Allergic Skin Disorders and HAE

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Disclosures

- Dr. Martin has no relevant financial relationships to disclose.
Objectives

• At the end of this presentation, the participant will have reviewed the recognition and treatment of allergic skin disorders, to include:

1. Urticaria and Angioedema
2. Hereditary Angioedema
3. Atopic Dermatitis
4. Allergic Contact Dermatitis

Improving People's Lives Through Innovations in Personalized Health Care
Urticaria and Angioedema

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THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER
Urticaria/Angioedema

- **Urticaria**
  - Pruritic, erythematous, cutaneous elevations that blanch with pressure, indicating the presence of dilated blood vessels and edema

- **Angioedema**
  - Similar pathologic alterations in deep dermis and subcutaneous tissue; swelling is predominant manifestation, little or no pruritis; may be painful or burning
Angioedema

- Unlike other forms of edema
  - Not characteristically in dependent areas
  - asymmetrically distributed
  - transient
- Often seen with urticaria
Urticaria

- **Acute vs chronic**
  - Urticaria that exceeds 6 weeks is arbitrarily designated chronic

- **Dermagraphics**
  - Ability to write on skin: 2-5% of population
  - Only small fraction warrant chronic treatment with antihistamines
**The EAACI/WAO Guideline**

Basic treatment: Avoidance of triggers and relevant physical factors if physical urticaria/angioedema is present.

**STEP 1**

- **Monotherapy with sgAH**
- Monotherapy with sgAH

If inadequate control: After 2-4 weeks or earlier, if symptoms are intolerable

**STEP 2**

- Increase sgAH dose (up to 4x)

If inadequate control: After 2-4 weeks or earlier, if symptoms are intolerable

**STEP 3**

- Add on to sgAH: Omalizumab

If inadequate control: Within 6 months or earlier, if symptoms are intolerable

**STEP 4**

- Add on to sgAH: Ciclosporin*

**The AAAAI/AACAI Guideline**

One or more of the following:
- Dose advancement of sgAH used in Step 1
- Add another sgAH
- Add H2-antagonist
- Add LTRA
- Add fgAH to be taken at bedtime

Assess for patient’s tolerance and efficacy

Dose advancement of potent antihistamine (e.g. hydroxyzine or doxepin) as tolerated

Assess for patient’s tolerance and efficacy

Add an alternative agent
- Omalizumab or ciclosporine*
- Other anti-inflammatory agents, immunosuppressants, or biologics
Urticaria Guidelines

- Relatively new Urticaria Guidelines have been published
  - **First line treatment** of Chronic Spontaneous Urticaria is 2nd Generation antihistamines
  - **Second line treatment** is to increase antihistamine dose
    - Often to 2 to 4 times recommended dose
    - US:
      - May add another 2nd gen antihistamine
      - May add H2-antagonist
      - May add LTRA
      - May add 1st gen antihistamine at bedtime
  - **Third line**, there is disagreement between US and European/WAO guidelines
    - US: dose advancement of potent (1st gen) antihistamines
    - European: Add on omalizumab
  - **Fourth line**
    - US: omalizumab or cyclosporine
    - European: Add on cyclosporine
- Not present: corticosteroids
CASE 1: MJ

- 42 y/o w/m with CC: “whelps” x 2 months
  - Itching
  - 1st episode: No lifestyle changes
  - Doctors didn’t help
    - Benadryl, Claritin, Tavist w/o relief
    - Lab work, x-rays normal

- PE: 0.5-5 cm urticarial lesions
Urticaria
Urticaria

- Papules and plaques:
  - pruritic
  - erythematous
  - edematous
  - blanchable
  - 1mm to several cm in diameter
  - last < 24 hours
Urticaria Evaluation

History

- Duration - < or > 6 weeks
- Triggers – identifiable cause more likely in acute but < 5% in chronic
  - ingestants, contactants, physical stimuli, infections
- Lesional hx
  - duration, purpura, pain
  - refer to Dermatology if suspected vasculitis for Bx
- PMH/ROS suggestive of systemic disease
Physical Urticaria

- Dermatographism
- Cholinergic
- Cold
- Delayed pressure urticaria/angioedema
- Solar
- Vibratory
- Aquagenic
Ice cube test

- Cold Urticaria

Similar images have been on the board in the past.
What’s this?

Again, similar images have been on past board exams
Urticaria Evaluation

Labs

- Skin tests
  - Seldom indicated
  - Of questionable value
    - can’t get the patient off antihistamines
    - many patients have dermatographism
  - Most urticaria is **not** triggered by food or aeroallergens

- Labs as indicated by Hx/PE (look for underlying cause – Not routine)
  - TSH, CBC, LFT’s, ESR, ANA, C4

- Skin Biopsy as indicated by History
Urticaria Differential Diagnosis
Other pruritic skin conditions

- Urticarial vasculitis
- Viral exanthema
- Contact dermatitis
- Parasites
- Liver disease
- SLE
- Malignancy
Urticaria Pigmentosa

- Persistent pigmented macular lesions
- Darier’s sign
- Adult cases more likely to progress to systemic disease
Mastocytosis

- Excessive Mast cells
- Four classifications
  - indolent
  - with hematologic abnormalities
  - aggressive
  - mast cell leukemia
- Multiple organ involvement
  - BM, GI, liver, skin, long bones
Urticarial Vasculitis

- Necrotizing vasculitis
  - endothelial cell edema
  - perivascular PMN infiltrate
  - fibrinoid deposits in venules
  - leukocytoclasis - nuclear debris

- Last > 24 hours

- Painful and leave purpura/bruising with resolution
Angioedema

- 10-20% of the population
- 94% of cases are drug induced
  - ACEI
  - NSAIDS
  - Others
- Hereditary
- Autoimmune acquired
  - very rare, < 50 case reports
Angioedema

- Non-pitting edema
- Occurs deeper than urticaria
- Overlying skin is usually normal
- Usually burns and is not pruritic
ACEI Induced Angioedema

- 1-2 cases per 1000 persons
- >70% symptomatic within first week of therapy
- Likely precipitated by increased bradykinin
  - Angiotensin II inhibits bradykinin
    - ACEI blocks conversion of angiotensin I → II
    - Vasodilatation, increased vascular permeability
- Can lead to life-threatening upper airway obstruction
  - 22% require intubation with 11% mortality
- Rare in Angiotensin II receptor blockers
Hereditary Angioedema

- Rare (1/150,000)
- Autosomal dominant
- Onset in adolescence
- Angioedema is
  - painless and non-pruritic
  - lasts 3-5 days
  - unresponsible to Epi, antihistamines, pred.
  - triggered by mild trauma
Hereditary Angioedema

- C1 Inhibitor (C1-INH) deficiency
  - Type I (85%)
    - Quantitative deficiency (5-30% normal)
  - Type II (15%)
    - Qualitative deficiency
    - Quantity is normal or elevated
    - Functional activity is markedly reduced
  - Type III
    - Unknown cause
    - C1q, C1-INH, C4 normal with suggestive history
    - C4, C1-INH normal during attack
Hereditary Angioedema

- C4 and C2 markedly low
  - both between and during attacks
  - **C4 is screening test**
- Autosomal dominant inheritance
- Symptoms related to subcutaneous and/or submucosal edema
- C1 normal
  - Low C1 consider acquired form
    - Lymphoma
    - Low C4, C2 and C3
Acquired Angioedema

- Very rare
- Present in adults
- CLL, NHL, cryoglobulinemia, Waldenstrom macroglobulinemia, myeloma
- Decreased C4 like in HAE
- Decreased C1q which distinguishes HAE from AAE
# HAE vs AAE

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HAE Treatments

- **Prophylaxis**
  - Cinryze: IV; C1-esterase inhibitor
  - Haegarda: SC; C1-esterase inhibitor
  - Takhzyro: SC; plasma Kallikrein inhibitor (monoclonal antibody)

- **Acute**
  - Berinert: IV; C1-inhibitor concentrate. Approved for self-administration
  - Ruconest: IV; Plasma free recombinant C1-inhibitor concentrate. Approved for self administration
  - Firazyr: SC; B2 bradykinin receptor antagonist. Approved for self-administration
  - Kalbitor: SC; kallikrein inhibitor. **Must be administered by healthcare professional**
Atopic Dermatitis

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Atopic Dermatitis

Atopic Dermatitis is a characteristic cutaneous inflammatory condition that typically occurs in individuals with a personal or family history of atopy.

Atopic Dermatitis (AD) is a chronic, relapsing, inflammatory skin manifestation of the *Atopic Triad*.

Incidence of AD is increasing in all industrialized nations.
Clinical features

Acute atopic dermatitis

- No primary lesion
- Intensely pruritic
- Erythematous papules associated with excoriations, vesiculation, and serous exudate
Clinical features

Chronic atopic dermatitis

**Lichenification**

- Extensor surfaces during infancy
- Flexural surfaces during childhood and adult years
2018 Atopic Dermatitis Yardstick

Diagnostic Features of AD Clinical

**Essential**

- Atopy
  - Personal Hx / FHx of Eczema, hay fever, asthma.
- Pruritus
- Eczema
  - Acute
  - Subacute
  - Chronic
Genetics of AD

- Atopy is the result of a complex interaction of multiple genes, and does not fit a simple autosomal dominant model.

- 81% of the offspring of two parents with AD will develop AD, 60% when one parent has AD and the other has respiratory allergies, 56% when one parent is atopic.
Attributes of AD

I. Atopy

- Polygenic immunologic aberrations
- Th1 / Th2 imbalance (transitory)
- Increased IgE antibody production
- Eosinophilia
- Hyper-releasable basophils (& mast cells)
- Increased E-selectin, VCAM-1, and ICAM levels
Attributes of AD

II. *Pruritus*

- Probably the “primary” symptom of AD
- Mildest mechanical stimulation of atopic skin is perceived as “itch”
- *Alloknesis* - once itching has started, the likelihood of the surrounding skin to itch increases
- Questionably induced by histamine (Antihistamines minimally effective)
Triggers of Itch for AD

- Irritants
  - Wool
  - Soaps / detergents
  - Disinfectants
  - “Occupational”
  - Tobacco smoke

- Xerosis (Dry skin)

- Microbial agents
  - *S. aureus*
  - Viral infection
  - ? Dermatophytes

- Heat / Sweating
- Contactants including dust mites
- Psychological
- Foods (IgE-induced) & those having vasodilatory properties
- Aeroallergens
- Hormones
- Climate
Attributes of AD

III. “Eczema”

- An “isomorphic” response to trauma (i.e. scratching and/or rubbing) with the distribution restricted to those areas
- Must be differentiated from all the “other” eczemas
- “Polymorphic” can appear as acute, sub-acute, and/or chronic
- “Excoriated”
- Chronic, or chronically relapsing
Differential Diagnosis of Adult Eczematous Eruptions

- Allergic Contact Dermatitis
- Irritant Contact Dermatitis
- Seborrheic Dermatitis
- Cutaneous T-cell Lymphoma
- Psoriasiform eruptions
- Pityriasis rubra pilaris
- Scabies
- Glucogonoma Syndrome
- Pellagra
Diagnosis of AD

- History and physical examination
- Laboratory - (*never routine*)
  - Serum IgE level
  - Serum test for allergen-specific IgE (CAP-RAST)
  - Skin Biopsy
  - Skin culture (bacterial, viral, fungal)
  - Patch test (corticosteroids, aeroallergens)
- Prick skin test - (*never routine*)
Complications of AD

- Secondary Infection
  a) bacterial
    - impetiginization
    - “super-antigenicity”
  b) viral
    - localized – verruca, molluscum, herpes
    - systemic – Kaposi’s herpetiform eruption
  c) mycotic
    - Dermatophyte
    - Candidal
Natural History of AD

- 60% of patients develop AD by 1 year of age
- 85% of patients develop AD by age 5
- Earlier onset often indicates a more severe course
- Many cases resolve by age 2, improvement by puberty is common
- 80% of occupational skin disease occur in atopics
- It is rare to see AD after age 50
- 50% - 60% of patients develop respiratory “allergies”
Managing AD (Preventative)

- Carefully eliminate all the triggers of itch
  - a) environmental, occupational, and temperature control
  - b) bathing - NO SOAP ON ECZEMA
  - c) lubrication

- Prevent “scratching” or rubbing
  - a) apply cold compresses to itchy skin
Managing AD (Therapeutic)

- Topical anti-inflammatory agents
  - a) corticosteroids (ointments > creams)
    - more potent - when “acute”
    - least potent needed for “chronic”
  - b) Tacrolimus 0.1% ointment
  - c) Ultra Violet Light
  - d) Tar preparations
Managing AD (Therapeutic)

- **Systemic**
  a) antibiotics
  b) anti-inflammatory drugs
    i. Prednisone
    ii. Cyclosporine A
  c) antihistamines (?)
“Take-home” Message

Atopic dermatitis has a profound impact on the social, personal, emotional and financial perspectives of afflicted families.

An excellent patient resource:
National Eczema Association for Science and Education
21220 SW Morrison, Suite 433
Portland, OR 97205
phone: (503)228-4430
e-mail: nease@teleport.com
21 year old with itchy rash.
Worse in winter and summer.
Worried about food allergies.
Presented for diagnosis and therapy.
Your patient with the this rash should be treated with?

- A. topical antibiotics
- B. topical corticosteroids
- C. oral steroids
- D. dapsone
- E. famciclovir

Ans:
Your patient with the this rash should be treated with?

- A. topical antibiotics
- B. topical corticosteroids
- C. oral steroids
- D. dapsone
- E. famciclovir

Ans: B
Atopic Dermatitis

- Adults - flexure areas, hands
- Eyes - think atopic kearatoconjunctivitis
- Exacerbations – think Staph or Herpes simplex
- Anergy: decreased TH-1 cell and decreased interferon predispose to skin infections
- Increase IgE, IL_4, IL_5, GM-CSF, IL_13, (lymphocytes T helper type 2 phenotype)
- Filaggrin gene defect is very important
- Rx - lubricants, topical steroids, pimecrolimus and tacrolimus and phosphodiesterase 4 inhibitor
IMPORTANT INFORMATION ABOUT TOPICAL CORTICOSTEROID THERAPY

- Potency - ointments > creams > lotions
- Limit use of high potency on face, breasts and genitals
- Skin side effects
  - Atrophy
  - Telangiectasia
  - Striae
  - Perioral dermatitis
TOPICAL IMMUNE MODULATORS

- Tacrolimus (Protopic) ointment
- Pimecrolimus (Elidel) cream

- Derived from fungal polypeptides and inhibit T-lymphocyte activation
- Potent immunosuppressive if given systemically
- Slow acting anti-inflammatory
- Great substitute for potent steroids on face
- Questionable risk of lymphoma with chronic use
TOPICAL IMMUNE MODULATORS
(Tacrolimus (Protopic) ointment
Pimecrolimus (Elidel) cream)

- Effective in childhood and adult AD
- No skin atrophy / steroid side effects
- Stinging and burning at initiation of therapy
- Slight increase in skin infections ?
- ? Risk of neoplasms?
- Long-term safety seems safe
20 year old male with isolated itchy rash below. WHAT IS THIS?
The preferred test to exclude the diagnosis is?

- A. Patch testing
- B. Delayed hypersensitivity intradermal skin testing
- C. IgE mediated skin tests
- D. No testing is effective

Answer:
The preferred test to exclude the diagnosis is?

- A. Patch testing
- B. Delayed hypersensitivity intradermal skin testing
- C. IgE mediated skin tests
- D. No testing is effective

Answer: A
Allergic Contact Dermatitis

- Type 4 cell mediated reaction with T-helper-type 1- lymphocytes
- delayed 48 hours
- Rhus is the best example
- patch test for diagnosis
- nickel, rubber additives (latex), thimerosal (eye gtt), benzocaine, neomycin, topical doxepin
- Rx - avoidance, topical steroids, or 2 weeks of oral steroids
GOOD LUCK ON THE EXAMS

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