Atopic Dermatitis: Etiology, Complications and Treatment

HEATHER D. VOLKMAN, D.O.
DERMATOLOGY

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Objectives

1. Understand the etiology and biology of atopic dermatitis.
2. Discuss other diseases in the differential diagnosis of atopic dermatitis.
3. Understand the role of atopic dermatitis in asthma, allergic rhinitis, and food allergies.
4. Discuss the current treatment options for atopic dermatitis.
5. Recognize the complications of atopic dermatitis.
Case #1: Child with Atopic Dermatitis

- 5 y/o girl
- Rashes since age 2 mo
- Greatest in skin folds
- Facial involvement
- Severe itching
- Poor sleep
- Recurrent infections requiring antibiotics
Case #1: Child with Atopic Dermatitis
Case #2: Teen with Atopic Dermatitis

- 16 y/o boy
- Rash since age 3 mo
- Severe itching
  - Greatest in skin folds of extremities/face
- Difficulty sleeping
- Recurrent infections
Case #2: Teen with Atopic Dermatitis
Case#2: Teen with Atopic Dermatitis
Definition of Atopic Dermatitis

- Hanifin and Rajka criteria
- Must have
  - Itching
- Plus three or more of
  - Onset under age 2
  - Flexural involvement
  - Personal history of asthma or allergic rhinitis
  - Dry skin
- Minor criteria
  - Keratosis pilaris
  - Icthyosis
  - Pityriasis alba
  - Denny’s lines
  - Hyperlinear palms

Williams HC.
Epidemiology

- Prevalence of atopic dermatitis in U.S.
  - 10-20% of children

- Higher prevalence
  - East Coast States, Nevada, Utah, Idaho
  - Metropolitan living
  - Black race
  - Higher education level of parents
  - Smaller families
  - Ethnic groups migrating from a country of low prevalence to high prevalence

Eichenfield LF, et al., Williams HC
Epidemiology

- More than 60% start by 2 years old
- Remission occurs in approx 65% by age 11
- Uncommon late onset form
- Adults over 16 y/o
  - one third of atopic dermatitis patients
- U.S. National annual costs in 2008
  - $3.8 billion dollars

Bieber Th., Williams HC
Age Dependent Distribution of Atopic Derm
Infantile Atopic Dermatitis
Infantile Atopic Dermatitis
Age Dependent Distribution of Atopic Derm
Childhood Atopic Dermatitis
Childhood Atopic Dermatitis
Childhood Atopic Dermatitis
Associated Features of Atopic Dermatitis
Keratosis Pilaris
Pityriasis Alba
Adult Atopic Dermatitis

Hand Dermatitis

- Exacerbations:
  - Frequent hand washing
  - Alkaline soaps
Etiology/Biology of Atopic Dermatitis

- **Interplay of the Environment and Genetics**
- **Epidermal Barrier Function**
  - **Filaggrin 2006**
    - Spink 5
    - Decreased expression of corneodesmosin, desmoglein I, desmocollin, TGM-3
    - Activation of epidermal proteases
    - Higher skin pH (ex: soaps) activates proteases and alters lipids and filaggrin of the stratum corneum
- **Immune System**
  - TLR2, TLR9, IL-4, IL-13, IL-22, IL-25, IL-31, FCERI, FCERIA, FCERIB, FCERIG, TSLP
  - IL-4 and IL-13 suppress filaggrin expression
  - Superantigen induction of cytokines
  - Kallikrein 5 induced by higher skin pH (ex: soaps)

- **IgE-associated (80%) and non-IgE-associated atopic dermatitis**

Bieber Th, Eichenfield LF et al, Paller A, Pride HB et al
Normal Skin

- Stratum corneum
- Stratum granulosum
- Stratum spinosum
- Stratum basale

Epidermis

Dermis

www.antibodyreview.com
Filaggrin staining in normal skin

ichthyosis vulgaris and atopic dermatitis

Normal skin barrier

Filaggrin granules

Defective skin barrier

No filaggrin granules
Role of barrier defects and Immune Dysregulation

Intrinsic barrier defects:
- Mutations in FLG, CLDN1, KLK7...

Secondary barrier defects:
- FLG
- CASP 14
- HRNR
- KLK 7
- FLG2
- LOR
- INVL

Transcriptional regulation

Enhanced penetration of allergens/irritants

Activation of Langerhans and dermal dendritic cells

Production of pro-inflammatory cytokines

Healthy skin

Atopic Dermatitis skin
Filaggrin

- Encodes profilaggrin, the major component of keratohyaline granules in the epidermal granular layer
- Binds keratins contributing to the protein-lipid cell envelope
- Degraded to release hygroscopic amino acids forming natural moisturizing factor
- Contributes to low surface pH
- Mutations lead to increased severity of atopic dermatitis and environmental allergies

Pride HB et al.
Lipids of the Stratum Corneum

- Ceramides
  - Decreased in patients with atopic dermatitis
- Cholesterol
- Fatty Acids
- Cholesterol Esters

Paller A, Sajic D et al.
Atopic March

- Loss of barrier function = Sensitization
- Induction of asthma, allergic rhinitis, and food allergies
- Increased transepidermal water loss and penetration of high-molecular wt allergens
  - Dust mite, foods, microbes
- Skin signals ex: thymic-stromal lymphopoietin (TSLP) to GI tract and lungs

Paller A
Role of Environmental Allergens

- Controversial
- Hygiene Hypothesis
  - Switch from previous theories
  - Increasing exposure to allergens early to induce tolerance
  - Past theory of reducing ubiquitous allergens ex: dust mite
- Conflicting data with atopic dermatitis and benefit from allergy immunotherapy
- Most current analyses disprove that exclusive breastfeeding has no effect on atopic dermatitis
- Frequency of contact allergens in atopic dermatitis
  - 89% of atopic dermatitis positive for at least 1 contact allergen vs. 66% in non-atopic pts
  - Higher EASI score correlated with higher number of contact allergens
  - Most common contact allergens in atopic derm
    - Nickel
    - Balsam of Peru/Fragrance Mix
      - Statistically significant difference between non-atopic pts
    - Wool alcohols
    - P-tert-butylphenol formaldehyde resin
    - Cobalt
    - Formaldehyde
    - Colophonium
    - Potassium dichromate
    - Neomycin sulfate
    - Tixocortol-21-pivalate

Williams HC, Cox L et al., Herro EM et al., Pride HB et al.
Contact Dermatitis
Contact Dermatitis
Contact Dermatitis
Contact Dermatitis
Contact Dermatitis
Sensitization to a food is reflected by positive RAST or skin prick testing and is not the same as food allergy (specific immune response upon food exposure)

- 50-90% of parent/patient presumed food allergies are not allergic in nature

- The introduction of solid foods should not be delayed beyond 4-6 mo of age due to paradoxical increase in food allergies

- Children <5 y/o with atopic dermatitis should be considered for food allergies to milk, egg, peanut, wheat, and soy if:
  - Moderate to severe disease not controlled by conventional tx
  - History of immediate reaction after ingestion of specific food

- Patients should not avoid potentially allergenic foods as a means of controlling atopic dermatitis

Pride HB et al.
Asthma and Atopic Dermatitis

- U.S. Asthma prevalence: 8.4%
- Increasing prevalence as with atopic dermatitis
- One in three children with atopic dermatitis will develop asthma after the onset of cutaneous disease
- Observation
  - Wheezing often starts before or at the time of onset of atopic dermatitis
  - Questions the atopic march

Williams HC, Cox L et al.
Role of Probiotics and Nutritional Supplements

- Controversial
- Review
  - 21 Articles, 6859 patients
  - Probiotics (10 studies)
    - Foods composed of live bacteria present in gut microflora
    - Given to children or mothers in pre- and post-natal periods
    - Most studies showed decreased development and severity
    - Conflicting studies
  - Prebiotics (2 studies)
    - Oligosaccharides that stimulate bacteria growth in colon
    - Showed lower risk of development but not severity of atopic derm
  - Hydrolyzed or Amino Acid Formulas (5 studies)
    - Mixed results
  - Fatty Acids (gamma-Linolenic acid)
    - Favorable trend in AD severity and prevalence reduction

Foolad N et al.
Severity Scale and Quality of Life

- Sleep loss
  - Difficulties initiating and maintaining sleep
- Depression/Anxiety
  - Social functioning
- Time missed from work
- High cost of medications
- ADHD

- Scoring Systems
  - SCORAD, EASI, PO-SCORAD

- Atopic Dermatitis Burden Scale (ABS) questionnaire
  - Burden questionnaire for families and children affected by atopic dermatitis

Bieber Th, Meni C et al., Pride HB et al.
Burden of Disease in Atopic Dermatitis
Atopic Dermatitis Mimics

Seborrheic Dermatitis
Atopic Dermatitis Mimics Tinea
Atopic Dermatitis Mimics Tinea
Atopic Dermatitis Mimics

Majocchi’s granuloma
Atopic Dermatitis Mimics Scabies
Atopic Dermatitis Mimics Scabies
Atopic Dermatitis Mimics

Langerhans cell histiocytosis
Atopic Dermatitis Mimics

Langerhans cell histiocytosis
Atopic Dermatitis Mimics Psoriasis
Atopic Dermatitis Mimics

Pityriasis Rubra Pilaris
Atopic Dermatitis Mimics

Acrodermatitis Enteropathica
Atopic Dermatitis Mimics

Netherton’s Syndrome
Role of Staphylococcus Aureus

- High rates of skin and nares colonization in atopic derm patients
  - Up to 90% of atopic derm patients
  - Role in exacerbation of disease
    - Correlation between severity of disease and bacterial load
- Lower rates of MRSA in atopic derm than thought

- Defective epidermal barrier
- Deficiency of antimicrobial peptides
- Role of superantigens
  - Inhibit T reg cells that normally suppress inflammation
  - Leads to alternatively spliced glucocorticoid receptor preventing corticosteroid binding to T cell

Eichenfield LF et al., Ryan C et al., Huang JT et al., Paller A
Impetigo
Impetigo
Secondary Infections
Secondary Infections
Role of Sodium Hypochlorite/Bleach

- Need to decrease antibiotic use due to increased community resistant organisms
- Topical antibiotics either not effective or cause irritant contact dermatitis or bad cosmetic look
- Bleach non-toxic to tissues and mucosal surfaces
- Two Studies
  - Bleach baths
    - 22 children: Blinded, placebo-controlled
    - Methods: 0.5 cup of 6% bleach to full tub (0.005%) 5-10 minutes twice weekly + intranasal mupirocin BID x 5 days/mo, followed at 4 and 12 weeks
    - EASI and BSA scores improved from neck down in treatment group, no difference at head and neck
    - Interestingly, all patients continued to show positive cultures for Staph aureus
    - Adverse events: one patient initially reported itching
    - Limitations: 12 week single-center
  - Body wash
    - 18 children, washed 3 days/week for 12 weeks from neck down, rinse after 1-2 min
    - Cultures before and at each f/u visit (q2weeks)
    - Decreasing trend of bacterial counts, statistically significant at 1 month only
    - No patient required oral abx
    - IGA score decreased at all time points
    - Adverse events: stinging and burning, itching
    - Limitations: non-blinded, no placebo, 12 week open-label, single-center, partially retrospective

Ryan C et al., Huang JT et al.
Molluscum Contagiosum
Eczema Herpeticum
Juvenile Plantar Dermatosis
First-Line Treatment of Atopic Dermatitis

- **Ceramide-based moisturizers**
  - Prevent epidermal water loss and inhibit exogenous peptides
  - Normalize skin pH
  - Steroid-sparing
    - Several reports shown ceramide based emollients to be equivalent to topical steroids in the treatment of mild to moderate atopic dermatitis
    - Reduced time to clearance when used in combination with topical steroids
  - EpiCeram, TriCeram, CeraVe
  - Promising studies on synthetic and pseudo-ceramides
  - Other emollients with promise: Atopiclair, MimyX, Eleton

Sajic D et al.
First Line Treatment of Atopic Dermatitis

- **Topical Steroids**
  - Within 2-3 days of application shown to:
    - Decrease epidermal proliferation and differentiation

- **Topical Calcineurin Inhibitors** (pimecrolimus/tacrolimus)
  - Safer on body regions more at risk for steroid atrophy
  - Shown to be more or as effective as topical steroids
  - Limitation: cost
  - Black box warning (2006) for lymphoma and nonmelanoma skin cancer
    - Results of ongoing long-term studies show no application to humans when topically applied

- **Proactive therapy**
  - Twice weekly treatment with topical tacrolimus or topical steroids resulted in few flares and increased time to next flare when compared to placebo

- **Antihistamines**
  - First-generation to aid in sleeping

- **Avoid systemic corticosteroids due to severe rebounding of disease**

Pride HB at al., Paller A, Tan AU et al.
In Office Instructions for Atopic Dermatitis

- Daily bathing followed by ceramide-based emollients
  - “Soak and smear”
- Flares (affected areas)
  - Use of topical steroids or topical calcineurin inhibitors BID
- Maintainance (trouble areas)
  - Topical steroids or calcineurin inhibitors twice weekly
- Bleach baths twice weekly
- In patients not improving consider:
  - Infection
  - Compliance
    - Stealth monitoring through electronic caps
    - Only 32% of atopic dermatitis patients/parents compliant
    - Extensive counseling necessary
    - Regular follow-ups
  - Consider contact dermatitis

Paller A, Tan AU et al.
Management of Severe Atopic Dermatitis

- **Wet dressing therapy**
  - Study at Mayo Clinic over 30 years: total of 218 patients
  - Wet dressings
    - Daily bath
    - Topical steroids creams (used BID)/emollients (other applications) for total of 5-8 applications/day
    - Cotton flannel clothing over wet gauze and then placement of warm blankets
    - Removed every 3 hours for 30-45 min
  - Extensive parent education
  - 40% not using topical treatments at the time of hospitalization
  - Mean duration of hospitalization was 3.61 days
  - Over 90% had greater than 50-75% improvement
  - Adverse events: some children uncomfortable initially
  - Limitations: skilled nursing

Dabade TS et al.
Management of Severe Atopic Dermatitis

- **Phototherapy (narrowband-UVB)**
  - Limitations: cost, time away from work

- **Systemic immunosuppressants**
  - Cyclosporine
  - Azathioprine
  - Mycophenolate moefetil
  - Methotrexate
  - Intravenous immunoglobulin (IVIg)
    - No comparative studies in pediatric atopic dermatitis between systemic immunomodulators

- **Future**
  - Biologic therapies targeting an individual’s gene defect or immune dysfunction

Paller A, Tan Au et al.
References

- Dabade TS, et al. Wet dressing therapy in conjunction with topical corticosteroids is effective for rapid control of severe pediatric atopic dermatitis: experience with 218 patients over 30 years at Mayo Clinic. JAAD 67:100-6, 2012.
Thank You

- Heather D. Volkman, D.O.
  - Email: heathervolkman@sbcglobal.net
  - Office: 817-989-1221