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
- 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
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

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Lichenification
Lichenification
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

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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

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Dennie Morgan Folds
Hertoghe’s Sign
Keratosis Pilaris
Accentuated Palmar Creases
Pityriasis Alba
DIFFERENTIAL DIAGNOSIS

• Seborrheic dermatitis
• Psoriasis
• Scabies
• Tinea
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
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 pruritus 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

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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

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TOPICAL STEROIDS

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

• **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 0.025% (Aristicort) Cream
  - Fluticasone (Cutivate) Cream
  - Prednicarbate (Dermatop) Cream
  - triamcinalone 0.025% (Kenalog) Cream
  - Cortisol (Westcort) Cream/Ointment

• **Group VI**
  - desonide (DesOwen) Cream/Ointment
  - hydrocortisone (Hytone) Cream

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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.
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
• 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
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

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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
References


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