ATOPIEC DERMATITIS:
PATHOPHYSIOLOGY AND
PHARMACOLOGY OF
MANAGEMENT

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Session Objectives

• List two treatment options for atopic dermatitis

• Describe one mechanism of action of topical corticosteroids

• Identify one option to break the scratch/itch cycle
Epidermis As a Barrier

Outer, thin layer
- Keratinocytes, basal cells, melanocyte cells, stratum corneum

Lacks blood vessels
Few nerve endings
Provides mechanical protection and barrier function
- Interruptions can lead to infections
- Filaggrin gene (FLG) contributes to protective function
- Loss of FLG function contributes to AD
- Phosphodieterase-4 (PDE-4): enzyme in the skin
  - Overactive PDE-4 has been shown to contribute to AD

Photosynthesis of Vitamin D

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Objective diagnosis

Pruritic, erythematous, dry patches

Scale and linear excoriations

Diffuse borders

Thickened skin with well-defined skin markings (lichenification)

Crusting and oozing common in children

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ATOPIC DERMATITIS: THE ITCH THAT RASHES

• The most common skin disorder seen in infants and children; **20% of children have AD**
• 60% present in first year of life
• 90% in the first 5 years
• **60% persist into adulthood**
• 10-15% of the population affected in the US
• “**Atopic March**”: atopic dermatitis → food allergies → allergic rhinitis → asthma
• Interruption of atopic dermatitis may ↓ incidence of asthma and allergic rhinitis
• Characterized by exacerbations and remissions
Lichenification

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PATHOPHYSIOLOGY

• Decreased ceramides in stratum corneum
  – Most abundant lipid in the skin
  – Crucial for water retention
• Increased permeability, decreased skin barrier function
• Elevated serum IgE levels
• Altered cell-mediated immunity
• Correlation of elevated IgE levels and the severity of atopic dermatitis
  – Unclear if high IgE levels are primary or secondary
• *Not all patients with elevated IgE levels have atopic dermatitis*
IMMUNOLOGIC ABNORMALITIES

• Proliferation of T-helper 2(Th-2)
• Cytokines are produced by Th-2 cells
• Release of calcineurin activates cytokines
• Cytokines irritate tissue and increase IgE synthesis, therefore maintaining inflammatory response
• Cytokines are central to the pathogenesis of skin inflammation in AD
IMMUNOLOGIC ABNORMALITIES

• IL-4 and IL-13 are major components with underlying inflammation that causes itch and inflammation
• Underlying chronic inflammation is the source of primary signs and symptoms of AD
• Th2 specific cytokines demonstrate dominance in tissue samples
Filaggrin Gene Impairment

- Increased skin pH
- Decrease hydration
- Decreased *S. aureus* resistance
- Increased allergen
- Disorders of keratinization
  - Contact allergy
  - Peanut allergy
  - Hay fever
  - Asthma

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AGGRAVATING FACTORS

- Dry skin
- Sweating
- Heat
- Seasonal changes
- Infections
- Stress
- Harsh soaps, detergents, wool
- Food allergies
ASSOCIATED FACTORS

• Dennie Morgan folds
• Hertoghe’s Sign
• Pityriasis alba
• Keratosis pilaris
• White dermatographism
• Accentuated palmar creases
Dennie Morgan Folds
Hertoghe’s Sign

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Keratosis Pilaris
Accentuated Palmar Creases
Pityriasis Alba
DIFFERENTIAL DIAGNOSIS

- Seborrheic dermatitis
- Psoriasis
- Scabies
- Tinea
Distribution Pattern Varies With Age
COMPLICATIONS

- Secondary bacterial infections
- Higher incidence of herpes simplex
- Molluscum contagiosum
- Warts
Secondary Bacterial Infection
Impetigo
Eczema Herpeticum

Viral cultures: fresh vesicular fluid

Tzanck smear of open vesicle

Bacterial cultures

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Eczema Herpeticum Kaposi Varicelliform Eruption

- Painful, edematous, crusted vesicles
- Areas of pre-existing dermatitis: burns, atopic dermatitis
- Transmission through contact with person infected with HSV
- Dissemination of primary or recurrent HSV
ATOPIC DERMATITIS MANAGEMENT

• Hydrate with tub soaks and moisturizers
• Control inflammation with topical corticosteroids
• Reduce flare and control disease with immunomodulators (Protopic®, Elidel®, Eucrisa®)
• Treat secondary bacterial infections with topical and systemic antibiotics
• UVA and UVB phototherapy
PERCUTANEOUS ABSORPTION DETERMINED BY:

• Vehicle of steroid
• Integrity of epidermal barrier
• Occlusive dressings
• Humidity
FACTORS ENHANCING PERCUTANEOUS ABSORPTION

• Epidermal injury
• Heat
• Increased water content of stratum corneum
• Inflammation
INCREASING HUMIDITY

• Immersing skin in water results in uptake of water by the stratum corneum cells and saturation of its intercellular spaces

• Stratum corneum triples in thickness

• Water exposure results in replacement of lipid covalent bonds between stratum corneum cells by weak hydrogen bonds (water)

• Stratum corneum cells separate (maceration)
DECREASING HUMIDITY

• Excessive shrinking of the stratum corneum results in microscopic and macroscopic cracks in the stratum corneum
• Dry feel to skin surface
• Thin scales and erythema
Dalton Rule

• Molecular weight equal to or less than 500 are able to penetrate normal and abnormal skin barrier
TOPICAL STEROID PHARMACOLOGY

• Anti-inflammatory
• Antipruritic
• Vasoconstrictive
TOPICAL STEROIDS TREATMENT GOALS

• Simplicity

• Preserving or restoring normal physiologic state of the skin

• Delivered in optimal concentrations at site needed

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Factors to Consider When Choosing a Topical Corticosteroid

• Age of patient

• Treatment site

• Extent/severity of disease

• Duration of treatment

• Potency

• Formulation
TOPICAL STEROIDS

• Anti-inflammatory effect
• Molecular weight ≈200: penetrate into subcutaneous tissue and circulatory system
• Side effects:
  – Stria
  – Telangiectasias
  – Tachyphylaxis
  – HPA axis suppression results in reduced cortisol
TACHYPHYLAXIS

• Decrease in responsiveness to a drug as a result of enzyme induction

• Acute tolerance to vasoconstrictive action

• Vasoconstriction decreases progressively when potent steroid applied continuously

• Instruct patients to apply medications on interrupted schedule
TOPICAL STEROIDS STRENGTHS

• Anti-inflammatory properties result in part from ability to induce vasoconstriction of small blood vessels in the upper dermis
• Group I strongest to VII weakest
• Concentration cannot be used to compare strength
• Fluorination increases potency and side effects
VEHICLE OF TOPICAL STEROIDS

• Vehicle (base) is the substance in which the steroid is dispersed
• Determines the rate at which the active ingredient is absorbed through the skin
• Some bases may cause irritation or allergy
# Choice of Vehicle Is Important

<table>
<thead>
<tr>
<th>Consistency/ Appearance</th>
<th>Ingredients</th>
<th>Application Sites</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Creams</strong></td>
<td>Smooth; Silky</td>
<td>Oil and water mixture</td>
<td>All, including intertriginous areas</td>
</tr>
<tr>
<td><strong>Ointments</strong></td>
<td>Translucent; Greasy</td>
<td>Oil base</td>
<td>All, <em>EXCEPT</em> intertriginous areas</td>
</tr>
<tr>
<td><strong>Gels</strong></td>
<td>Jelly-like</td>
<td>Glycol and water mixture</td>
<td>Scalp, hairy areas</td>
</tr>
<tr>
<td><strong>Lotions and Solutions</strong></td>
<td>Thin, watery; Clear</td>
<td>Water and alcohol base</td>
<td>Scalp, hairy areas</td>
</tr>
<tr>
<td><strong>Aerosols</strong></td>
<td>Spray</td>
<td>Medication suspended in a base, pressurized</td>
<td>Scalp, most lesions</td>
</tr>
<tr>
<td><strong>Foams</strong></td>
<td>Frothy</td>
<td>High water content</td>
<td>Scalp, hairy areas</td>
</tr>
</tbody>
</table>
## Topical Steroids Potency Chart

<table>
<thead>
<tr>
<th>Group I</th>
<th>Group IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clobetasol, cream/oointment</td>
<td>Fluocinolone, cream/oointment</td>
</tr>
<tr>
<td>Halobetasol, cream/oointment</td>
<td>Cortisol, ointment</td>
</tr>
<tr>
<td>Diflorasone, cream/oointment</td>
<td>Prednicarbate, ointment</td>
</tr>
<tr>
<td>Betamethasone, ointment</td>
<td>Clocortolone, cream</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group II</th>
<th>Group V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone, cream</td>
<td>0.025% triamcinolone, cream</td>
</tr>
<tr>
<td>Halcinonide, cream/oointment</td>
<td>Fluticasone, cream</td>
</tr>
<tr>
<td>Fluocinonide, cream/oointment</td>
<td>Prednicarbate, cream</td>
</tr>
<tr>
<td>Desoximetasone, cream/oointment</td>
<td>0.025% triamcinolone, cream</td>
</tr>
<tr>
<td></td>
<td>Cortisol, cream/oointment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group III</th>
<th>Group VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone, ointment</td>
<td>Desonide, cream/oointment</td>
</tr>
<tr>
<td>0.1% triamcinolone, cream/oointment</td>
<td>Hydrocortisone, cream</td>
</tr>
<tr>
<td>Desoximetasone, cream</td>
<td></td>
</tr>
</tbody>
</table>

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IMMUNOMODULATORS IN ATOPIC TREATMENT

Calcineurin Inhibitors: (TCI’S)

Decrease atopic flare by:

- Decrease pruritis
- Decrease use of topical steroids
- Low systemic absorption
- Burning and warmth most frequent adverse event
TCI’s

• Tacrolimus (Protopic): first FDA approved immunomodulator
  – For moderate to severe AD
  – 0.03% 2-15 years of age
  – 0.1% 15 year and older

• Pimecrolimus (Elidel cream): second FDA approved immunomodulator
  – For mild to moderate AD
  – 2 years and older
Mechanism of Action

- Molecular weight 800: does not penetrate beyond the dermis
- Inhibits calcineurin, thereby suppressing T-cell activation
- Breaks the “scratch-itch” cycle
- Inhibits the release of inflammatory cytokines
- Systemic absorption minimal
- ↓Substance “P”: neurotransmitter which ↑itching
- Lipophilic
- Attach to T-cells, which sit high in the epidermis
- Local irritation, burning, pruritis, and erythema common, but decrease as skin heals

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Controversies: TCI’s

• Lymphomas:
  – Elidel: 5 million patients treated topically, over 50% children (Pediatric Advisory Committee 2005): 4 lymphomas, 2 cutaneous malignancies (1 SCC, 1 BCC) as of 12/31/04
  – Protopic: 1.7 million patients treated topically, ~33% were children. During first 3 years on the US market, 11 lymphomas reported as of 12/31/04: 5 cutaneous, 6 CTCL; none were children.

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Crisaborole 2% Ointment (Eucrisa)

• Approved December 2016
• Nonsteroidal PDE4 inhibitor (phosphodiesterase-4)
• Mild to Moderate AD > 2 years
• Reduces itching and inflammation
• Maintains skin barrier
• Supresses proinflammatory TH1 and TH2 cytokines, thereby inhibiting TNF alpha
• Molecular Weight 251
Dubilumab (Dupixent)

- Approved March 2017
- Injectable biologic therapy
- Blocks cytokines IL4 and IL13
- Indicated for adults with moderate to severe AD
Antihistamines

• Act by blocking the H1 receptors in the dermis

• Sedative effect provides relief to help patients sleep through the itch

• Nonsedating antihistamines may help treat co-existing allergies
Probiotics

• Currently explored as therapeutic option in treating atopic dermatitis

• Bacterial products may induce an immune response of Th-1 cells instead of Th-2 cells

• Probiotics may inhibit development of allergic IgE antibody production
Additional Treatment

- **Mimyx**: Antipruritic, Olive oil, glycerin, vegetable oil, hydrogenated lecithin, squalene
- **Epiceram**: Ceramides, cholesterol, free fatty acids. Normalizes pH
- **Eletone**: Petrolatum, H2O, mineral oil
- **Hylatopic**: Hyaluronic acid, ceramides, natural free fatty acids
Bathing

• Soaking in water: most effective method of hydrating the skin
  – Enhance penetration of topical treatments
• 10-20 minutes, lukewarm water: until fingertips prune
• Bleach Baths: 4oz bleach : 40 gallons H2O: reduce staph colonization; reduce antibiotic resistance and the need for antibiotics

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Moisturizing

• Apply to damp skin within 3 minutes of pat-drying
  – trap water in the stratum corneum
  – decrease further trans-epidermal water loss

• Reapply 3-4 x/day to maintain high level of hydration in the stratum corneum
A word about Preservative-free Moisturizers

• 125 samples: 49.6% contaminated with bacteria
  – 24% S. *Aureas*
  – .8% MRSA
  – 2.4% Group A *streptococcus*
  – 6.4% other bacteria
  – 16% Skin Flora
  – 50.4% No growth
Precautions

• Wash hands before using creams
• Use only products with approved preservatives
• If dispensed in a pump or tube, avoid contact with nozzle; wipe after each use
• Refrigerate open containers of unpreserved products such as ointments

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References

- Perry, Tamara T. Effects of Probiotics on Atopic Dermatitis: A Randomised Controlled Trial. Pediatrics; 2006, Vol 118

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