The Management of Atopic Dermatitis & Urticaria

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Disclosures:

- 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

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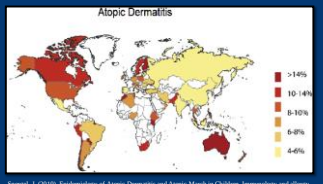
Epidemiology

- 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



Spergel, J. (2010). Epidemiology of Atopic Dermatitis and Atopic March in Children. Immunology and allergy clinics of North America.

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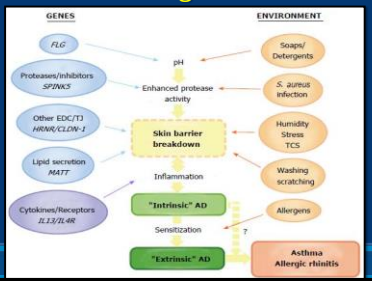
Pathogenesis



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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

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Pathogenesis

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

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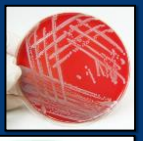
Pathogenesis

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



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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

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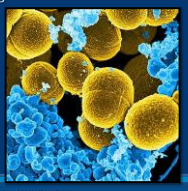
Environmental Factors

- 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



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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

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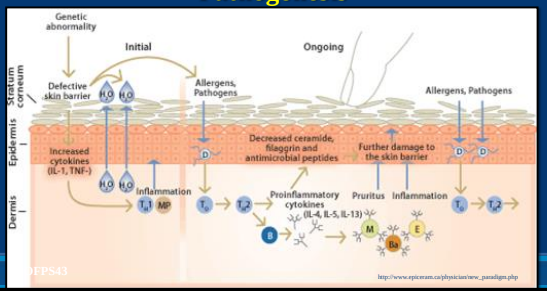
Pathogenesis



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

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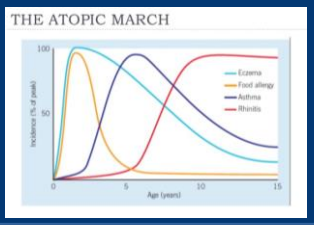
Clinical Presentation

- Classic Triad
  - Allergies
  - Atopic Dermatitis
  - Asthma



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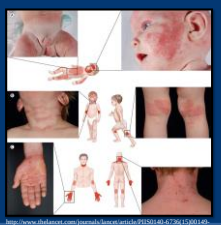
Clinical Presentation

- 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



http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00149-X/fulltext

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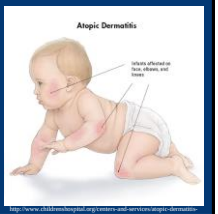
Clinical Presentation

- 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



http://www.childrenshospital.org/centers-and-services/atopic-dermatitis-center-program

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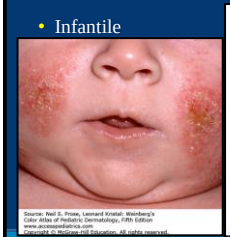
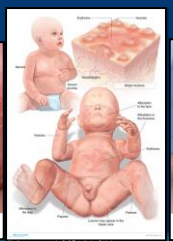
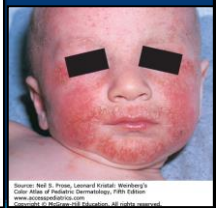
Clinical Presentation

- Infantile



Source: Neil S. Prose, Leonard Kristal: Weinberg's Color Atlas of Pediatric Dermatology, Fifth Edition www.accesspediatrics.com Copyright © McGraw-Hill Education. All rights reserved





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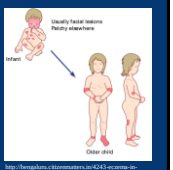
Clinical Presentation

- 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



http://bengaluru.citizenmatters.in/4243-eczema-in-children-itching-for-solutions-4243

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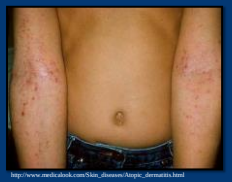
Clinical Presentation

- Childhood



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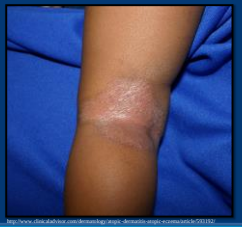

http://www.clinicaladvisor.com/dermatology/atopic-dermatitis-atopic-eczema/article/593102/

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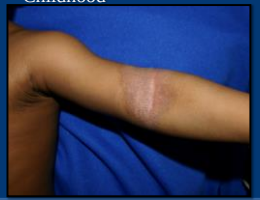
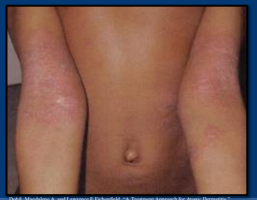
Clinical Presentation

- Childhood



http://www.clinicaladvisor.com/dermatology/atopic-dermatitis-atopic-eczema/article/593102/



Dahl, Magdalene A, and Lawrence F Eichenfield. "A Treatment Approach for Atopic Dermatitis." Pediatric Annals, vol. 34, no. 5, Jan. 2005, pp. 399–406. doi:10.3928/0090-4481-20050501-09.

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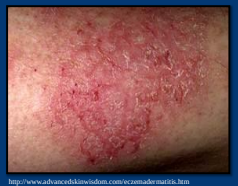
Clinical Presentation

- 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

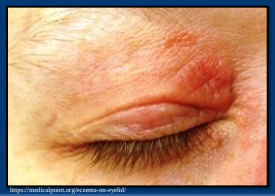


http://www.advancedskinwisdom.com/eczemadermatitis.htm

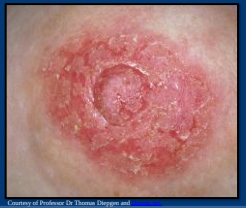
http://www.dermis.net/bilder/CD003/550px/img0060.jpg

Clinical Presentation

- Adulthood/Adolescent



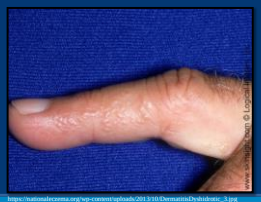
https://meticalpoint.org/eczema-on-eyelid/

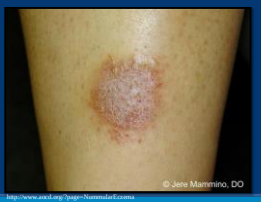


Courtesy of Professor Dr Thomas Dueggen and

Clinical Presentation

- Adulthood/Adolescent





https://nationaleczema.org/wp-content/uploads/2013/10/DermatitisDyshidrotic_3.jpg
http://www.aocd.org/?page=NummularEczema

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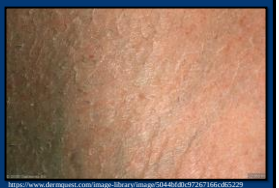
Clinical Presentation

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



https://www.dermquest.com/image-library/image/5044bfd0c97267166cd85229

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Diagnostic Criteria

DIAGNOSTIC GUIDELINES FOR ATOPIC DERMATITIS

Must have:
- An itchy skin condition (or parental report of scratching or rubbing in a child)

Plus three or more of the following:
- History of involvement of the skin creases such as folds of elbows, behind the knees, fronts of ankles, the neck and around the eyes*
- A personal history of asthma or hayfever (or history of atopic disease in a first-degree relative in children under 4 years of age)
- A history of generally dry skin in the last year
- Visible flexural eczema (or eczema involving the cheeks/forehead and extensor limbs in children under 4 years of age)
- Onset under 2 years of age (not used if child is under 4 years of age)

*Original 1994 guidelines also included the cheeks in young children.

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Associated Features

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

Fig. 12.14 Infant with atopic dermatitis of the face with central facial sparing. Note the Dennie-Morgan lines and central facial pallor.

Fig. 12.12 Keratosis pilaris. A Discrete perifollicular papules with central keratotic cores on the extensor surface of the upper arm.

Fig. 12.13 Exaggerated palmar creases. This patient had both atopic dermatitis and ichthyosis vulgaris.

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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

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Complications

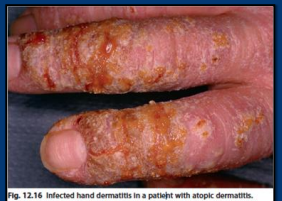
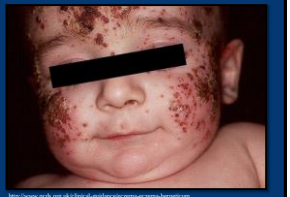


Fig. 12.16 Infected hand dermatitis in a patient with atopic dermatitis. There is impetigo-like crusting as well as pustules. Courtesy Louis A Fragola, Jr, MD.



http://www.pcds.org.uk/clinical-guidance/eczema-eczema-herpeticum

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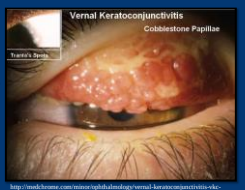
Complication

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



http://medchrome.com/minor/ophthalmology/vernal-keratoconjunctivitis-vkc-or-spring-catarrah/

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Histopathology

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

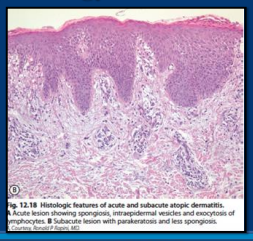

Fig. 12.18 Histologic features of acute and subacute atopic dermatitis. **A**, Acute lesion showing spongiosis, intraepidermal vesicles and exocytosis of lymphocytes. **B** Subacute lesion with parakeratosis and less spongiosis. (Courtesy Ronald P. Rapini, MD)

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Differential Diagnosis

	CHRONIC DERMATOSES	
C>A	Seborrheic dermatitis	Common
B	Contact dermatitis (allergic* or irritant)	Common
B	Psoriasis (especially palmoplantar)	Common
	INFECTIONS AND INFESTATIONS	
B	Scabies	Common
B	Dermatophytosis*	Common
	MALIGNANCIES	
A>C	Mycosis fungoides and Sézary syndrome	Uncommon

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Treatment

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

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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

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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

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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

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Treatment

- 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

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Treatment

- 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

http://www.webmd.com/skin-problems-and-treatments/eczema/treatment-16/slideshow-eczema

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Treatment

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

Treatment

- Adjunctive therapy
  - Antihistamines: diphenhydramine, doxepin, hydroxyzine
    - Break the "itch-scratch cycle"

https://nationaleczema.org/eczema/

Treatment

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


LATEST NEWS

Dupilumab: FDA approves first biologic for atopic dermatitis

Publish date: March 28, 2017

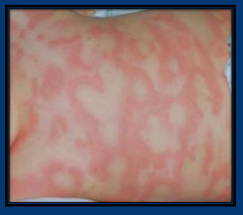
Summary

- 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

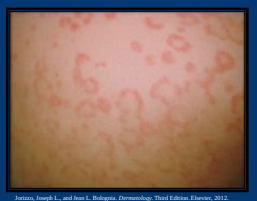
- Urticaria may present at any age
- Estimated to have an overall lifetime prevalence of 10-25%
- Chronic urticaria is more common in females (2:1)



Jorizzo, Joseph L., and Jean L. Bolognia. *Dermatology*. Third Edition. Elsevier, 2012.

Urticaria

- Term used for recurrent whealing of the skin
  - Also encompasses angioedema



Jorizzo, Joseph L., and Jean L. Bolognia. *Dermatology*. Third Edition. Elsevier, 2012.

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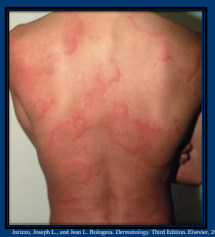
Urticaria

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



Jorizzo, Joseph L., and Jean L. Bolognia. *Dermatology*. Third Edition. Elsevier, 2012.

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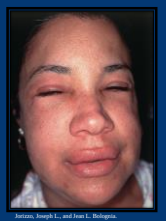
Urticaria

- 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



Jorizzo, Joseph L., and Jean L. Bolognia. *Dermatology*. Third Edition. Elsevier, 2012.

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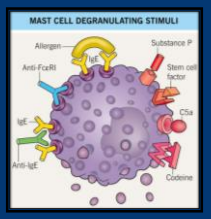
Pathophysiology

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



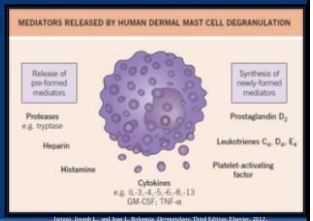
Jorizzo, Joseph L., and Jean L. Bolognia. *Dermatology*. Third Edition. Elsevier, 2012.

Pathophysiology

- Immunologic
  - IgE mediated
    - Autoantibodies
    - Type 1 hypersensitivity reaction
- Non-immunologic
  - Cause direct release of mast cell mediators
    - Opiates
    - Polymyxin B
    - Tubocurarine
    - Radiocontrast dye
    - Aspirin & NSAIDs
    - Tartrazine
    - Benzoate
    - Dietary pseudoallergens
    - Vasoactive stimuli (i.e. nettle stings)

Pathophysiology

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



Jorizzo, Joseph L., and Jean L. Bolognia. *Dermatology*. Third Edition. Elsevier, 2012.

Acute vs. Chronic Urticaria

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

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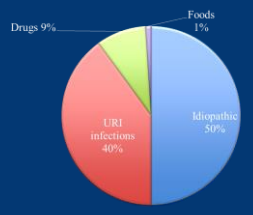
Acute Urticaria



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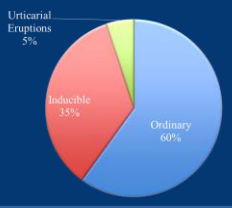
Chronic Urticaria



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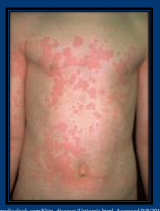
Chronic Urticaria

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



<http://www.medicalook.com/Skin_diseases/Urticaria.html, Accessed 9/8/2017.

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

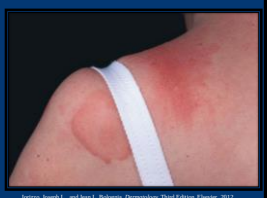
Chronic Inducible Urticaria

- 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

Jorizzo, Joseph L., and Jean L. Bolognia. Dermatology. Third Edition. Elsevier, 2012.

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



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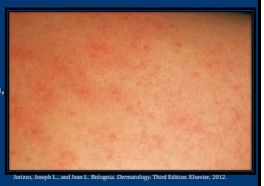
Chronic Inducible Urticaria

- 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)



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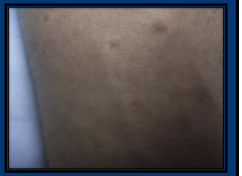
Chronic Inducible Urticaria

- 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



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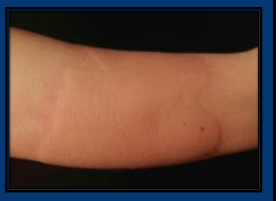
Chronic Inducible Urticaria

- 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



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Chronic Inducible Urticaria

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

www.theguac.com/sports/wwwimdive/2012-13/releases/20121119jfleyy; accessed 8/24/17

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

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

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Differential Diagnosis

- Urticarial dermatoses
  - 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

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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

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Diagnosis of Urticaria

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

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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

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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

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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

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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)

Initial Management

- 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

Initial Management

- 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

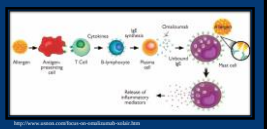
- Refer to dermatology or allergy & immunology
  - Mycophenolate mofetil
  - Methotrexate
  - Cyclosporine
  - Dapsone
  - Colchicine
  - Omalizumab

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



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
  - ≥ 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

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Thank You

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