate application of corticosteroid cream or emollient
  - Bleach soaks (pool baths): decrease S. aureus colonization
    - ½ cup unscented bleach to full bath tub
Treatment

- Topical corticosteroids
  - Mainstay of treatment
  - 1st line in acute flares
  - Consider strength and vehicle of corticosteroid
    - Low potency for face
    - Mid to high potency for body

- Topical calcineurin inhibitors
  - Tacrolimus and pimecrolimus
    - Used in children older than 2 years old
    - Useful for face and intertriginous areas
    - Used in conjunction with topical corticosteroids for maintenance therapy
- Crisaborole
  - Phosphodiesterase-4 inhibitor
  - Children older than 2 years old and adults with moderate to severe AD

- Phototherapy
  - UVA and narrowband UVB is used for AD
    - 2-3 visits per week for UV therapy in light booth
    - Risk of burn, premature aging and skin cancer
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Naeha Gupta, DO, MS

**Treatment**

- **Systemic anti-inflammatory therapy**
  - Severe refractory cases of AD
    - Cyclosporine
    - Azathioprine
    - Mycophenolate mofetil
    - Methotrexate

- **Adjunctive therapy**
  - Antihistamines: diphenhydramine, doxepin, hydroxyzine
    - Break the “itch-scratch cycle”

- **Biologic therapy**
  - Dupilumab
    - Injectable monoclonal antibody to IL-4 receptor with signaling modulation of IL-13
    - AD in adults
Summary

- The etiology of AD is complex and multifactorial
- The clinical presentation changes based on the age of onset
- Avoidance of allergens and irritants is important in management
- Topical corticosteroids are first line therapy for flares
  - Choose corticosteroids appropriately based on location treating
- For refractory cases consider systemic therapies

Urticaria

Epidemiology

- Urticaria may present at any age
- Estimated to have an overall lifetime prevalence of 10-25%
- Chronic urticaria is more common in females (2:1)


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Urticaria

• Term used for recurrent whealing of the skin
  – Also encompasses angioedema

Urticaria

• Wheals
  - Superficial dermal swelling
  - Pale center
  - Pruritic
  - Individual lesions last < 24 hours

Urticaria

• Angioedema
  – Deep swelling of the skin/mucosa
  – Painful or burning
  – No color change
  – Less well defined
  – Can last 2-3 days
  – Can affect mouth, GI tract, & respiratory tract
Pathophysiology

- Mast cell: primary effector cell
  - Express high affinity IgE receptor (and non-IgE receptors)
  - Various stimuli bind receptors
    - Immunologic
    - Non-immunologic

Immunologic
- IgE mediated
  - Autoantibodies
  - Type I hypersensitivity reaction

Non-immunologic
- Cause direct release of mast cell mediators
  - Quinine
  - Polymyxin B
  - Tubocurarine
  - Radiocontrast dye
  - Aspirin & NSAIDs
  - Tartrazine

- Cause direct release of mast cell mediators
  - Opiates
  - Polymyxin B
  - Tubocurarine
  - Radiocontrast dye
  - Aspirin & NSAIDs
  - Tartrazine

Degranulation - release of mediators
- Mediators bind receptors of post-capillary venules
  - Vasodilation
  - Inflammation
  - Increased permeability and leakage of plasma

Acute vs. Chronic Urticaria

- Acute Urticaria
  - Repeated appearance of wheals < 6 weeks
- Chronic Urticaria
  - ≥ 6 weeks
  - Occurring at least twice a week

Acute Urticaria

Chronic Urticaria
Chronic Urticaria

- Spontaneous “Ordinary” Urticaria
  - Often appear in the evening & are present on waking
  - 60% of chronic urticaria
    - Autoimmune
    - Pseudoallergens
    - Infections
    - Idiopathic

Chronic Urticaria

- Inducible Urticarias
  - Induced by exogenous physical stimulus
  - 35% of chronic urticaria
  - Location & history
  - Can occur in association with spontaneous urticaria

Causes of Inducible Urticaria

Physical Urticarias
- Mechanical Stimuli
- Temperature Changes
- Sweating & Stress
- Sun (Solar)
- Water (Aquagenic)

Contact Urticaria

Chronic Inducible Urticaria

• Physical Urticarias
  - Dermatographism
    - Most common of the physical urticarias
      - 10% of the general population
    - Linear wheals at sites of scratching or friction
    - No association with systemic disease, atopy, food allergies, or autoimmunity
    - Test: Gentle stroking of the skin
Chronic Inducible Urticaria

• Physical Urticarias
  – Delayed Pressure Urticaria
    • Sites of sustained pressure
      – Waistline, Socks, Shoes
    • Test: 5lb. weight to the thigh or back for 20 min.: wheal occurs in 30 minutes to 8 hours

Chronic Inducible Urticaria

• Physical Urticarias
  – Cholinergic Urticaria
    • Due to increased body temperature
      – Within 15 min. of physical exertion, hot bath, emotional stress, alcohol, or spicy food
    • Characteristic monomorphic papular wheals (2-3mm)
    • Prominent on upper body
    • Test: Increase body temp (i.e. physical exertion)

Chronic Inducible Urticaria

• Physical Urticarias
  – Adrenergic Urticaria
    • Distinguished from cholinergic urticaria by the presence of halos of blanched vasoconstricted skin surrounding small pink wheals
    • Induced by sudden stress
      – Increased serum catecholamines
    • Tx: Propanolol
    • Test: Intradermal injection of norepinephrine
Chronic Inducible Urticaria

- Physical Urticarias
  - Cold Urticaria
    - Occurs within minutes of exposure
    - AD familial variant
    - Avoid cold baths & swimming - potential risk of anaphylaxis
    - May be assoc. with cryoglobulinemia
    - Test: Ice cube on arm
      - 30 seconds to 20 minutes

Chronic Inducible Urticaria

- Physical Urticarias
  - Aquagenic Urticaria
    - Contact with water of any temperature
    - Resembles cholinergic urticaria
    - Upper body and last less than 1 hour

Chronic Inducible Urticaria

- Physical Urticarias
  - Solar Urticaria
    - Within minutes of UV exposure
    - Exact mechanism is unknown
    - May be triggered by exogenous substance (i.e. medications)
    - Test: Phototesting

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**Chronic Inducible Urticaria**

- **Contact Urticaria**
  - Percutaneous penetration of the urticant
  - Development of urticaria at the site of contact within minutes
    - Resolve within 2 hours
  - Can lead to anaphylaxis
  - Tx: NSAIDS (Prostaglandins)

**Immunologic** (i.e. IgE dependent) **Non Immunologic** (i.e. Irritant)
- Environmental allergens (i.e. grass, foods)
- Latex glove allergy
- Due to direct effects of urticants on blood vessels
- Usually plant toxins containing histamine

**Differential Diagnosis**

- **Urticaria**
  - Urticarial vasculitis
  - Urticarial drug eruptions
  - Eosinophilic cellulitis
  - Bullous pemphigoid
  - Schnitzler’s Syndrome
  - Periodic fever syndromes

- Think of alternative diagnosis if:
  - Lesions last >24 hrs
  - Associated fevers or arthritis
  - Associated pain/burning
  - Resolve with pigmentation changes

**Urticarial Vasculitis**

- Immune complexes
- Lesions last longer than 24 hours
- Painful/burning sensation
- Evidence of leukocytoclastic vasculitis on biopsy

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Diagnosis of Urticaria

- History: Duration, frequency, occupation/leisure activities
  - Duration
    - > 24 hours: Consider biopsy (urticarial vasculitis)
    - <1 hour: Consider physical challenge
    - < 2 hours and localized: Consider contact challenge
- Review of Systems: Symptoms of anaphylaxis
  - i.e. respiratory distress, nausea, abdominal pain

Diagnosis of Urticaria

- Episodes occurring less than 6 weeks
  - Acute urticaria does not warrant lab testing
  - Majority of patients have mild disease that responds to antihistamines

Diagnosis of Urticaria

- Chronic Urticaria Laboratory Work-up
  - Complete Blood Count (CBC)
    - Eosinophilia
  - Elevated Sedimentation Rate (ESR)
    - Elevated in periodic fever syndromes & urticarial vasculitis
  - Thyroid stimulating hormone (TSH) & Thyroid autoantibodies
    - Treatment does generally not affect the course

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Diagnosis of Urticaria

- Further Investigations
  - Complete Metabolic Panel (CMP)
  - Antinuclear antibody (ANA)
  - Epstein-Barr virus (EBV)
  - Hepatitis B Surface Antigen/ Hepatitis C
  - Urinalysis
  - Cryoglobulins

Diagnosis of Urticaria

- Referral for Further Studies:
  - Skin prick testing & Serum Radioallergosorbent Test (RAST)
    - IgE-mediated reactions to environmental allergens
  - Autologous serum skin test (ASST)
    - Autoantibodies
    - Negative test
      - Good negative predictive value

Diagnosis of Urticaria

- Angioedema without urticaria
  - C1 esterase inhibitor (C1 inh) deficiency
    - Hereditary: Activation mutation in C1 inh
    - Acquired: Persistent activation of C1q
      - B-cell lymphoproliferative disorders, plasma cell dyscrasias, connective tissue disease
  - Medication induced (i.e. ACE-I)

http://www.medicalook.com/Skin_diseases/Urticaria.html
Initial Management

- **Antihistamines**
  - Non-sedating H1 antihistamines (i.e. fexofenadine 180mg)
  - A European consensus paper has recommended increasing the daily dose of second-generation H1 antihistamines up to fourfold
  - Scheduled dosing
  - May add sedating H1 antihistamine at night (i.e. diphenhydramine 10-25mg or doxepin 10-50mg)

- **May add H2 antagonist**
  - Ranitidine is preferable to cimetidine
    - Does not interfere with hepatic metabolism of other drugs & does not bind androgen receptors
  - Leukotriene inhibitors - Montelukast
    - May play a role in delayed pressure urticaria

- **Antipruritic lotions** (i.e. calamine or 1% menthol)
- **Avoid common aggravating factors:**
  - NSAIDS, aspirin, opiates
  - Systemic corticosteroids should be avoided
    - Rebound effect
    - Prolonged duration not recommended due to numerous side effects
      - Hypertension, glucose intolerance, osteoporosis, femoral head necrosis
If Refractory

• Refer to dermatology or allergy & immunology
  – Mycophenolate mofetil
  – Methotrexate
  – Cyclosporine
  – Dapsone
  – Colchicine
  – Omalizumab

Omalizumab

• Anti-IgE monoclonal antibody
• Indicated for chronic idiopathic urticaria
  – 12 years of age and older
  – Symptomatic despite antihistamine treatment
• 70% of patients significantly improve

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Omalizumab

- Risks & Warnings:
  - Anaphylaxis (2 hours)
  - Malignancies
  - Acute Asthma Symptoms
  - Do not abruptly discontinue corticosteroids upon initiation
  - Serum sickness-like Rxn: Stop if patient has fever, arthralgia, and rash
  - Eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy

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The Role of Diet in Urticaria

- Most Allergenic foods:
  - Chocolate
  - Shellfish
  - Nuts
  - Tomatoes
  - Strawberries
  - Melons
  - Pork
  - Cheese
  - Garlic
  - Onions
  - Eggs
  - Milk
  - Spices

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The Role of Diet in Urticaria

- Latex Cross-Reaction
  - Avocado
  - Bananas
  - Chestnuts
  - Kiwi
- Preservatives: yeast, salicylates, citric acid, azo dyes, benzoic acid, sulfite, penicillin

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The Role of Diet in Urticaria

- Pseudoallergen free diet
- Substances that induce hypersensitivity
- Avoidance of fermented foods
  - i.e. cheese, wine
- Will work quickly (1-3 weeks) if going to make a difference
- Generally not high yield

Prognosis of Chronic Urticaria

- Average duration of chronic urticaria is 2-5 years
  - 50% of patients clear within a year
  - May persist for many years

Summary

- Urticaria are pruritic superficial dermal swellings
- Individual lesions last less than 24 hours
- Acute Urticaria
  - < 6 weeks
  - Idiopathic, infections, medications, foods
  - Does not warrant lab testing
**Summary**

- **Chronic Urticaria**
  - $\geq 6$ weeks (2 or more episodes per week off treatment)
  - Labs: CBC, ESR, TSH/Thyroid autoantibodies
- **First line treatment is non-sedating H1 antihistamines**
- **Oral corticosteroids should be avoided**
- **Immunosuppressive agents for refractory cases**
  - i.e. Omalizumab

**References**


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