LiVDerm
REVOLUTIONIZING DERMATOLOGY EDUCATION

LIVE WEBINAR
A COMPLIMENTARY CME/CE-CERTIFIED

A New Wave of Systemic Treatments: ATOPIC DERMATITIS, MEET JAK

EDUCATIONAL **PRIMER**

Melinda Gooderham, MD

Brett King, MD

Kim Papp, MD

EXPERT SPEAKERS

Melinda Gooderham, MD

Assistant ProfessorQueens UniversityMedical Director SKiN Centre for Dermatology Investigator with Probity Medical Research Consultant Peterborough Regional Health CentrePeterborough, Ontario, Canada

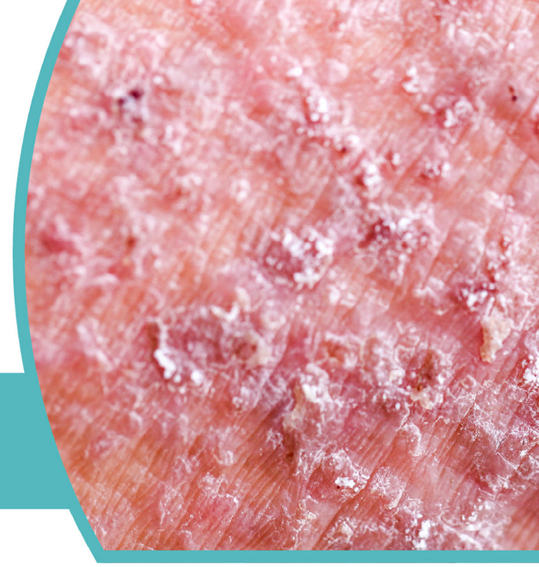
Brett King, MD

Associate Professor of Dermatology Yale School of Medicine New Haven, Connecticut

Kim Papp, MD

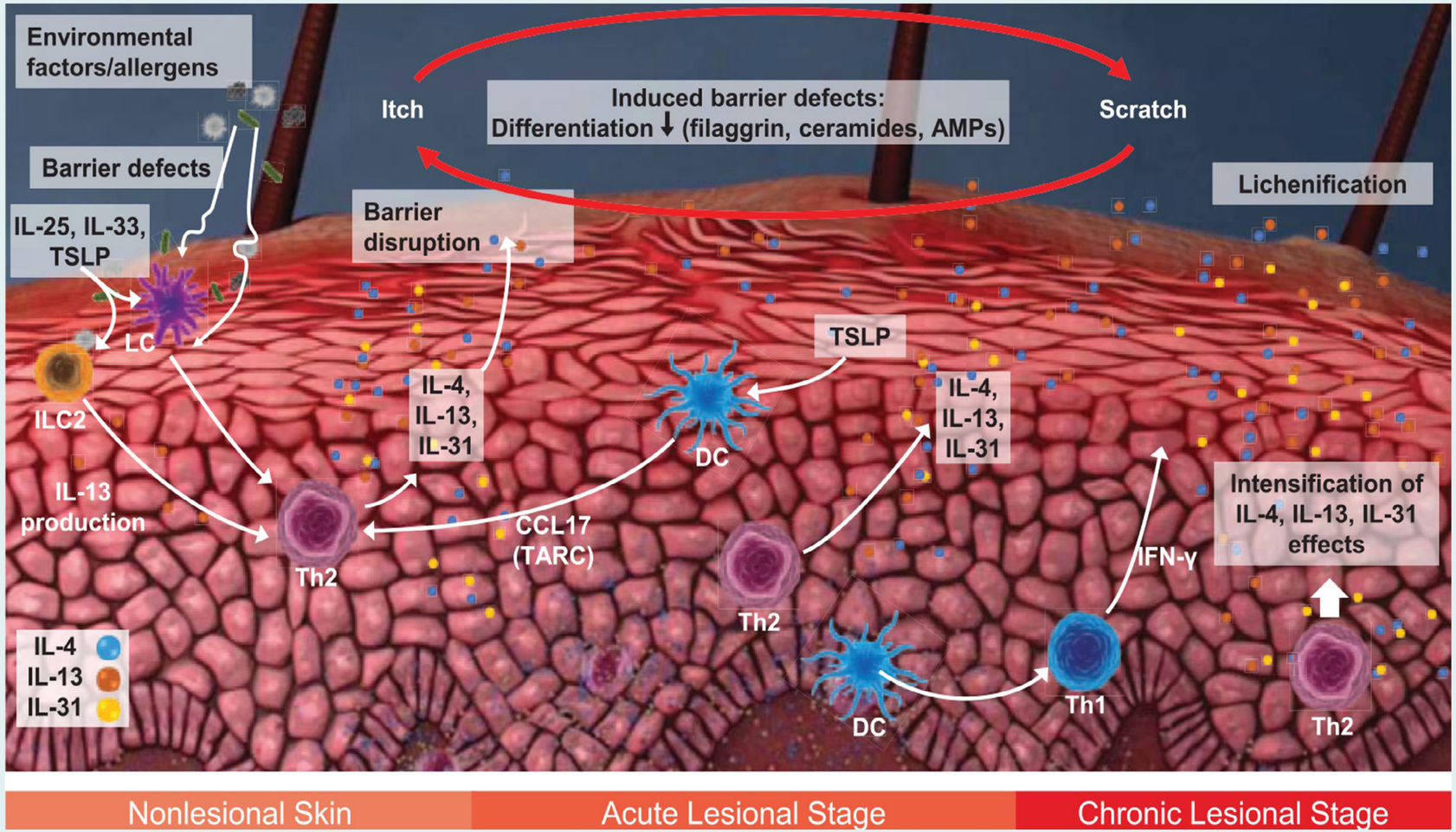
President and Director of Research, IncProbity Medical Research Waterloo, Ontario, Canada

LiVDerm
REVOLUTIONIZING DERMATOLOGY EDUCATION



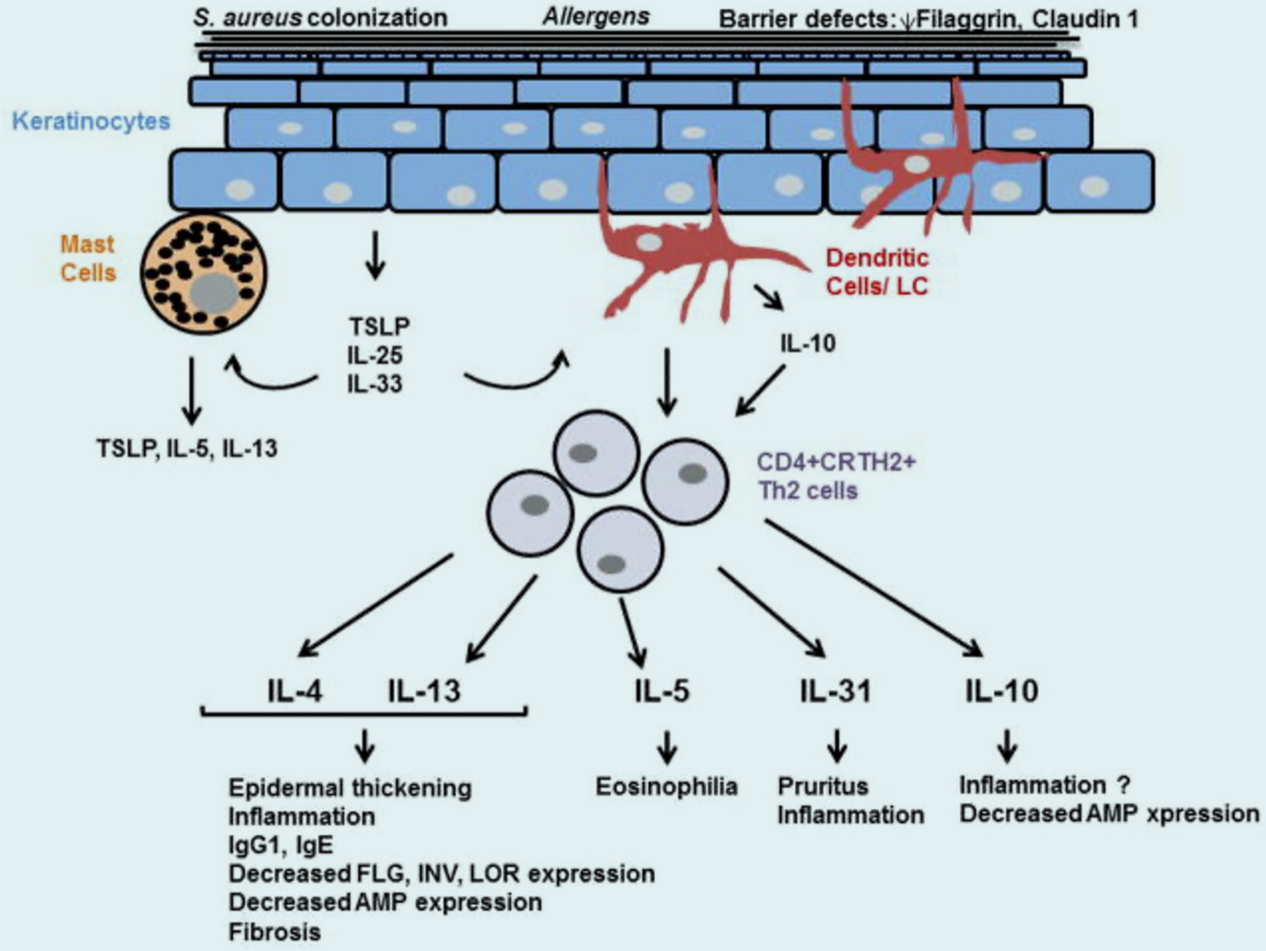
AD PATHOGENESIS

SKIN BARRIER INTEGRITY BREAKDOWN AND TRIGGERS



Kichhof MG, Landells I, Lynde CW, et al. J Cut Med Surg. 2018

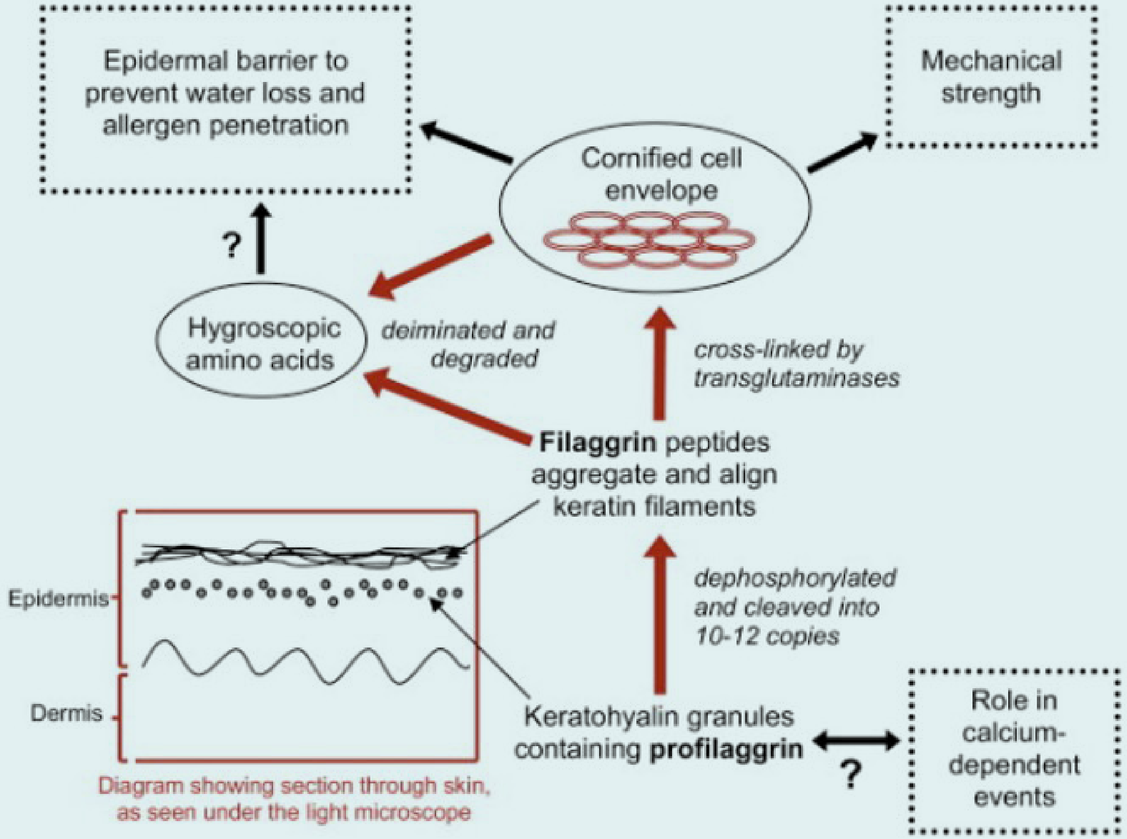
SKIN BARRIER INTEGRITY BREAKDOWN AND TRIGGERS, SIMPLIFIED



Brandt EB, Sivaprasad U. J Clin Cell Immunol 2011

THE ROLE OF FILAGGRIN IN AD PATHOGENESIS

filament-aggregating protein



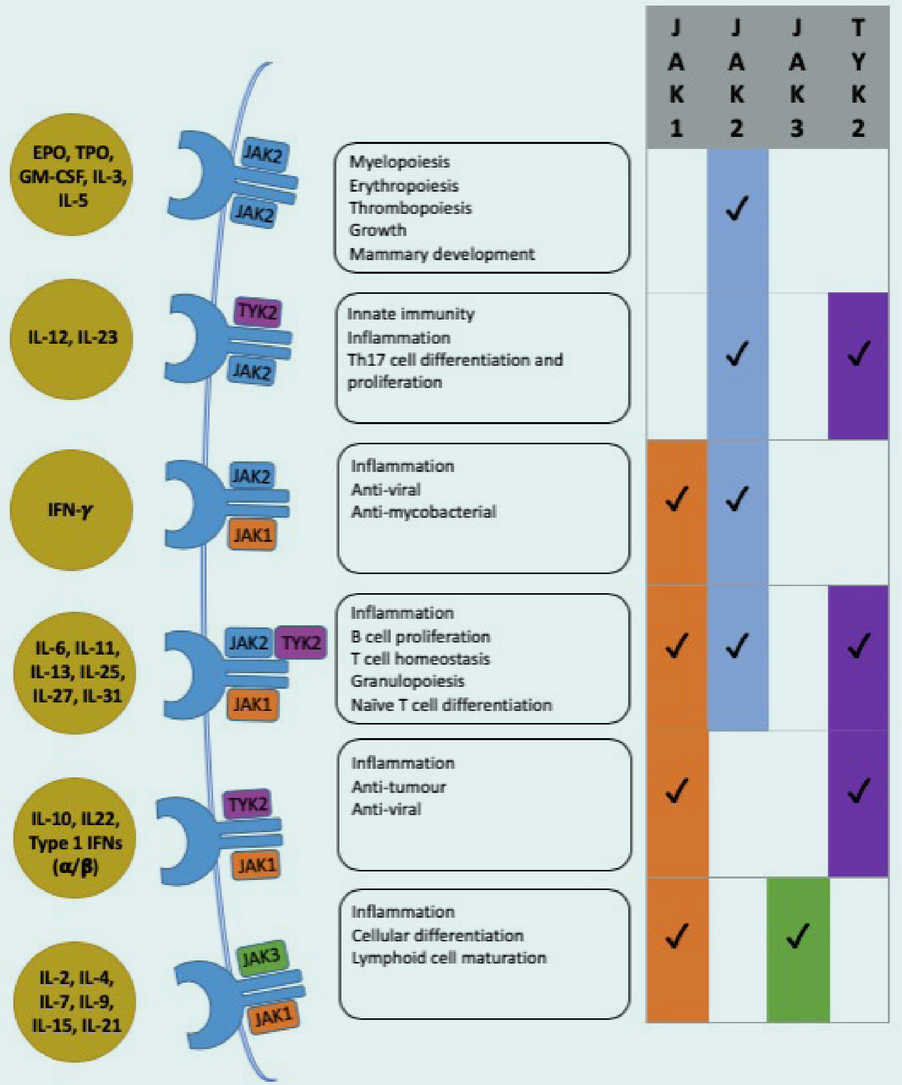
Brown SJ, Irvine AD. Atopic eczema and the filaggrin story. Semin Cutan Med Surg. 2008 Jun;27(2):128-37.

KEY CYTOKINE SIGNALING PATHWAYS IN AD PATHOPHYSIOLOGY

IL-5: Jak1/Jak2

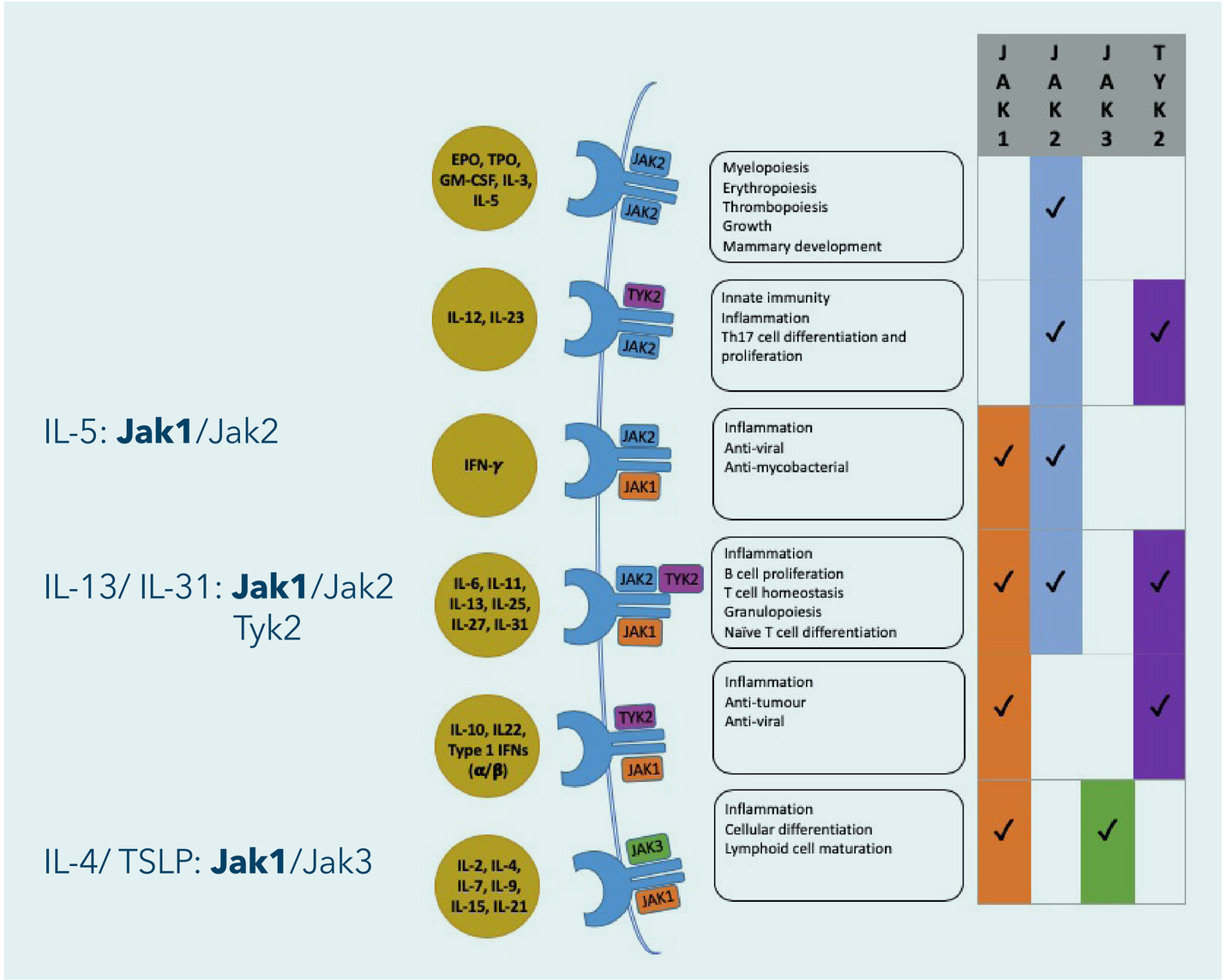
IL-13/ IL-31: Jak1/Jak2 Tyk2

IL-4/ TSLP: Jak1/Jak3



Lin CMA, Cooles FAH, Isaacs JD. Medit J Rheum. 2020; Murray PJ. J Immunol 2007; Morris R, Kershaw N, Babon JJ. Proetin Sci. 2018

JAK PATHWAYS USED BY KEY CYTOKINES



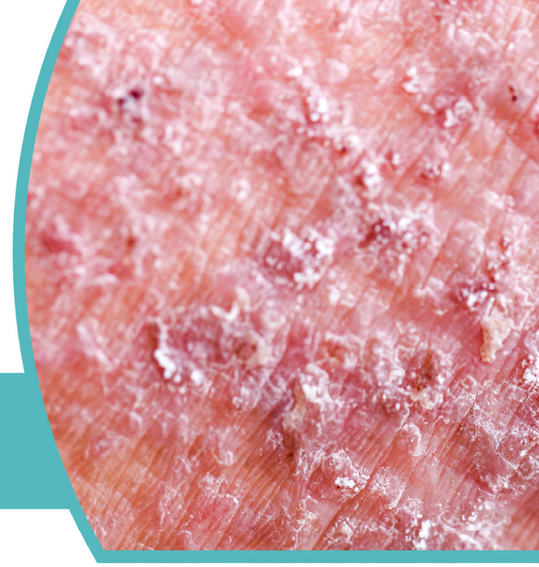
IL-5: **Jak1**/Jak2

IL-13/ IL-31: **Jak1**/Jak2 Tyk2

IL-4/ TSLP: **Jak1**/Jak3

Lin CMA, Cooles FAH, Isaacs JD. Medit J Rheum. 2020; Murray PJ. J Immunol 2007; Morris R, Kershaw N, Babon JJ. Proetin Sci. 2018

LiVDerm
REVOLUTIONIZING DERMATOLOGY EDUCATION



DIAGNOSIS

AD: DIAGNOSTIC FEATURES

- **ESSENTIAL FEATURES**; must be present:
  - Pruritus
  - Eczema (acute, subacute, chronic):
    - Typical morphology and age-specific patterns*
    - Chronic or relapsing history

  Patterns include:
  1) facial, neck, and extensor involvement in infants and children;
  2) current or prior flexural lesions in any age group;
  3) sparing of groin and axillary regions.

- **IMPORTANT FEATURES**; seen in most cases, adding support to the diagnosis:
  - Early age of onset
  - Atopy
    - Personal and/or family history
    - IgE reactivity
  - Xerosis

- **ASSOCIATED FEATURES** ; these clinical associations help to suggest the diagnosis of AD but are too non-specific to be used for defining or detecting AD for research and epidemiologic studies:
  - Atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response)
  - Keratosis pilaris / pityriasis alba / hyperlinear palms / ichthyosis
  - Ocular / periorbital changes
  - Other regional findings (e.g., perioral changes / periauricular lesions)
  - Perifollicular accentuation / lichenification / prurigo lesions

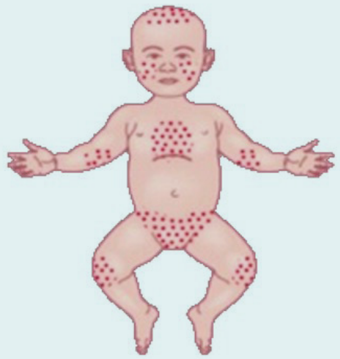
- **EXCLUSIONARY CONDITIONS;** it should be noted that a diagnosis of AD depends on excluding conditions such as:
    - scabies
    - seborrheic dermatitis
    - contact dermatitis (irritant or allergic)
    - ichthyoses
    - cutaneous T-cell lymphoma
    - psoriasis
    - photosensitivity dermatoses
    - immune deficiency diseases
    - erythroderma of other causes

Eichenfield LF, et al. J Am Acad Dermatol. 2014;70:338-351.

AD PRESENTATION OVER TIME

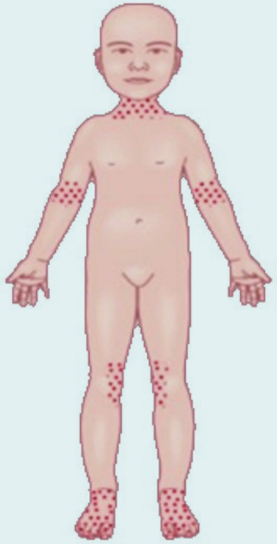
INFANTILE TYPE

Face, scalp, trunk, extensor surfaces or extremities



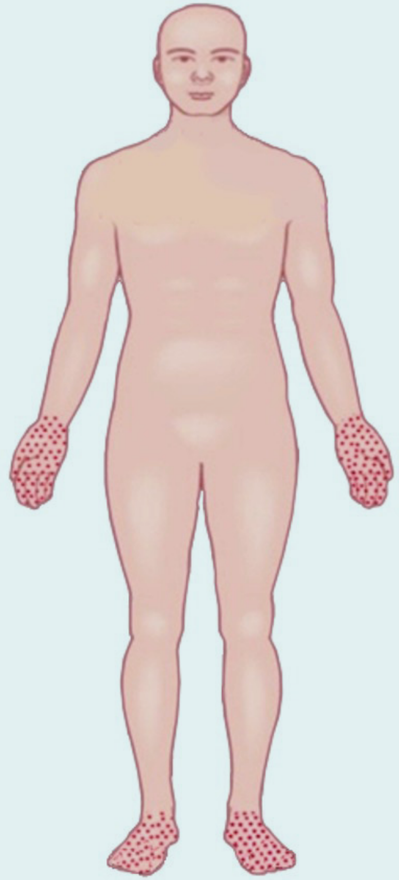
CHILDHOOD TYPE

Flexural folds of extensors (antecubital, popliteal fossa, neck, ankles)



ADULT TYPE

Upper arms, back, wrists, hands, fingers, feet, toes



Eichenfield LF, et al. *J Am Acad Dermatol*. 2014;70:338-351. Napolitano M, et al. G Ital Dermatol Venereol. 2016;151:403-411. Krafchik BR. Atopic dermatitis. In: Schachner LA, Hansen RC. *Pediatric Dermatology*. 4th ed. Elsevier: 2011;851-866.

ASSESSMENT OF AD SEVERITY • OBJECTIVE

- Validated AD-specific severity scales
  - **SCORAD** (**SCOR**ing **A**topic **D**ermatitis index): includes extent, sleep, and itch
  - **EASI** (**E**czema **A**rea and **S**everity **I**ndex): includes extent
  - **IGA** (**I**nvestigator's **G**lobal **A**ssessment): simple 0- to 5-point scale
- SCORAD and EASI may be too cumbersome for clinical practice
- IGA is simple, quick, and useful

1. Charman CR et al. Arch Dermatol 2004;140:1513-19. 2. Vakharia PP et al. Br J Dermatol 2018;178:925-30. 3. Schmitt J et al. Allergy 2012;67:1111-17. 4. Hill MK et al. J Am Acad Dermatol 2016;75:906-17. 5. Lewis V and Finlay AY J Investig Dermatol Symp Proc 2004;9:169-80. 6. Heinl D et al. Allergy 2016;71:358-70. 7. Phan N et al. Acta Derm Venereol 2012;92:502-7. 8. Ständer S et al. Acta Dermo Venereol 2013;93:509-14

ASSESSMENT OF AD SEVERITY
• SUBJECTIVE

- Validated Patient Reported Outcome (PRO) measures
  - **POEM**, **P**atient-**O**riented **E**czema **M**easure
  - **DLQI**, **D**ermatology **L**ife **Q**uality **I**ndex;
  - **Pruritus NRS**, numerical rating scale
- POEM is specific for AD and captures itch and sleep
- DLQI is well-known and already used in many practices, but not AD specific

1. Charman CR et al. Arch Dermatol 2004;140:1513-19. 2. Vakharia PP et al. Br J Dermatol 2018;178:925-30. 3. Schmitt J et al. Allergy 2012;67:1111-17. 4. Hill MK et al. J Am Acad Dermatol 2016;75:906-17. 5. Lewis V and Finlay AY J Investig Dermatol Symp Proc 2004;9:169-80. 6. Heinl D et al. Allergy 2016;71:358-70. 7. Phan N et al. Acta Derm Venereol 2012;92:502-7. 8. Ständer S et al. Acta Dermo Venereol 2013;93:509-14

AD MANAGEMENT ISSUES

IMPACT ON TREATMENT CHOICE

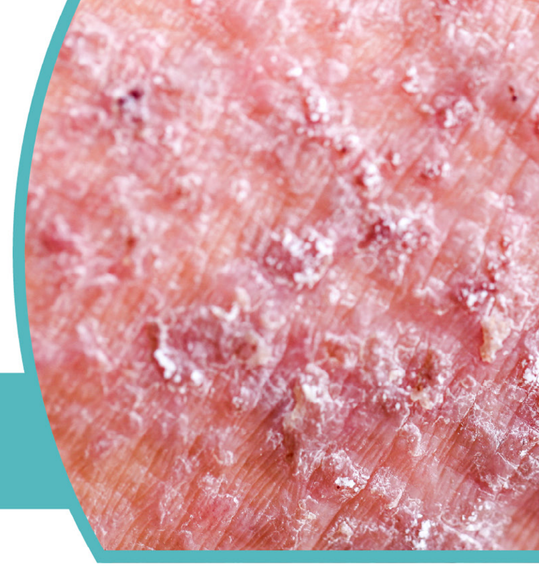
- Patient preference and ability
- Safety and efficacy
- Cost and access
- Comorbidities

THERAPEUTIC GOALS

- To reduce symptoms, prevent exacerbations and minimize therapeutic risks
- Prolonged remission and infrequent flares
  - Improved adherence through easy-to-use and simple, effective regimen
  - Improved QoL, including restful sleep and undisturbed activities of daily living

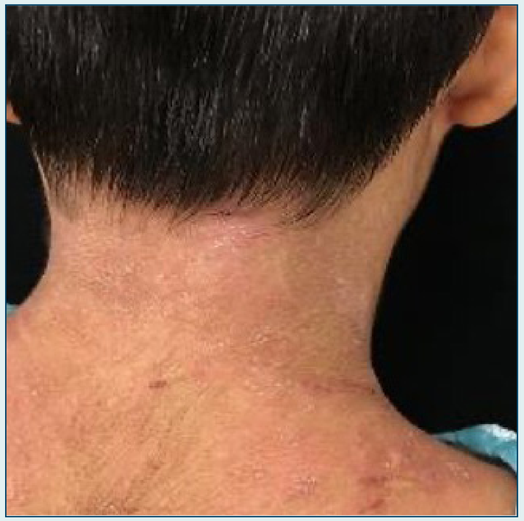
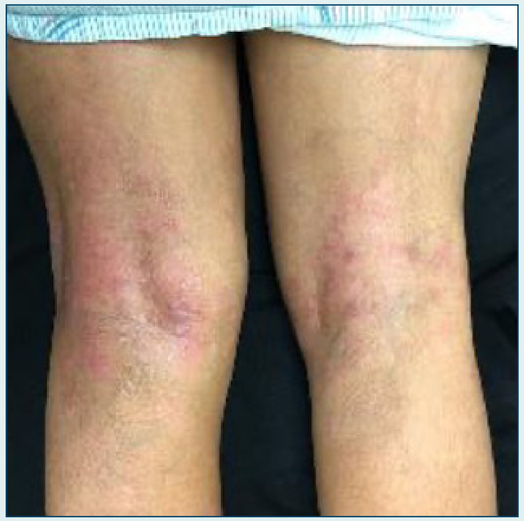
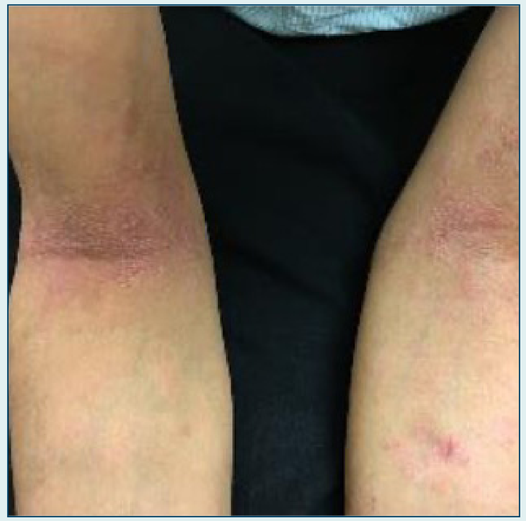
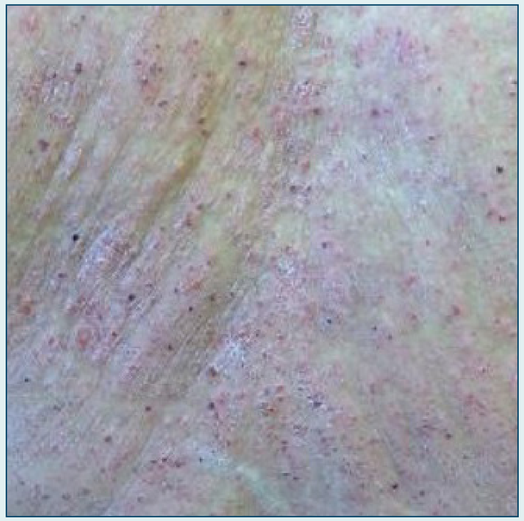
Retzler J, et al. Qual Life Res. 2019;28:2373-2381. Tollefson MM, Bruckner AL. Pediatrics. 2014;134:e1735-e1744. Weston WL, Howe W. Treatment of atopic dermatitis. 2020 (https://www.uptodate.com/contents/treatment-of-atopic-dermatitis-eczema).

LiVDerm
REVOLUTIONIZING DERMATOLOGY EDUCATION



CURRENT TREATMENT

A New Wave of Systemic Treatments: Atopic Dermatitis, Meet JAK

Brett King, MD, PhD
Yale University School of Medicine

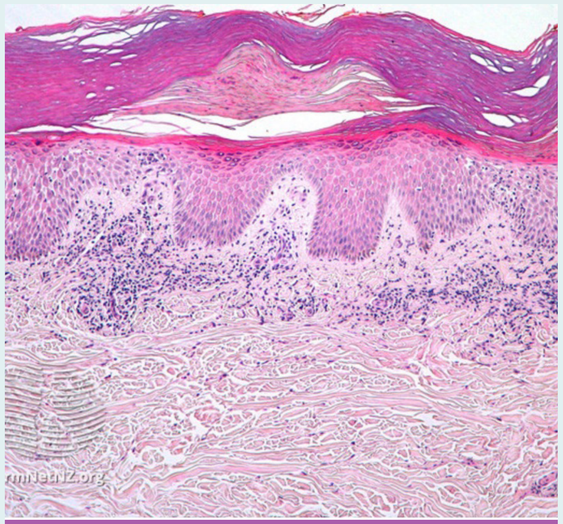
AD ASSESSMENT TOOLS

- **Investigator's Global Assessment (IGA)** = 5-point scale assessing AD signs (e.g., erythema, edema, excoriation, lichenification)
- **EASI, SCORAD** = composite assessments of AD signs over body regions -/+ patient reported symptoms (pruritus, sleep disturbance)
- **Pruritus NRS** = patient-reported itch intensity on a 0 (no itch) – 10 (worst imaginable itch) point scale

NRS=numerical rating scale

Simpson E, et al. J Am Acad Dermatol 2020;83:839-46. Hanifin JM, et al. Exp Dermatol.2001;10:11-18. Phan NQ, et al. Acta Derm Venereol. 2012;92:502-7.

WHAT IS KNOWN IS…



Predominantly T cell infiltrate on H&E

TREATMENT IS…

- Prednisone
- Cyclosporine
- Mycophenolate
- Methotrexate
- Azathioprine

DermNet.NZ.org

CYCLOSPORINE

Double-blind, controlled, crossover study of cyclosporin in adults with severe refractory atopic dermatitis

- 33 patients who had failed conventional therapy
- Double-blind, placebo-controlled, crossover study
- Treatment: Cyclosporin 5 mg/kg per day

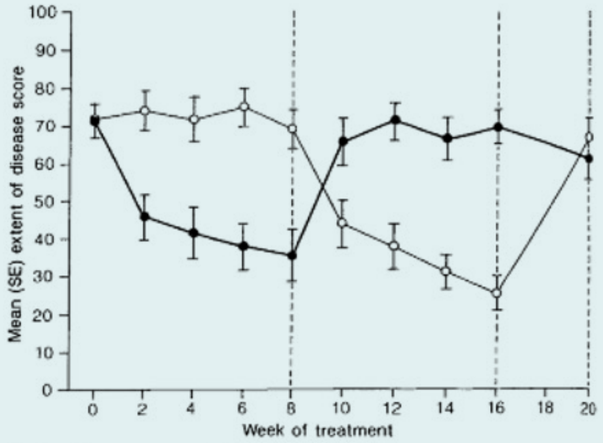


Fig 3—Mean extent of disease score.

——○—— Placebo/cyclosporin sequence, ——●—— cyclosporin/placebo sequence. Mean score with cyclosporin treatment = 30·3%; mean score on placebo = 69%; treatment difference (95% CI) = −38·7% (−46·1 to −31·4), p < 0·001.

Extent of disease=% BSA affected by AD

Sowden JM, et al. Lancet. 1991:338;137-40.

METHOTREXATE, AZATHIOPRINE

A randomized trial of methotrexate versus azathioprine for severe atopic eczema

- 42 patients who were unresponsive, contraindicated, or intolerant to cyclosporine treatment
- Treatment: 1:1 to methotrexate 10-22.5 mg/wk or azathioprine 1.5-2.5 mg/kg/d for 12 weeks, followed by a 12-week follow-up period

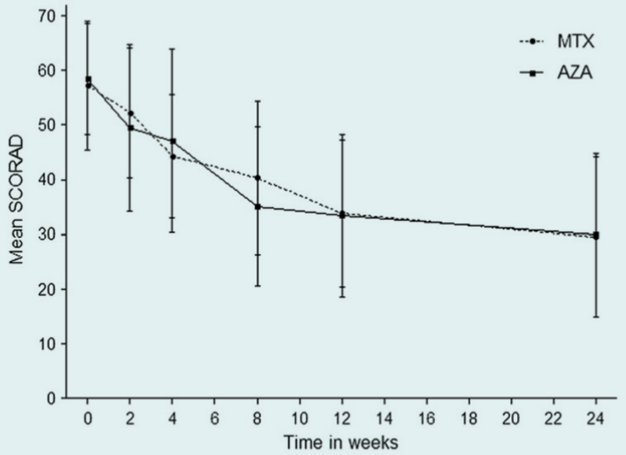


FIG 2. Mean (SD) scores for the SCORAD score at baseline, during treatment, and during follow-up. *AZA*, Azathioprine; *MTX*, methotrexate.

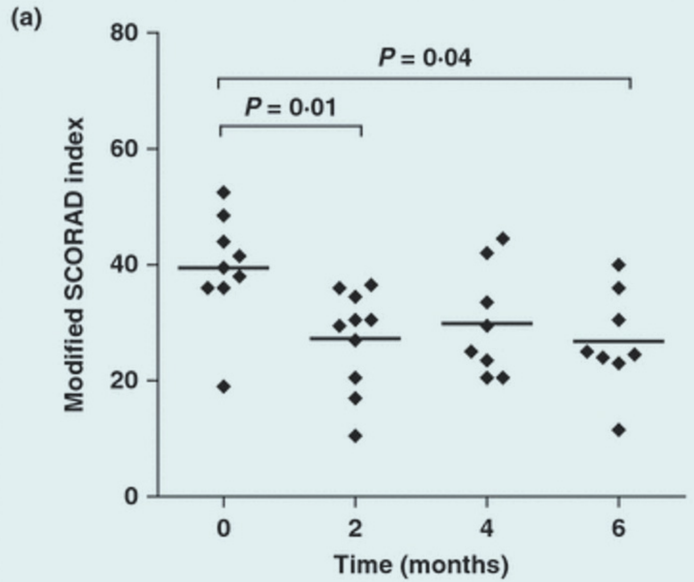
SCORAD=Scoring of Atopic Dermatitis

Schram ME, et al. J Allergy Clin Immunol. 2011;128:353-9.

MYCOPHENOLATE

First experience with enteric-coated mycophenolate sodium (Myfortic®) in severe recalcitrant adult atopic dermatitis: an open label study

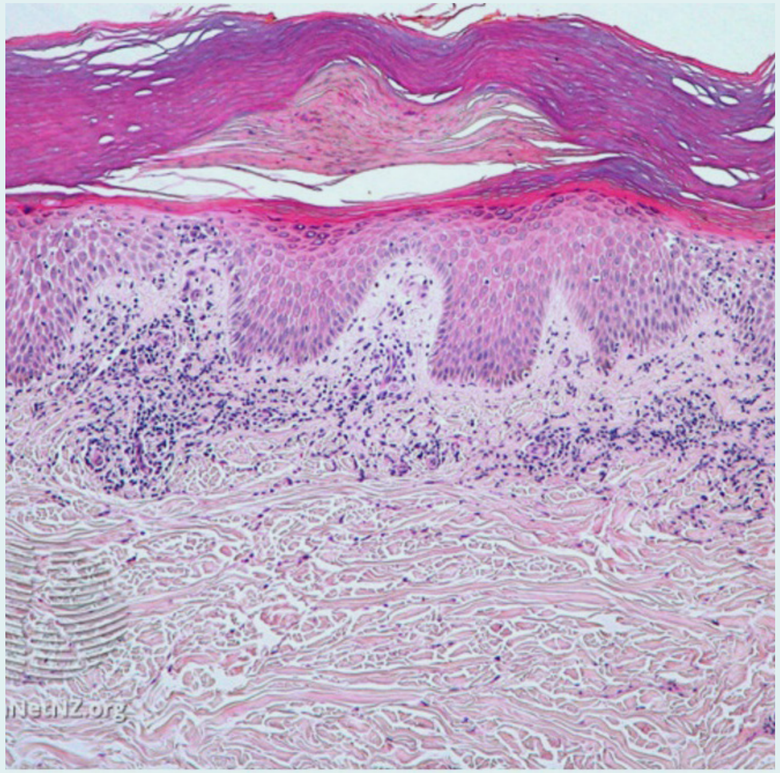
- 10 patients who had failed treatment with topical corticosteroids, cyclosporine, +/- phototherapy
- Treatment: Enteric-coated mycophenolate 720 mg* BID for 6 months



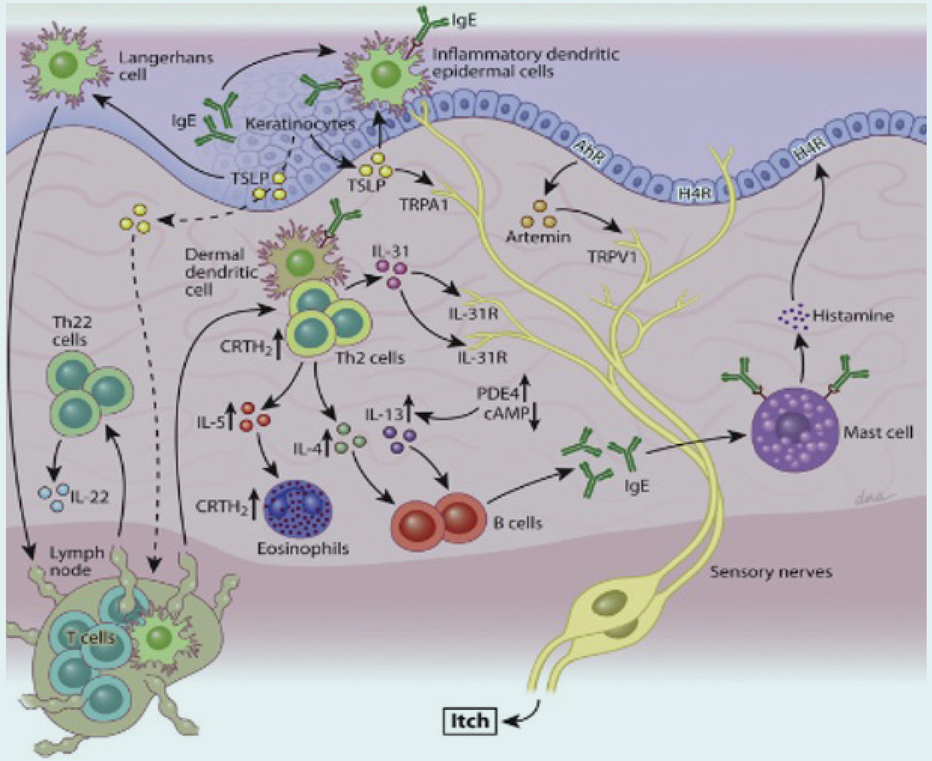
*Same as MMF 1000 mg BID
SCORAD=Scoring of Atopic Dermatitis

Van Velsen SGA, et al. Br J Dermatol. 2009:160;687-91.

FROM THE PAST TO THE PRESENT



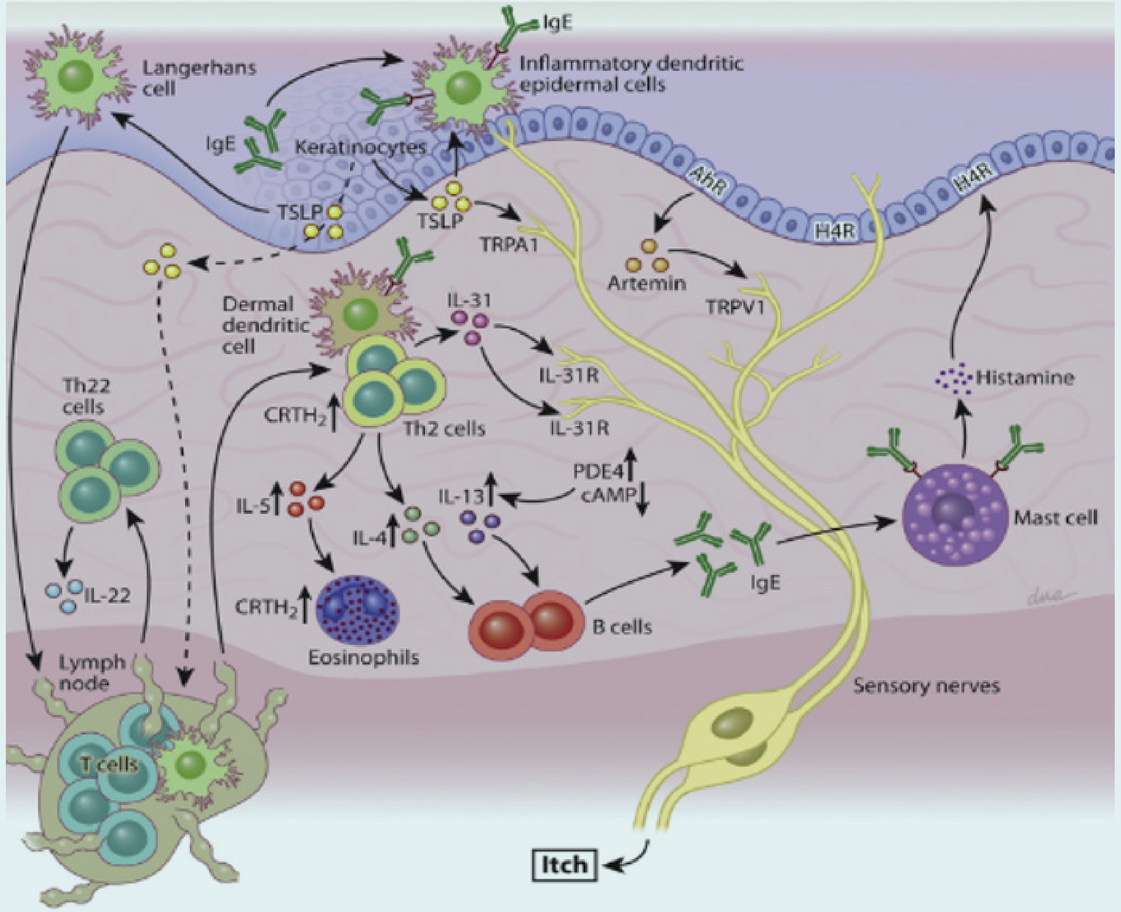
DermNet.NZ.org



Paller AS, et al. J Allergy Clin Immunol. 2017;140(3):633-643.

AD PATHOGENESIS (REVIEW)

IL-4, IL-13, IL-31, IL-5, TSLP, and IL-22 signal through the JAK-STAT pathway



CRTH2=chemoattractant receptor homologous molecules expressed on Th2 lymphocytes; IL=interleukin; TSLP=thymic stromal lymphopoietin;TRPA1=transient receptor potential A1; TRPV1=transient receptor potential cation channel subfamily V member 1.

Paller AS, et al. J Allergy Clin Immunol. 2017;140(3):633-643.

AD MANAGEMENT

TOPICAL THERAPY

Limited BSA dermatitis

Non-targeted	**MORE** Targeted
• TCS • TCI	• Crisaborole ointment • Ruxolitinib 1.5% cream

SYSTEMIC THERAPY

- >10% BSA dermatitis
- Multifocal/diffuse pruritus
- Topical therapies ineffective

Non-targeted	**MORE** Targeted	Targeted

• Cyclosporine
• Methotrexate
• Azathioprine
• Mycophenolate
	• JAK inhibitors
	  • Baricitinib
	  • Abrocitinib
	  • Upadacitinib
	• Estrasimod (S1PR modulator)
	• RPT193 (CCR4 ant.)
		• Dupilumab
		• Tralokinumab
		• Lebrikizumab
		• Nemolizumab
		• OX40

SEVERITY

TCS=topical corticosteroid, TCI=topical calcineurin inhibitor

CURRENT AND EMERGING ORAL THERAPIES FOR AD

AGENT	DESCRIPTION	ADVERSE EVENTS
Azathioprine	Antimetabolite	Serious infection, nausea, vomiting, diarrhea, hepatotoxicity
Methotrexate	Antimetabolite	Serious infection; renal, GI, hepatic, pulmonary toxicity; hypersensitivity and dermatologic reactions
Mycophenolate	Antimetabolite	GI side effects, headache, serious infection, peripheral edema, and cytopenias.
Cyclosporine	Calcineurin inhibitor	Serious infection, nephrotoxicity, hepatotoxicity, neurotoxicity, HTN
Baricitinib	JAK inhibitor	Acne, headache, nausea Black box warning for: cancer, infection, blood clots (e.g. PE, DVT, arterial thrombosis)
Abrocitinib	JAK inhibitor	Acne, headache, nausea
Upadacitinib	JAK inhibitor	Acne, headache, nausea Black box warning for: cancer, infection, blood clots (e.g. PE, DVT, arterial thrombosis)

White box=black box warning