The Itch that Rashes: A Review of Atopic Dermatitis for the Primary Care Physician

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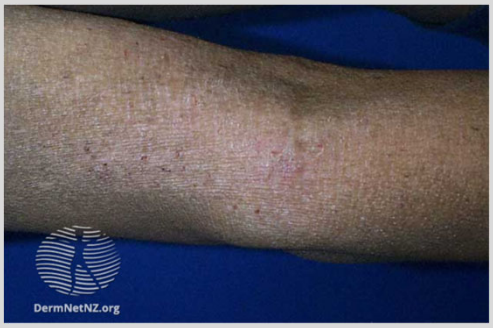
Atopic Dermatitis

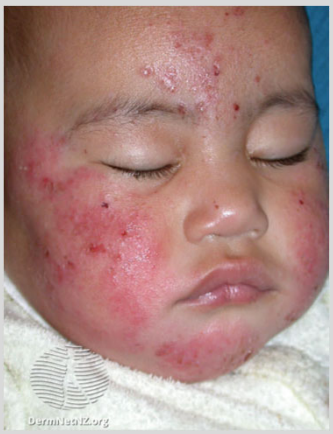
- Chronic inflammatory skin disease with intermittent episodes of intense itching and eczematous lesions
- 13% of U.S. children
  - 2.6 million with mod-severe disease
- 16.5 million U.S. adults (approx 7.3% of U.S. adult population)[1]
  - 6.6 million with mod-severe disease

1. Asthma and Allergy Foundation of America. Atopic Dermatitis 2021.

Hallmarks of AD

- Skin barrier dysfunction
- Inflammatory immune response
- Pruritus and skin dryness





Atopic Dermatitis as a Systemic Disease

AD's impact on overall health self-assessment

- 31.6% of self-reported severe AD rate QOL as **POOR**[1]

AD's association with other comorbidities

- Incr vascular inflammation
  - Higher odds of CAD/heart disease
- Diabetes

1. Silverberg J, et. Al. "Patient burden and quality of life in atopic dermatitis in U.S. adults: A population-based cross-sectional study." *Ann Allergy Asthma Immuno.* 2018: 121:340-347.

AD Comorbidities

Atopy: allergic rhinitis, asthma, and food allergy

- Not proven cause and effect: current hypothesis is skin barrier disruption incr risk of allergic disease

Behavioral Health Effects

- ADHD/ADD
- Depression/anxiety
  - Sleep deprivation
  - Higher rates of depression/anxiety (AD 20% vs nonAD 14.8%) and higher degrees of suicidal ideation[1]

1. Patel KR, et al. "Association between atopic dermatitis, depression, and suicidal ideation: A systematic review and meta-analysis." *J Am Acad Dermatol*. 2019;80(2):402. Epub 2018 Oct 23.

Risk Factors for AD: Genetic factors

- Family history of atopy
  - Approx 70% have a + family hx
  - Risk increase 3-5 fold if both parents with +atopy history[1]
- Filaggrin gene mutation→ barrier dysfunction[2]
  - RF for atopic dermatitis, allergies, allergic rhinitis

1. Eichenfield L, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol. 2014;70(2):338
2. van den Oord RA, Sheikh A SO Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. BMJ. 2009;339:b2433. Epub 2009 Jul 9.

Exacerbating Factors: Sensitizers/Allergens

Environmental allergens
- dust mites
- cat dander

Food sensitivities/allergens:
- cow's milk
- eggs
- wheat
- peanut

Exacerbating Factors: Environmental

Environmental Factors
- Climate: cold temperatures/winter weather
- Humidity: low humidity
  - Dry/arid environment
  - High altitude
  - Dehumidifiers
- UV Exposure
- Water (Hard water)
- Chemical exposures (Chlorine)
- Heat/Overheating

Pathophysiology: Skin Barrier Dysfunction

- Bricks and mortar: keratinocytes and intercellular adhesion molecules
- Stratum corneum
  - 1st line epidermal barrier to environment
  - Critical for transepidermal water retention[1]

- When stratum corneum altered:
  - increased TEWL
  - increased permeability
  - decr water retention/decr hydration
  - change in lipid composition ("mortar")

1. Kelleher M, et al. "Skin barrier dysfunction measured by transepidermal water loss at 2 days and 2 months predates and predicts atopic dermatitis at 1 year." J Allergy Clin Immunol. 2015;135(4):930. Epub 2015 Jan 22.

Pathophysiology: Epidermal Barrier Dysfunction

Filaggrin: structural protein critical for maintaining skin hydration and water retention

Filaggrin deficiency

- FLG gene mutation
- Loss of water retention
- Loss of cell-cell function adhesion
- Impaired keratinocyte differentiation and integrity

Pathophysiology: Inflam Immune Response

- Complex immune-mediated disease
- Type 2 helper T cells (Th2) cell-mediated inflammatory reaction
  - Th2 cytokines at play: **IL4, IL13, IL31, IL22**
  - Binding of IL4 or IL13 to the IL4 receptor complex
  - Activation of **JAK** 1, 2, 3
  - Activation of Signal Transducer and Activator of Transcription (**STAT**) 6 and STAT 3
  - ***Th2 cytokine production that promotes inflammation and inhibits skin barrier function***

AD Pathophysiology

- Skin barrier disruption
- Incr Type 2 Immune response: overexpression of Th2 cytokines, increased IgE, eosinophilia, and mast cell activation
- Acute response: IL 4, IL13
- Chronic phase: TH 1, IL17, IL22
- Neuropruritus: centralized sensitization of itch

AD Pruritus

Neuroinflammation– contributing to itch

- Transmitted along *unmyelinated, histamine-sensitive* and *non-histamine-sensitive* peripheral C-nerve fibers from dorsal root ganglia
- AD: itch transmitted along **non-histamine-sensitive** peripheral C nerve fibers and Th 2 immune cells

Impact of Microbes

- Altered skin microbiome with overgrowth of *Staph aureus*
  - Normal skin flora: *Streptococcus, Corynebacterium, Cutibacterium (formerly Propionibacterium)*
  - In AD: decrease in skin microbiome diversity
  - Bacterial proteins, incl Staph enterotoxins→ incr T cell cytokines and incr inflammation

Clinical Presentation

- Fluctuating course: intermittent episodes
- Disease activity: Acute vs chronic
- Consider age (pediatric, adult)
- Ethnicity: higher incidence in Asians and African-Americans
- Most common sx: dry skin and pruritus

Amer Acad of Derm Diagnostic Criteria[1]

Diagnosis based on clinical history and exam

Major criteria:

- Pruritus
- Eczema (acute, subacute, chronic)
  - Facial, neck, and extensor involvement in peds pts
  - Flexural lesions in adults
  - Sparing of groin and axillae
- Chronic or relapsing course

1. Eichenfield LF, et al. "Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis." *J Am Acad Dermatol*. 2014;70(2):338.

AAD Diagnostic Criteria (cont)

Minor Criteria

- Early age of onset (in childhood)
- Personal and/or family history of atopy
- Personal and/or family history of eczema
- Xerosis
- Elevated IgE levels

Atopic Dermatitis

Acute

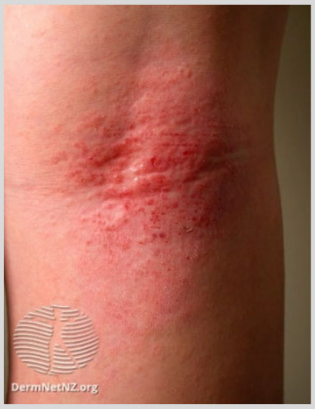
- Erythematous papules and patches, often with vesicles, exudative crusting

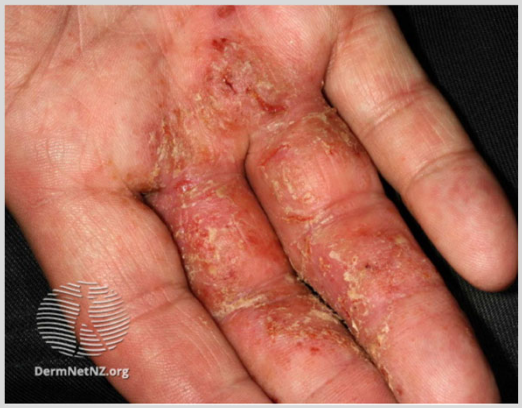
Chronic

- Erythematous papules and patches
- Dry scaliness with skin thickening (lichenification) and fissuring
- Pigmentary change: either hypo- or hyper- pigmentation
- Excoriations from chronic scratching

Acute AD

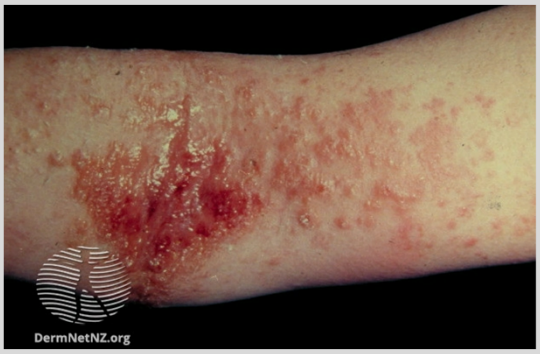
- Erythematous papules/patches
- Crusting

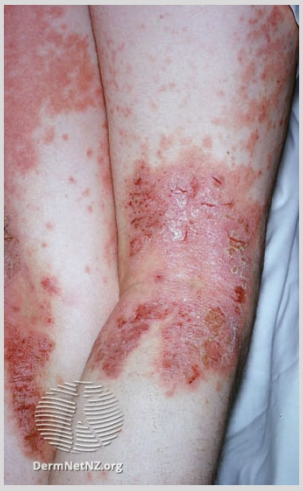




Acute AD

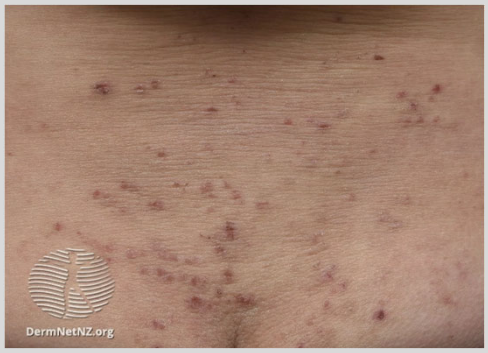
- Erythematous papules/patches
- Vesiculations

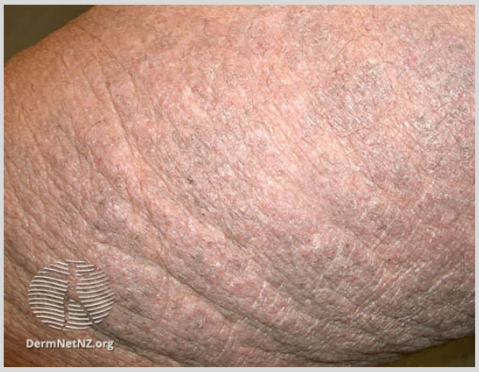




Chronic Atopic Dermatitis

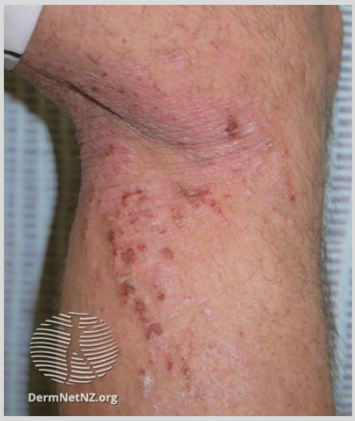
- Lichenification
- Excoriations
- Pigment change

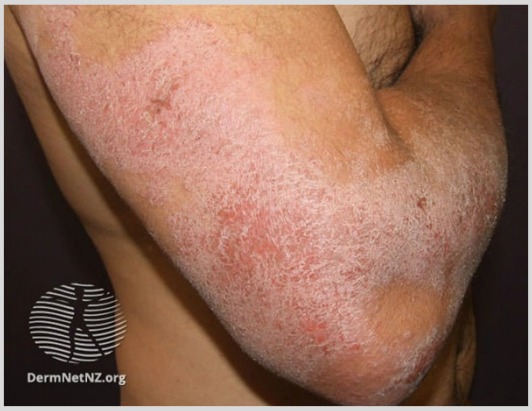




Chronic AD

- Dry scaliness and lichenification
- Pigment changes, esp on skin of color
- Excoriations





Chronic AD

- Skin of color: hyper- or hypo-pigmented areas
- Hyperlinearity of skin markings

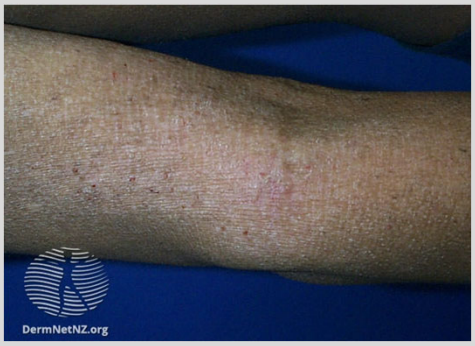
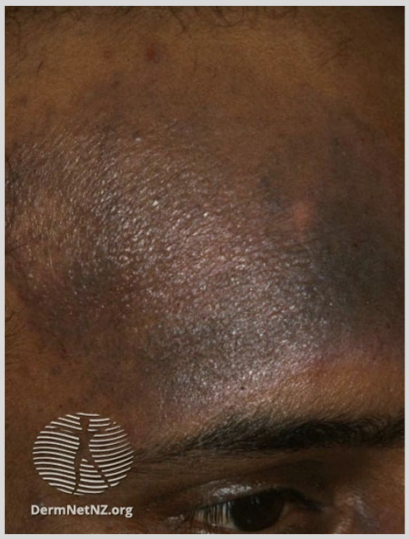


Image courtesy of Waikato District Health Board for DermNetNZ.org

Chronic AD: Postinflammatory dyspigmentation

- Hypopigmentation in some
- Hyperpigmentation in others



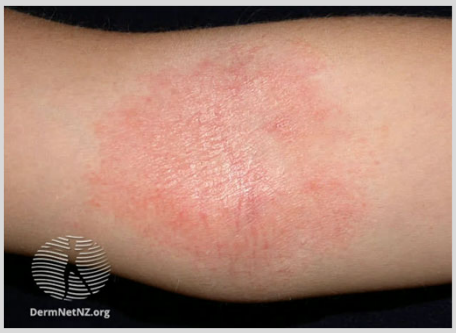
AD Distribution

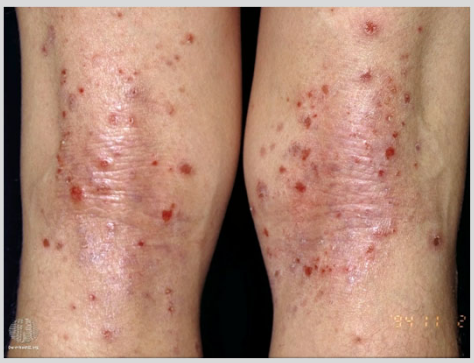
- Common locations:
  - Flexural antecubital and popliteal fossae
  - Volar wrists, ankles, neck
  - Infants: often on cheeks

  - Hand eczema
  - Eyelid dermatitis
  - Nipple dermatitis

Flexural Involvement

- Antecubital or popliteal fossae





Hand Involvement

- Acute AD on different skin types

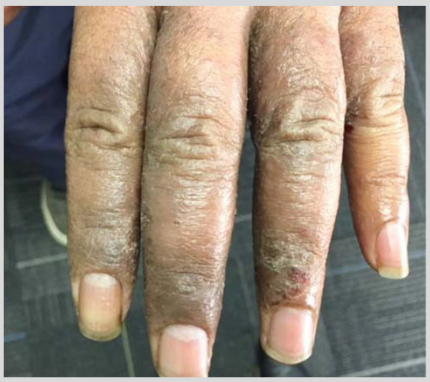
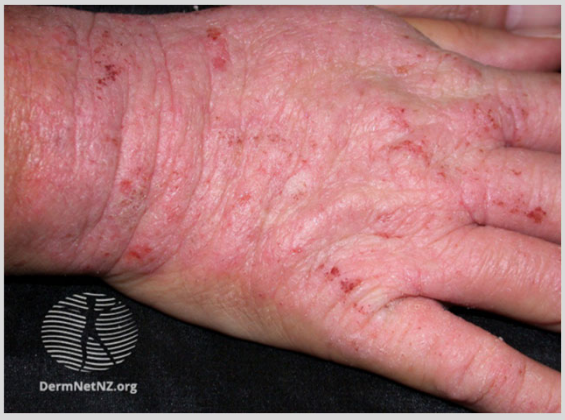
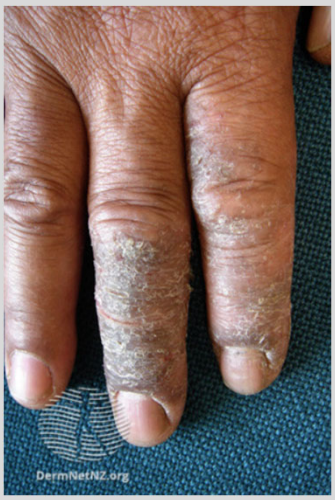


Image courtesy of Waikato District Health Board for DermNetNZ.org

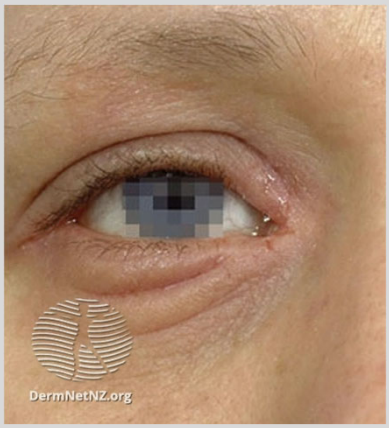
Hand involvement

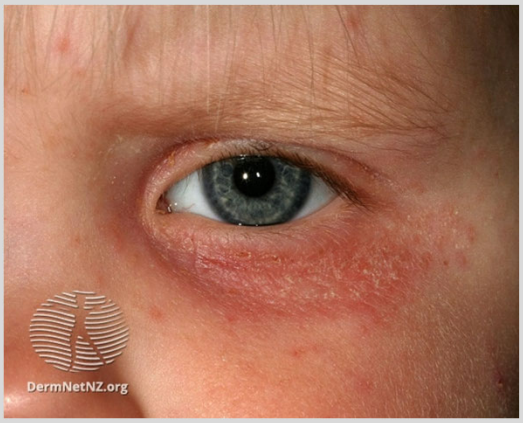
- Chronic AD on different skin types





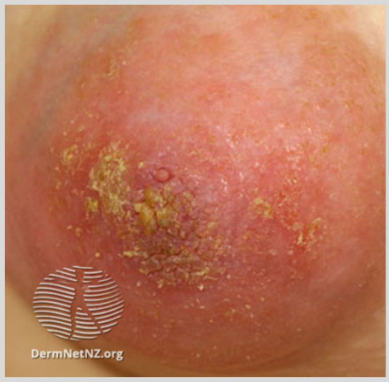
Eyelid Involvement





Infraorbital Dennie-Morgan folds

Nipple Involvement



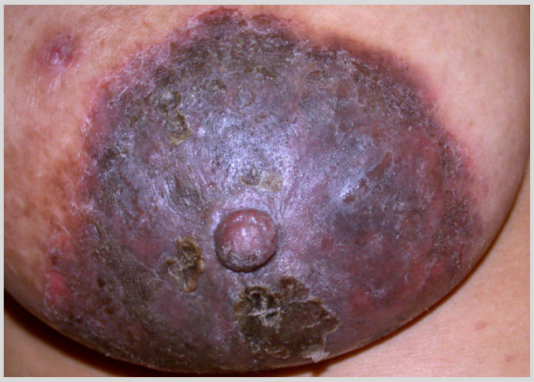


Image courtesy of Waikato District Health Board for DermNetNZ.org

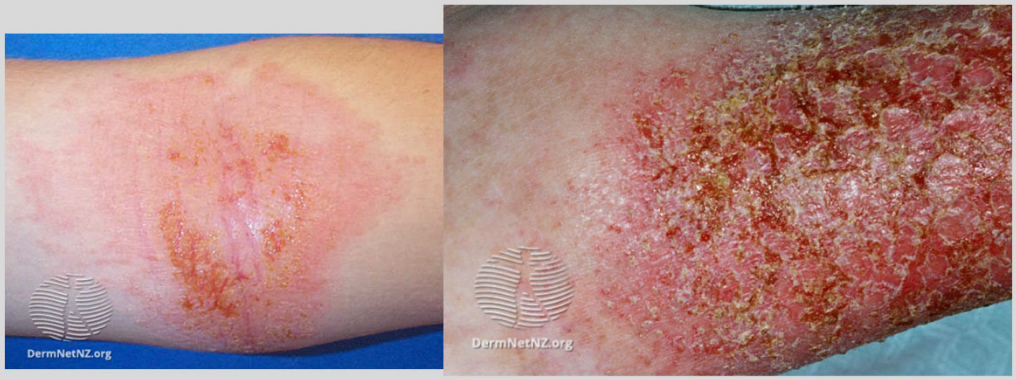
AD Complications

- Secondary bacterial infections
  - Predisposition with *S. aureus* colonization
  - Disruption of normal skin flora, altered skin microbiome
  - Impetiginization
  - Excoriations/scratching

- Viral infections: Eczema herpeticum
  - Disseminated *HSV* infection
  - Recurrent atypical Hand, Foot, and Mouth (HFMD *Coxsackievirus A6*)

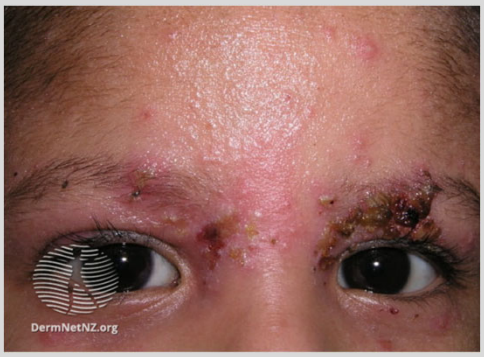
Secondary infection: bacterial

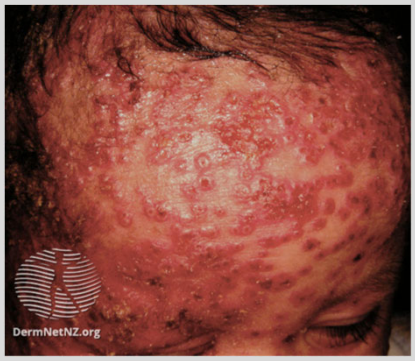
- Disrupted skin barrier + scratching→ bacterial infection
- Impetiginized areas with crusting



Secondary infection: Viral infections

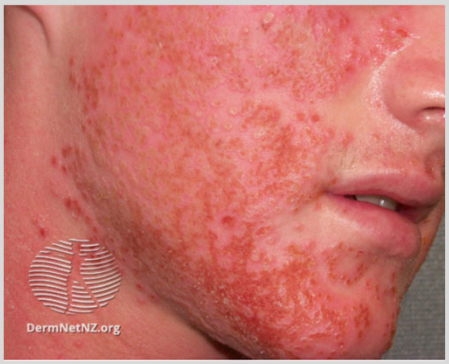
- HSV infection: Ezcema Herpeticum
- Widespread punched-out erosions, crusts, blisters
- Itchy from AD, painful from HSV
- Must treat with systemic antivirals

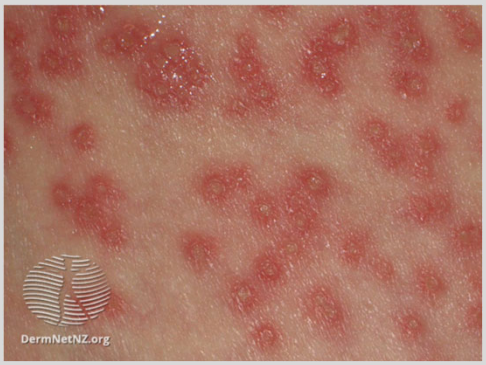




Eczema Herpeticum

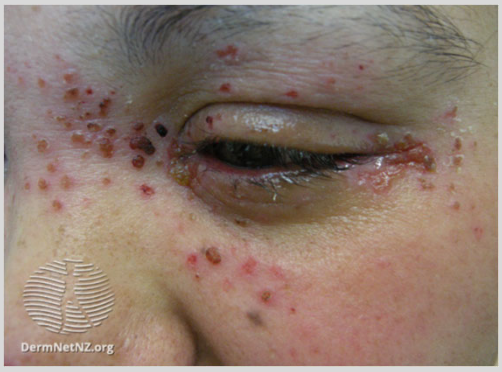
- Punched out ulcerations
- Increased pain
- Can be mistaken for bacterial infection: look for punched out ulcers

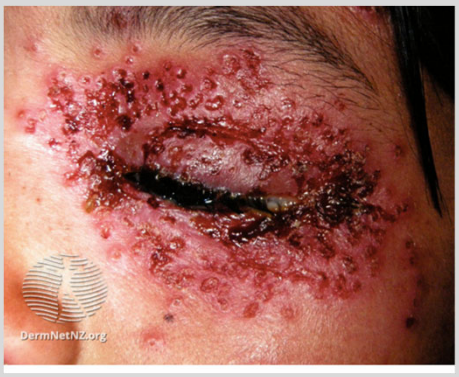




Secondary infection: Eczema Herpeticum

- TREAT ASAP





How to assess disease severity?

- Extent of disease
  - Clinical Symptoms
  - Body surface area involved
- Impact on quality of life
  - Psychosocial impact
  - Sleep deprivation
  - Daily activities

How to quantify disease severity in AD?

EASI: Eczema Area and Severity Index (0-72)

- Disease severity in terms of surface area involvement and clinical symptoms

Body Region	Clinical Signs (4 pt scale)	% Area Involved (7 pt scale)
Head/Neck	Erythema	% Area involved
Upper Extremities	Induration	
Trunk	Excoriation	
Lower Extremities	Lichenification	

How to assess disease impact?

SCORAD: **SCOR**ing **A**topic **D**ermatitis

- Disease severity and clinical signs
- Extent of disease: body surface area
- Patient self-reporting symptoms (Scale 0-10)
  - Pruritus
  - Sleep disturbances over past week

Goals of Treatment: Control, not cure

- Symptom relief/itching
- Prevent flares
- Control disease/skin lesions
- Minimize risks of therapy

Treatment considerations:

- Efficacy
- Safety
- Ease of use
- Cost

Treatment Management

- Skin hydration
- Restore skin barrier function
- Eliminate exacerbating factors
- Patient/Parent education

Decrease inflammation ➡ Decrease itch

Patient compliance

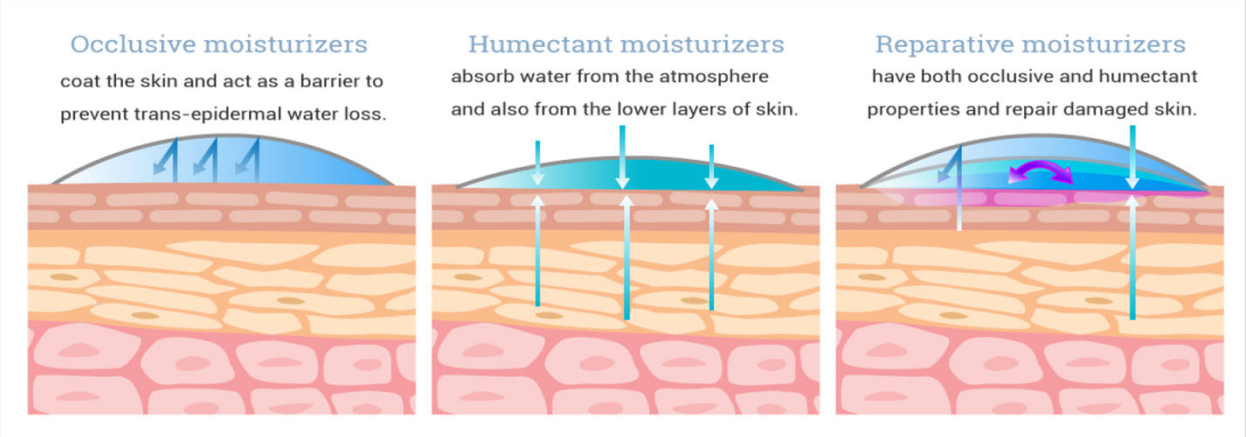
- Regular daily regimen
- Tools to manage flares

Skin Moisturization: Critical for AD control

- Xerosis (Dryness): Loss of moisture in skin→ **MOISTURIZE, MOISTURIZE, MOISTURIZE**

More water, less oil; easier to apply LOTIONS → Water and oil CREAMS → More oil, less water; thicker and most moisturizing OINTMENTS

Moisturizers



Schematic courtesy of Toni Lewis McCullough, MD

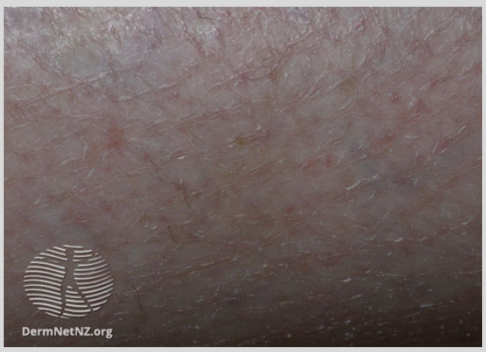
Moisturizer 101

Emollients/Occlusives	Humectants	Reparatives
Coat the skin, acts as barrier protection, and prevent TEWL	Absorb water from atmosphere and lower layers of skin	Improved lipid function to repair damaged skin barrier
Lanolin	Glycerin	Ceramides
Petrolatum	Hyaluronic Acid	Free Fatty Acids
Dimethicone	Lactic Acid	
	Urea	

Skin Hydration

- Apply twice daily
- Apply immediately after bathing/showering
- Apply multiple times to areas if needed
  - Ex: hands after hand washing

↓ Itch ↓ # of flares



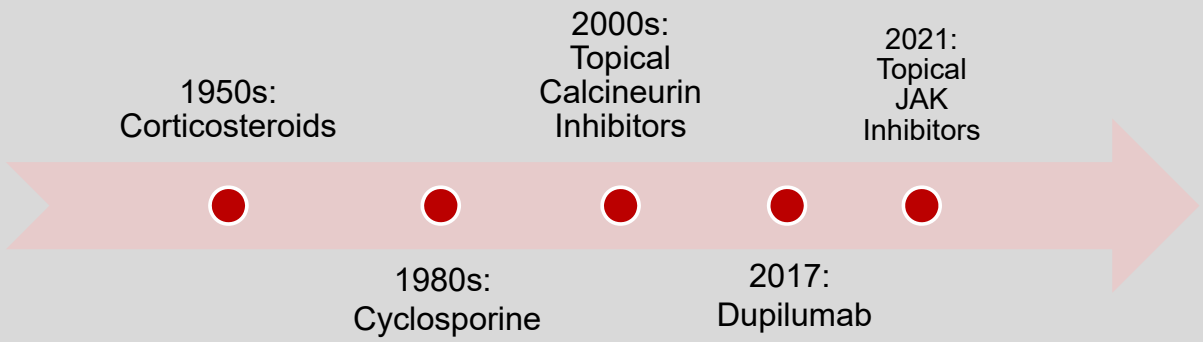
Moisturize, Moisturize, Moisturize

- Moisturize consistently
- Ceramide moisturizers can help treat the symptom (dryness) and the cause (barrier dysfunction)
- Tailor moisturizer to area you are treating
- Avoid scents, perfumes, fragrances
- “organic” and “natural” can still be sensitizers and irritants

Moisturizing and Bathing Recs

- Daily bathing <10-15 min in shower/bath
- Lukewarm temperatures (avoid hot showers)
- Mild soaps: avoid fragrances, perfumes, harsh ingredients
- Avoid additives in general with exceptions:
  - can use colloidal oatmeal
  - can use diluted bleach (½ cup in full bath/40 gallons, 1tsp/1gallon)
  - can use diluted vinegar/acetic acid
  - Pat dry and immediately apply emollients to damp skin

Treatment Breakthroughs



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Topical steroids

- Recommend ointment over creams
- Familiarize yourself with a few in each class/potency
- Once daily dosing as efficacious as twice daily

Class/Potency	Steroid
Class 1: Ultrapotent	clobetasol propionate 0.05%, halobetasol propionate 0.05%
Class 2	betamethasone dipropionate 0.05%, desoximetasone 0.25%
Class 3	betamethasone valerate 0.1%, triamcinolone 0.1%
Class 4	hydrocortisone valerate 0.2%
Class 5	hydrocortisone butyrate 0.1%
Class 6	aclometasone dipropionate 0.05%, desonide 0.05%
Class 7: Low potency	hydrocortisone 2.5%

Wet Wraps

Wet wraps (new version of “sauna suits”) 2-3 x weekly

- Apply emollients +/- topical steroids
- Wrap area with damp cotton pajamas covered with a dry pair of cotton PJs
- Keep on for minimum of 4 hours if tolerated
- Make sure wet layer does not dry out, repeat if needed

Nonsteroidal Topicals: Calcineurin Inhibitors

Tacrolimus (Brand Protopic) and pimecrolimus (Brand Elidel)

- Tacrolimus 0.1% ointment > tacrolimus 0.03% > pimecrolimus 1% cream
- Inhibit cytokines production → decr immune response to Ag
- FDA approved for > age 2
- No skin atrophy
- Pts often note transient burning and stinging
- No definitive incr risk of lymphoma (tacrolimus, black box warning)
- Still $$$

Nonsteroidal Topicals

Topical phosphodiesterase inhibitors

Crisaborole (Brand Eucrisa)

- PDE4 inhibitor for mild-mod AD ≥ 3 months
- Target cytokines that cause pruritus
- Pain and burning when applied

Phototherapy

- Narrow band ultraviolet B phototherapy (NBUVB) 311 nm
- Ultraviolet A phototherapy + Psoralen= PUVA, 320-400 nm

- Decreased immune response in the skin→ decr pruritus
- 2-3 sessions each week, < 10-15 min per session
- Improvement within 15-20 treatments, switch to weekly maintenance
- In-office or home unit

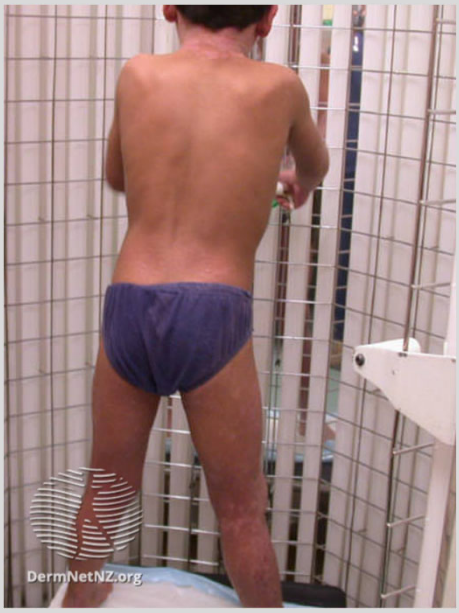
Phototherapy

Pros

- Highly effective for most
- Improved pruritus and clearance of skin lesions
- No systemic therapy required

Cons

- Cost
- Inconvenience if in-office treatment
- Incr risk of skin cancer with UVA or UVB exposure



Traditional Systemic Medications

Systemic Steroids

- IM triamcinolone (40-60 mg)
- Prednisone taper over several weeks
- Short term option while transitioning to other immunosuppressants
  - With severe flares
  - When need rapid relief of flare
  - Transition to other systemic meds

Traditional Systemic Medications

Cyclosporine

- Rapid control of disease, particularly itching
- Short-term option as bridge to more longterm systemic option
- Avoid longterm use
- 2.5-5 mg/kg daily dosing
- Monitoring CBC, renal function, BP

- Add'l options: methotrexate, mycophenolate mofetil, azathioprine

Dupilumab (Brand name: Dupixent)

- Fully human monoclonal antibody inhibiting IL4 and IL13
  - Binds to α subunit IL4 R→ inhib ILK4 and IL13 from Th2 helper cells
- 1st FDA approved 2017 in adults
- Now FDA approved ≥ age 6
  - Adult Loading dosage: 600 mg SQ
  - Adult Maintenance: 300 mg SQ every other week
- Significant improvement in pruritus and skin lesions
- Majority achieving EASI-75 and EASI-90 scores

Dupilumab

- No lab monitoring required

- Adverse SE
- OCULAR
  - *Conjunctivitis* most common, 10-25%
  - Keratitis
  - Eye dryness/stinging
- Facial Redness ?hypersensitivity reaction
- Injection site reactions
- HSV cold sores

New Targeted Therapies

JAK Inhibitors targeting JAK-STAT pathway

- Particularly effective b/c JAK signal itch
- Targeting cytokine pathways to decrease inflammatory response
- Quick in onset, usually w/i 1-2 weeks
- Dramatic relief of itching

JAK Inhibitors

Topical	Targets
Ruxolitinib	JAK 1, JAK 2
Delgocitinib	JAK 1, JAK 2, TK2, TK3
Oral	
Baricitinib	JAK 1, JAK2
Abrocitinib	JAK 1
Upadicitinib	JAK 1

Topical JAK inhibitors

- Likely best suited for mild-mod AD (<20% BSA)
- Rapid itch relief
- Well tolerated/less irritating than calcineurin inhibitors
- Comparable to medium potency topical steroids without the adverse steroid effects, ie no skin atrophy

Ruxolitinib ointment (Brand Opzelura)

Delgocitinib cream (mainly available in Japan)

Oral JAK inhibitors

Baricitinib

Abrocitinib

Upadicitinib

- Rapid relief of itching and improved skin lesions
- Improvement us within 1-2 weeks
- BUT…

JAK Inhibitor Adverse Events

Black box warnings
- Serious infections
- DVT/Thromboembolism
- Malignancies

Common SE:
- Nasopharyngitis/URI
- Nausea
- Headache
- Acne

Less common SE:
- Infections
  - HSV/Eczema Herpticum
  - VZV/Zoster
- Abnl labs: neutropenia, elev CPK

New Therapies

Tralokinumab: FDA approved 12/2021

- Fully human monoclonal anti-IL13 antibody
- Approved for mod-severe AD
- Dosage: 300 mg SQ every other week

Ongoing Clinical trials

Nemolizumab: anti-IL31 monoclonal Ab

Lebrikizumab: anti-IL13 monoclonal Ab

Fezakinumab: anti IL-22 monoclonal Ab

Approach to AD Treatment

- Skin care regimen
- Avoid triggers
- Decrease skin infection burden

AD Treatment Algorithm

- Start with emollients applied multiple times a day and topical steroids once daily
- Consider areas being treated and severity of flare when choosing topical steroids and limit to 2-4 weeks
  - Trunk/extremities: higher potency topical steroids
  - Head/neck, axillae: lower potency topical steroids
- Transition to lower potency topical steroids if able
- Institute non-steroidal anti-inflammatory topical options
- Maintenance topicals: frequent moisturizers, intermittent rx topical

Manage secondary infection

Disruption of skin barrier → higher susceptibility to infection

Bacterial *Staph aureus*

- Localized infection can be treated with topical mupirocin
- More extensive, then treat with oral abx (cephalosporin or penicillinase-resistant PCNs).
- If recurrent infection or recalcitrant infection, check culture for bacterial resistant staph or other organisms

Staph decolonization

- Frequent bathing with diluted bleach/diluted vinegar
- Antibacterial soaps/chlorhexidine showers
- Mupirocin in nares, perirectal
- Eliminate Staph carriers in the household/household contacts

Moderate-Severe AD→ Systemic therapy

- Longterm phototherapy
- Systemic therapy
  - Short-term cyclosporine/methotrexate
  - Short-term systemic steroids
  - Mycophenolate mofetil
  - Azathioprine
  - Dupilumab
  - Oral JAK inhibitors

Causes of Treatment Failure

- Refractory disease requiring systemic immunosuppressants
- Noncompliance, particularly with daily moisturizing regimen
- Undertreatment with topical steroids/skin care techniques
- Environmental factors
- Untreated infection
- Hypersensitivities/allergens
  - Allergic contact dermatitis
    - Lanolin, propylene glycol, perfumes/fragrances
  - Food/Environmental

Treatment failures: Incorrect diagnosis?

Is it really atopic dermatitis? Other dermatologic conditions can look like eczema

Skin biopsy

- Cutaneous T-Cell Lymphoma
- Psoriasis
- Allergic Contact Dermatitis
- Vitamin deficiencies, such as zinc
- Primary immunodeficiencies (Severe Combined ID, Hyper-IgE)

Summary of AD

- Chronic inflammatory skin disease
- Pruritus and skin dryness
- Targeted therapy
  - Address inflammation
  - Many new therapeutic options
  - JAK inhibitors as potential game-changers

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Thank you for your attention.

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