

ATOPIC 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

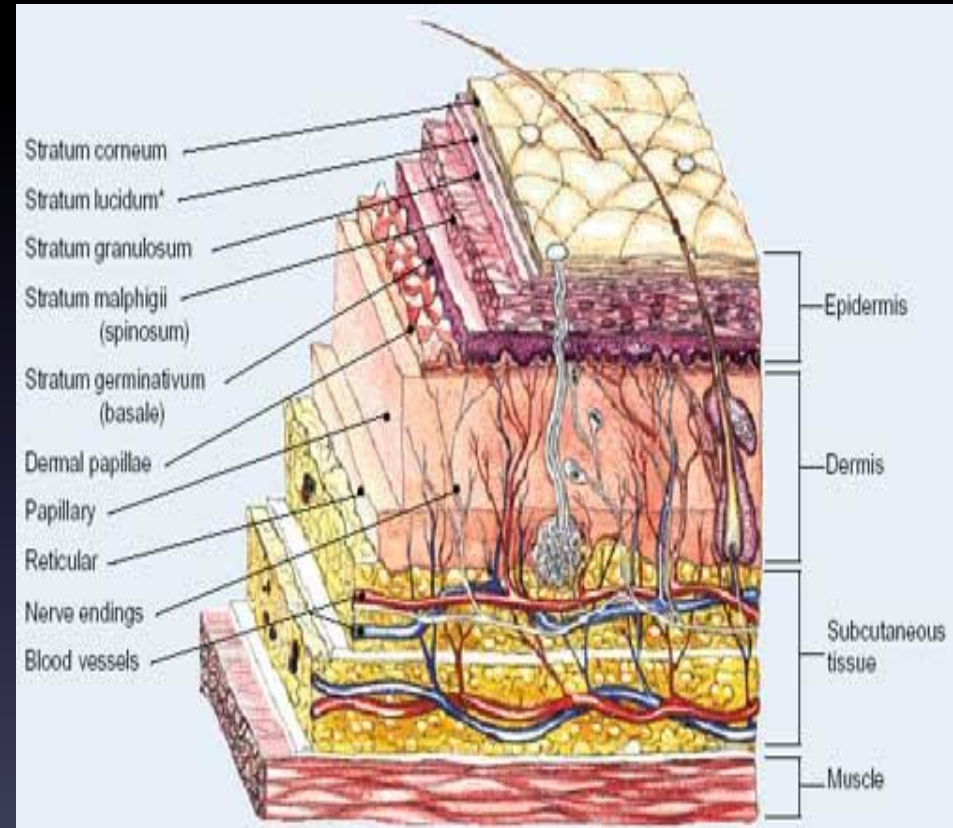
Lacks blood vessels

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
- Phosphodiesterase-4 (PDE-4): enzyme in the skin
 - Overactive PDE-4 has been shown to contribute to AD

Photosynthesis of Vitamin D



CLINICAL PRESENTATION

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





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



Lichenification



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Filaggrin Gene Impairment

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

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

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



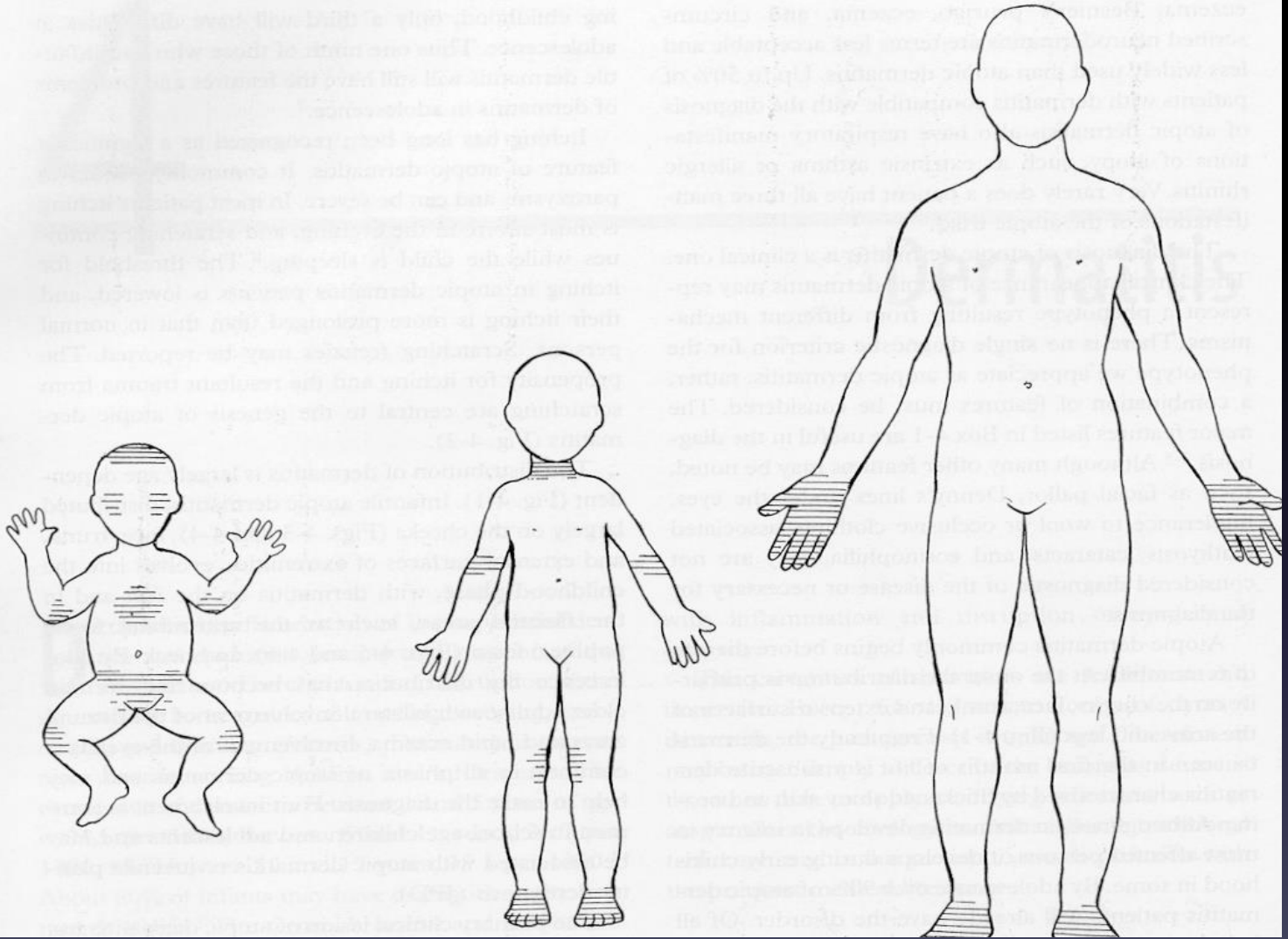
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Pityriasis Alba



DIFFERENTIAL DIAGNOSIS

- Seborrheic dermatitis
- Psoriasis
- Scabies
- Tinea



COMPLICATIONS

- Secondary bacterial infections
- Higher incidence of herpes simplex
- Molluscum contagiosum
- Warts

Secondary Bacterial Infection



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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[®])
- Treat secondary bacterial infections with topical and systemic antibiotics
- Manage pruritis with antihistamines
- UVA and UVB phototherapy

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

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

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

VEHICLES

- Creams
 - Mixture of oils and water
 - Emollient
 - May be used in all areas
 - Most useful in intertriginous areas
 - Cosmetically acceptable
 - Components may cause stinging, burning, or allergy

VEHICLES

- Ointments
 - Translucent
 - Greasy
 - More lubricating
 - Greater penetration of steroid, therefore higher potency
 - Too occlusive for intertriginous areas
 - Insoluble in water: difficult to wash off

VEHICLES

- Gels
 - Greaseless mixtures of glycol and water
 - Some contain alcohol
 - Jelly-like consistency
 - Cooling effect
 - Useful for exudative inflammation and in the scalp and hairy areas

VEHICLES

- Solutions and lotions
 - Water or alcohol base
 - Clear appearance
 - Useful for scalp: penetrate through hair
 - Leave no residue
 - May cause stinging in intertriginous areas

VEHICLES

- Aerosols
 - Steroids suspended in a base and delivered under pressure
 - Useful for scalp
 - Convenient for patients who lack mobility
 - Useful for moist lesions

Vehicles

- Foams
 - Minimal residue after application
 - Spread easily: helpful if treating larger BSA
 - High water content
 - Useful in hair-bearing areas

PERCUTANEOUS ABSORPTION DETERMINED BY:

- Vehicle of steroid
- Integrity of epidermal barrier
- Occlusive dressings
- Humidity

PERCUTANEOUS ABSORPTION

- Related to skin hydration
- In normal state of hydration, medications must pass through tight lipid barrier
- Hydration of the skin allows binding of water molecules to hydrophilic lipids, allowing water-soluble medications to pass between cells

PERCUTANEOUS ABSORPTION

- Factors that enhance hydration enhance percutaneous absorption
 - Plastic wrap
 - Airtight occlusion
 - Oils or ointments
 - Urea compounds
 - Propylene glycol

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

Factors to Consider When Choosing a Topical Corticosteroid

- Age of patient
- Treatment site
- Extent/severity of disease
- Duration of treatment
- Potency
- Formulation

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

•Group I

- clobetasol (Temovate) Cream/Ointment
- Halobetasol (Ultravate) Cream/Ointment
- Diflorasone (Psorcon) Cream/Ointment
- Betamethasone(Diprolene) Ointment
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•Group II

- Betamethasone (Diprolene) Cream
- Halcinonide (Halog) Cream/Ointment
- Fluocinonide (Lidex)Cream/Ointment
- desoximetasone
(Topicort)Cream/Ointment
-

•Group III

- fluticasone (Cutivate)Ointment
- Triamcinalone 0.1%
(Kenalog)Cream/Ointment
- Desoximetasone (Topicort) Cream

•Group IV

- Fluocinolone (Synalar) Cream/Ointment
- Cortisol (Westcort) Ointment
- prednicarbate (Dermatop)Ointment
- clocortolone (Cloderm)cream
-

•Group V

- triamcinalone .025% (Aristicort) Cream
- Fluticasone (Cutivate) Cream
- Prednicarbate (Dermatop)Cream
- triamcinalone .025% (Kenalog)Cream
- Cortisol (Westcort) Cream/Ointment
-

•Group VI

- desonide (DesOwen) Cream/Ointment
- hydrocortisone (Hytone) Cream

IMMUNOMODULATORS IN ATOPIC TREATMENT

Calcineurin Inhibitors:

Decrease atopic flare by:

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

Immunomodulators

- 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

Controversies: Immunomodulators

- 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
- Specific mechanism of action not well-defined

Antihistamines

- Act by blocking the H1 receptors in the dermis
- Sedative effect provides relief
- Treatment of 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
- Eleton: 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

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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