

# Atopic Dermatitis - A Patient Centered Management Approach

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President , Global Allergy and Asthma European Network (GA²LEN)  
Member, Committee on Allergy Diagnosis and Molecular Allergology, World Allergy Organisation (WAO)

# What is AD?

- AD is a chronic, relapsing-remitting disease characterized by intense pruritus and eczematous lesions (1,2)
- AD is heterogenous, which contributes to the complexity of the presentation (3)

## Clinical signs evaluated by the EASI score<sup>4-6</sup>

**Erythema<sup>a</sup>**



**Excoriation<sup>b</sup>**



**Induration/papulation<sup>c</sup>**



**Lichenification<sup>d</sup>**



<sup>a,b</sup>Reproduced with permission from DermNet NZ Copyright © 2022. <sup>c</sup>Used with permission of American Academy of Family Physicians, from Eczema, Berke R, et al. American Academy of Family Physicians website. <http://www.aafp.org/afp/2012/0701/p35-s1>. Accessed July 3, 2021; permission conveyed through Copyright Clearance Center, Inc. <sup>d</sup>Atopic dermatitis in diverse racial and ethnic groups-Variations in epidemiology, genetics, clinical presentation and treatment, Kaufman BP, et al. Copyright © 2018 and Experimental Dermatology. Reproduced with permission of John Wiley & Sons Ltd.<sup>5</sup>

- Assessment of disease severity may be performed considering clinical signs (erythema, induration/papulation, excoriation, lichenification) as well as additional indicators including symptoms, affected BSA or impact on QoL<sup>7,8</sup>
- While many clinician-reported AD severity scales exist, many do not measure specific symptoms, such as itch<sup>7</sup>

AD=atopic dermatitis; BSA=body surface area; EASI=Eczema Area and Severity Index; QoL=quality of life.

1. Wollenberg A, et al. *Ann Dermatol*. 2012;24(3):253-260. 2. Silverberg JI, et al. *J Dermatolog Treat*. 2016;27(6):568-576. 3. Weidinger S, Novak N. *Lancet*. 2016;387(10023):1109-1122. 4. DermNet NZ website. <https://www.dermnetnz.org/topics/easi-score/>. Accessed May 13, 2021. 5. Berke R, et al. American Academy of Family Physicians website. <http://www.aafp.org/afp/2012/0701/p35-s1>. Accessed July 3, 2021. 6. Kaufman BP, et al. *Exp Dermatol*. 2018;27(4):340-357. 7. Chopra R, Silverberg JI. *Clin Dermatol*. 2018;36(5):606-615. 8. Wollenberg A, et al. *Eur Acad Dermatol Venereol*. 2020;34(12):2717-2744.

# Challenge: What is atopic dermatitis?































# Clinical Signs and Patient-Reported Symptoms of AD Are Characterised in a Variety of Scoring Systems<sup>1-6</sup>

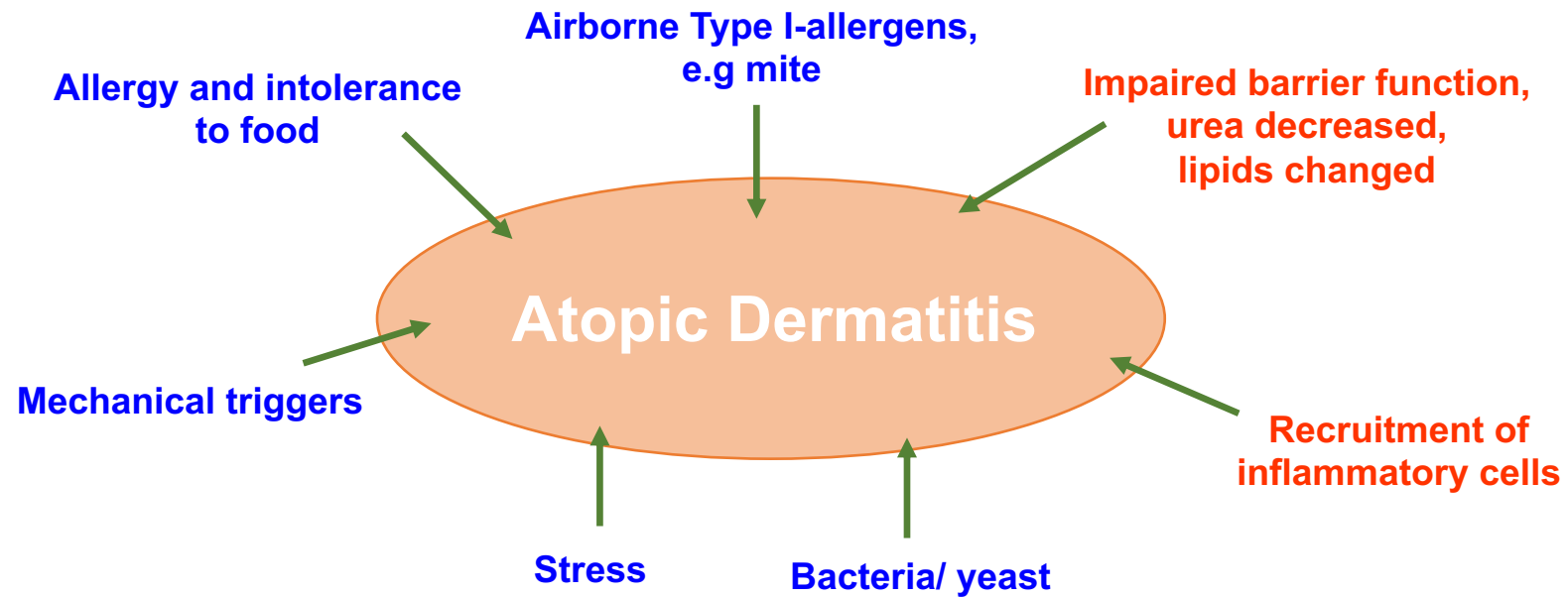
AD Severity Scoring Systems	EASI <sup>1</sup>	IGA <sup>2</sup>	PP-NRS <sup>3</sup>	SCORAD <sup>4</sup>
Name	Eczema Area and Severity Index	Investigator Global Assessment for AD	Peak Pruritus Numerical Rating Scale <sup>a</sup>	Scoring Atopic Dermatitis
Measures	Affected BSA and Clinical Signs	Overall Clinical Signs	Intensity of Itch	Affected BSA, Clinical Signs and Subjective Symptoms: Itch and Sleep
Outcome type	Clinician-reported	Clinician-reported	Patient-reported	Clinician- and patient-reported

AD=atopic dermatitis.

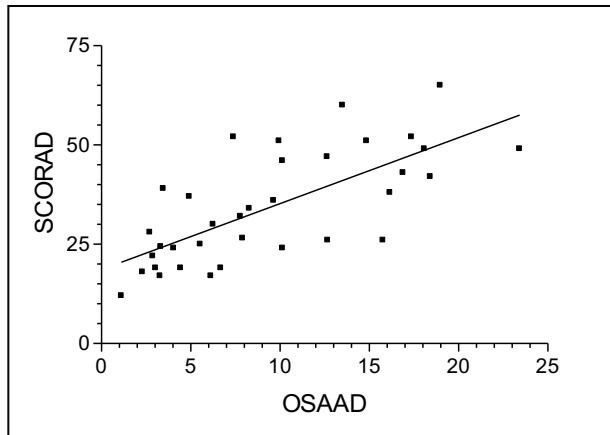
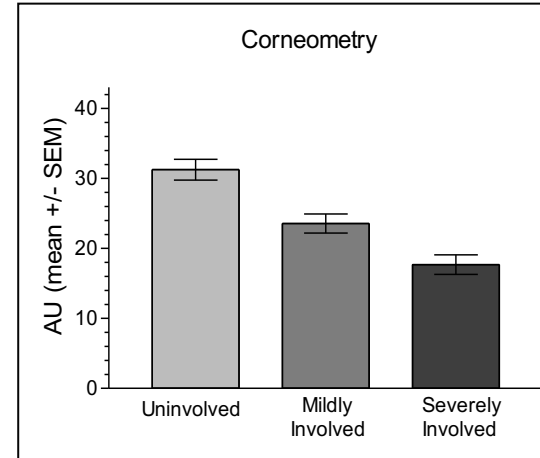
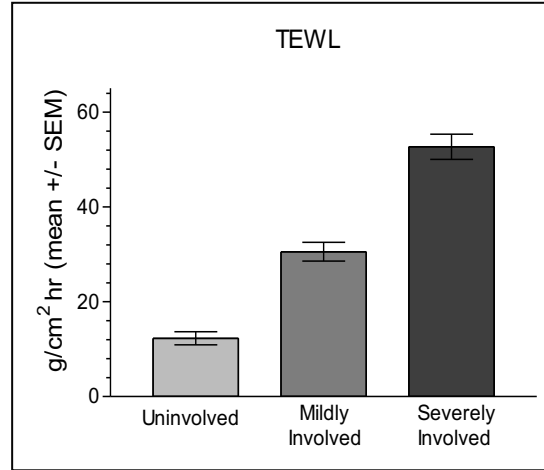
<sup>a</sup>Used with permission from Regeneron Pharmaceuticals, Inc and Sanofi SA.

1. Hanifin JM, et al. *Exp Dermatol.* 2001;10(1):11-18. 2. Futamura M, et al. *J Am Acad Dermatol.* 2016;74(2):288-294. 3. Yosipovitch G, et al. *Br J Dermatol.* 2019;181(4):761-769. 4. Kunz B, et al. *Dermatology.* 1997;195(1):10-19. 5. Chopra R, et al. *Clin Dermatol.* 2018;36(5):606-615. 6. Leshem YA, et al. *J Am Acad Dermatol.* 2020;82(5):1181-1186.

## AD: **Causes** and **Triggers**

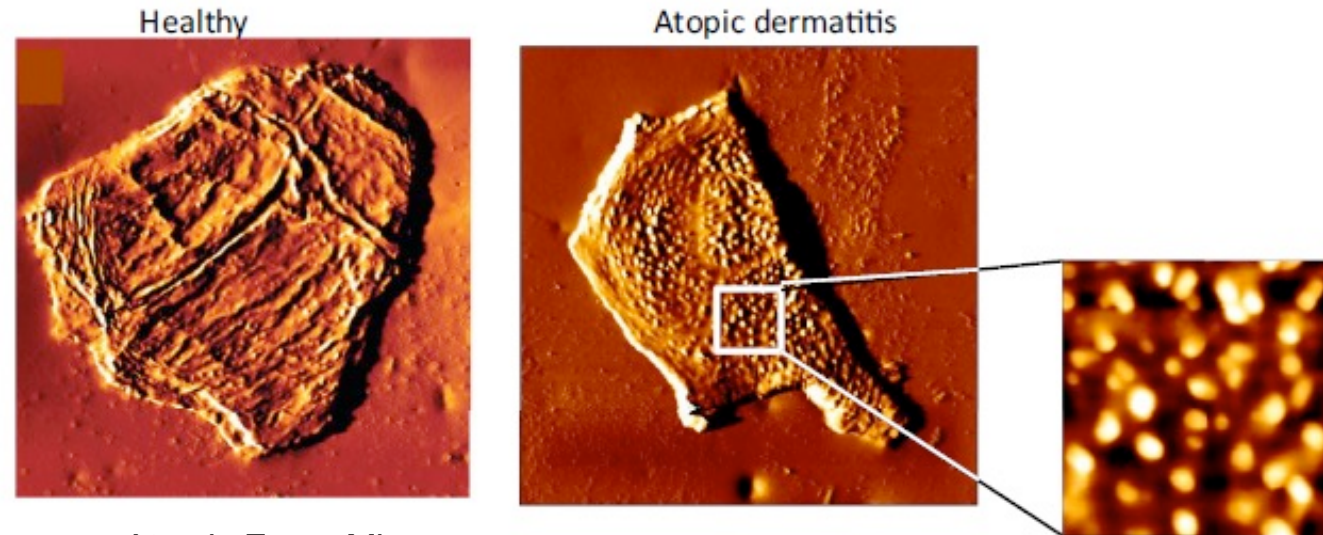


# Epidermal Barrier



- TEWL and SCH- based OSAAD
- Good correlation with SCORAD

# Corneocyte Morphology in AD



- Atomic Force Microscopy
- Specific surface pattern in AD

Invited Review Article

## Sweat is a most efficient natural moisturizer providing protective immunity at points of allergen entry

Tetsuo Shiohara <sup>a, \*</sup>, Yoshiko Mizukawa <sup>a</sup>, Yurie Shimoda-Komatsu <sup>a</sup>, Yumi Aoyama <sup>b, c</sup>

<sup>a</sup> Department of Dermatology, Kyorin University School of Medicine, Tokyo, Japan

<sup>b</sup> Department of Dermatology, Kawasaki Medical School, Kurashiki, Japan

<sup>c</sup> Dermatology, Kawasaki Hospital, Okayama, Japan

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#### Keywords:

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Impression mold technique

Inducible sweating

Leakage of sweat

#### Abbreviations:

AD, atopic dermatitis; FLG, filaggrin;

HZ, herpes zoster; IMT, impression mold

technique; DCD, demcadin; SC, stratum

corneum; SSH, skin surface hydration;

TEWL, transepidermal water loss; TJ, tight

junction; VZV, varicella-zoster virus

### ABSTRACT

Although there is a growing acceptance that sweat could play a detrimental role in various allergic skin diseases, the possibility that sweat is also involved in maintenance of skin hydration and skin-specific immune responses has not been acknowledged. We initially describe physiological role of sweat in both maintaining skin hydration and thermoregulation. The purpose of this article is to provide the reader with objective evidence that sweating is intimately linked to vital stratum corneum barrier function and usefulness of application of moisturizers in clinical care of allergic skin diseases. This review also covers how sweating disturbance would leave the skin vulnerable to the development of various allergic skin diseases, such as atopic dermatitis. New therapeutic approaches would specifically target such sweating disturbance in these allergic skin diseases.

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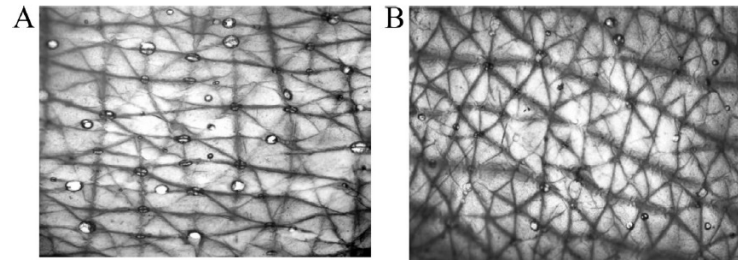


Fig. 3. Inducible sweating responses evaluated by IMT in AD and healthy controls. Decreased inducible sweating responses 30 min after thermal stimulus are observed in the uninvolved skin in the acute stage of AD (B), as compared with those in healthy controls (A). Modified from the reference Shimoda-Komatsu *et al.* <sup>2</sup>.

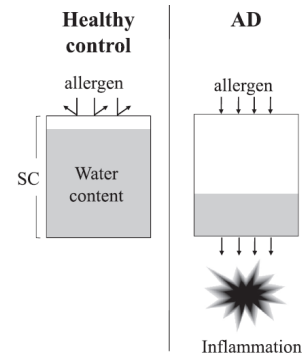


Fig. 4. The difference in the penetration of hapten through the SC in healthy control and AD. Epicutaneously applied hapten can penetrate more rapidly and abundantly through the SC with low water content (AD skin) than that with higher content (healthy control skin). Increased sweating responses would serve to limit penetration of allergen by increasing water content in the SC.

Shiohara, T., *et al.* (2018). "Sweat is a most efficient natural moisturizer providing protective immunity at points of allergen entry." *Allergol Int.*

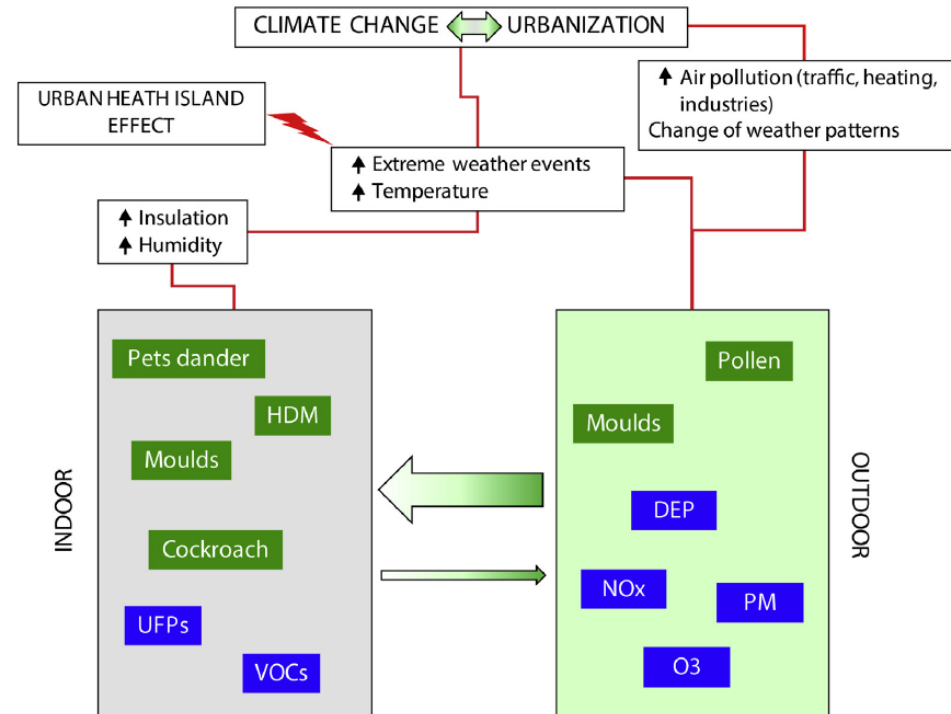
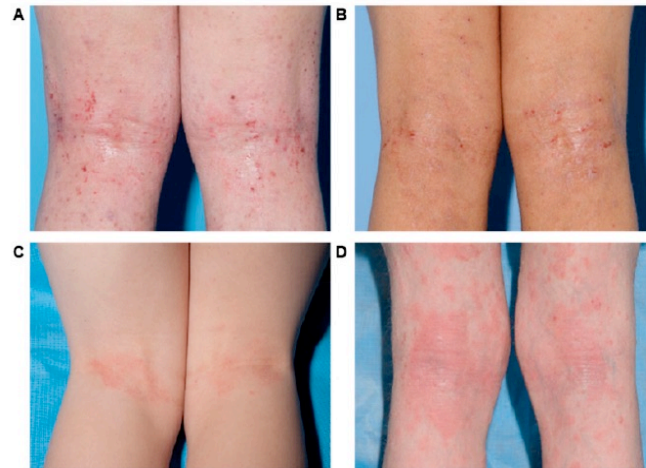


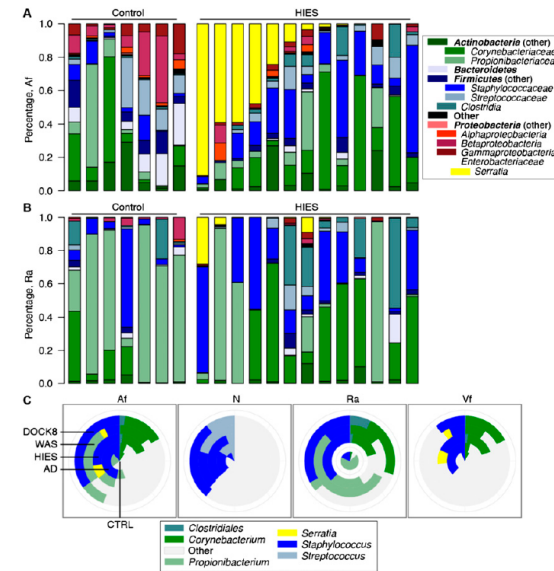
FIG 2. Indoor and outdoor exposures to aeroallergens and air pollutants and environmental factors affecting their production and concentrations. *NOx*, Nitrogen oxides; *UFPs*, ultrafine particles; *VOCs*, volatile organic compounds.

Cecchi, L., et al. (2018). "External exposome and allergic respiratory and skin diseases." *J Allergy Clin Immunol* 141(3): 846-857.

- Hyper IgE S., Atopic Dermatitis, Wiskott-Aldrich-S., DOCK8
- Colonization with microbes not observed in ctrl. (**Clostridium, Serratia marcescens** )
- **Increased of opportunistic fungi** vs Ctrl. (Candida, Aspergillus)



**Figure 1.** Representative clinical images of disease severity in the different patient groups. (A) Non-PID atopic dermatitis, (B) Hyper IgE syndrome, (C) Wiskott-Aldrich, and (D) DOCK8 deficiency.





# Allergens?





IgE > 100 ku/l for Dpt 1

# Food as an IgE-mediated allergen

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› Allergy. 2021 Jun 22. doi: 10.1111/all.14982. Online ahead of print.

## When and how to evaluate for immediate type food allergy in children with atopic dermatitis

Charlotte G Mortz<sup>1</sup>, George du Toit<sup>2</sup>, Kirsten Beyer<sup>3</sup>, Carsten Bindslev-Jensen<sup>1</sup>, Knut Brockow<sup>4</sup>, Helen Annaruth Brough<sup>2</sup>, Pasquale Comberiati<sup>5 6</sup>, Thomas Eiwegger<sup>7 8 9</sup>, Alexandra Santos<sup>2 10</sup>, Margitta Worm<sup>11</sup>, Barbara K Ballmer-Weber<sup>12 13</sup>

Affiliations [+ expand](#)

PMID: 34157156 DOI: 10.1111/all.14982

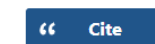
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**Keywords:** allergy diagnosis; atopic dermatitis; food allergy.

### FULL TEXT LINKS



### ACTIONS



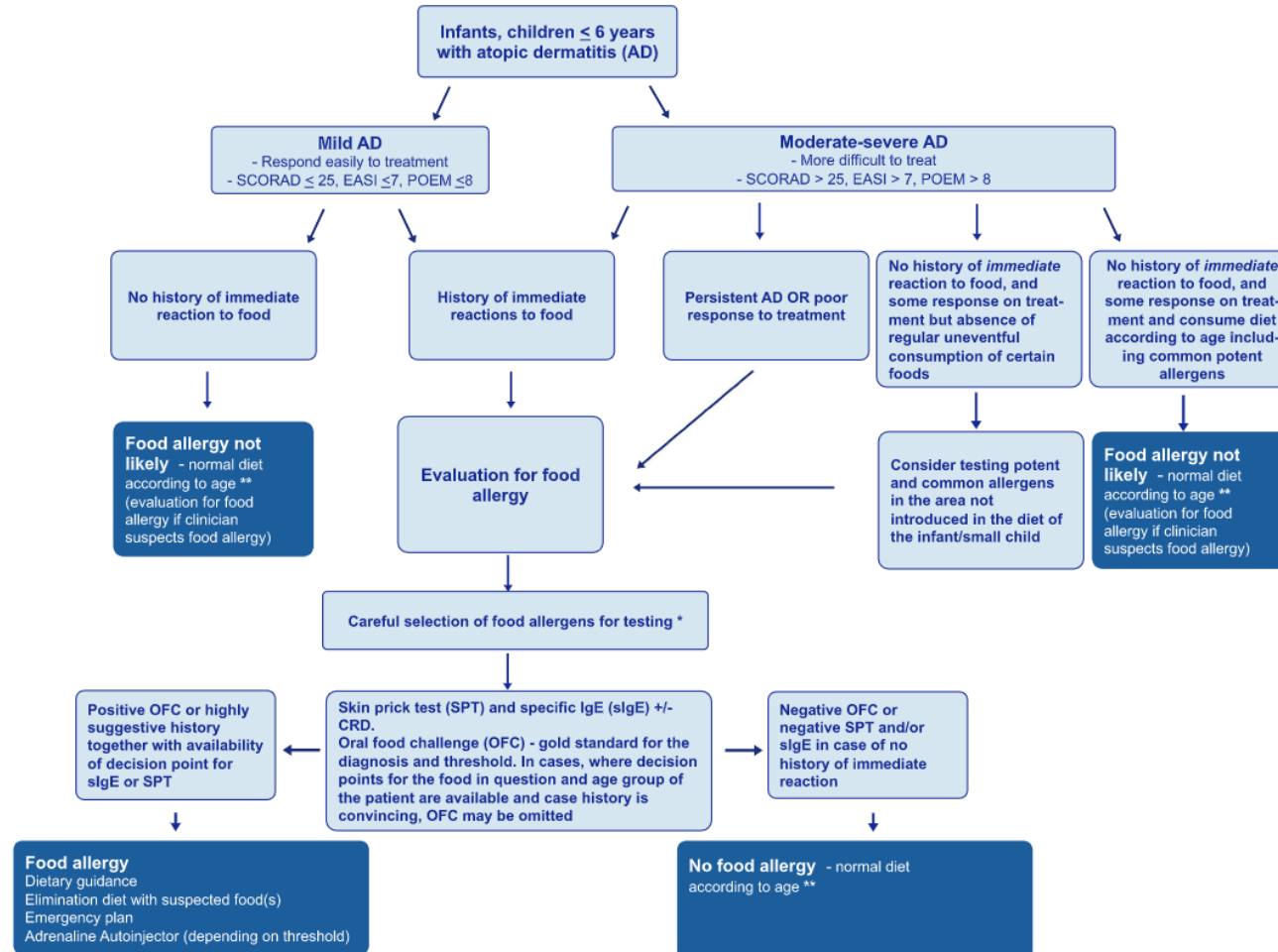
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### PAGE NAVIGATION

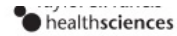
# Food as an IgE-mediated allergen

3846



# Other aspects of AD and food: non-allergic reactions

Acta Derm Venereol 2003; 83: 44–48



## CLINICAL REPORT

### Orange-Induced Skin Lesions in Patients with Atopic Eczema: Evidence for a Non-IgE-Mediated Mechanism

KNUT BROCKOW<sup>1</sup>, CHRISTIAN HAUTMANN<sup>2</sup>, KAY FÖTISCH<sup>3</sup>, JÜRGEN RAKOSKI<sup>1</sup>, SIEGFRIED BORELLI<sup>2</sup>, STEFAN VIETHS<sup>3</sup> and JOHANNES RING<sup>1,2</sup>

<sup>1</sup>Division Environmental Dermatology and Allergy GSF/TUM at Department of Dermatology and Allergy Biederstein, Technical University Munich, Germany, <sup>2</sup>German Hospital for Dermatology and Allergy Alexanderhaus Davos, Switzerland, and <sup>3</sup>Paul-Ehrlich Institute, Department of Allergology, Langen, Germany



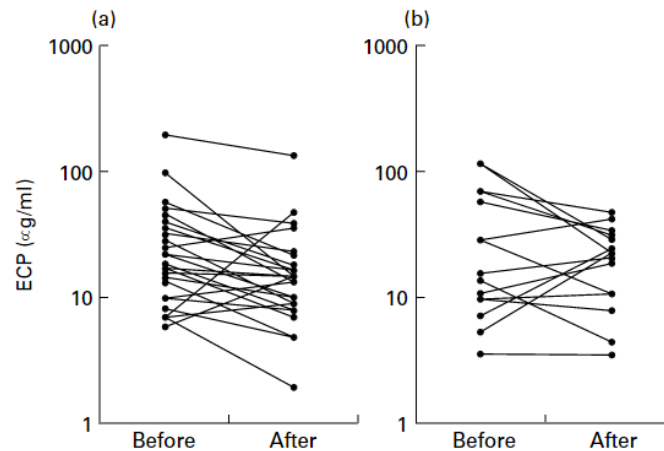
Fig. 2. Newly developed eczematous skin lesion on the left forearm (a) 6 h after oral provocation test and (b) improvement seen after 48 h.

Clinical Trial > Clin Exp Allergy. 2000 Mar;30(3):407-14. doi: 10.1046/j.1365-2222.2000.00722.x.

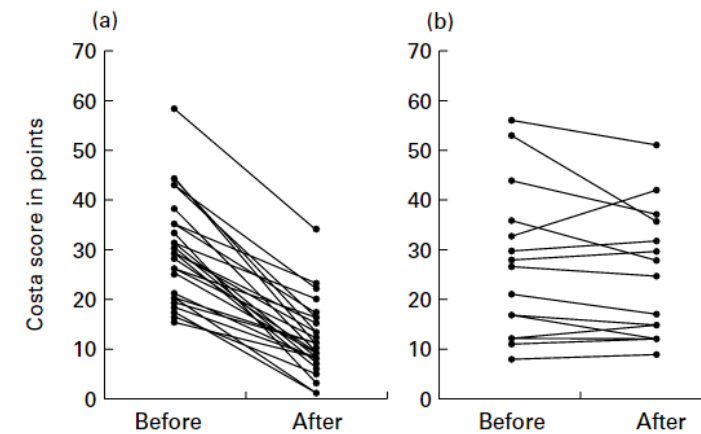
## Clinical relevance of food additives in adult patients with atopic dermatitis

M Worm<sup>1</sup>, I Ehlers, W Sterry, T Zuberbier

**Conclusion** These results indicate that a subgroup of adult patients with AD clinically improve on low-pseudoallergen diet but only a small subgroup respond to oral provocation with food additives.

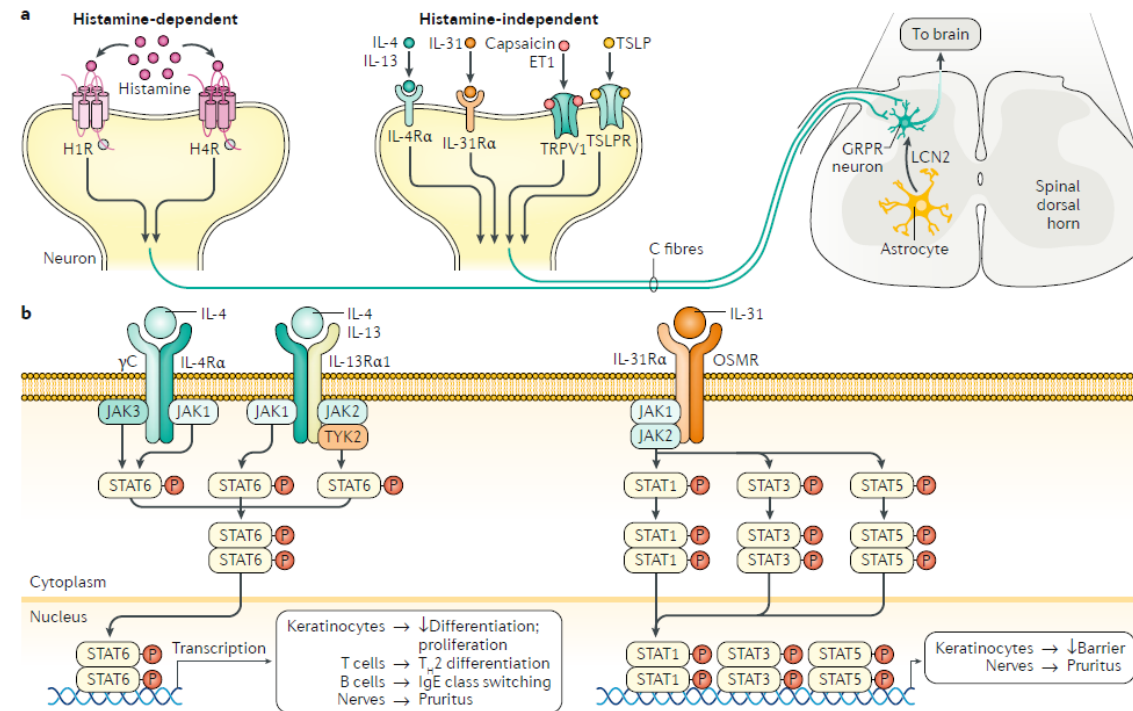


**Fig. 2.** ECP values before and after the low-pseudoallergen diet. (a) Responder group ( $n = 26$ ), mean ECP value before the diet was  $27 \mu\text{g/mL}$  and after the diet  $14 \mu\text{g/mL}$  ( $P < 0.05$ ). (b) Non-responder group ( $n = 15$ ), mean ECP value before the diet was  $27 \mu\text{g/mL}$  and after the diet  $25 \mu\text{g/mL}$ .



**Fig. 1** Skin score before and after the low pseudoallergen diet in adult patients with atopic dermatitis. (a) Responder group ( $n = 26$ ), mean score value before the diet was 29 points and after the diet 11 points ( $P < 0.05$ ). (b) Non-responder group ( $n = 15$ ), mean score value before the diet was 27 points and after the diet 24 points.

# Two Mechanisms of Itch in AD



Weidinger, S., et al. (2018). "Atopic dermatitis." *Nat Rev Dis Primers* 4(1): 1.

## **EUROGUIDERM GUIDELINE ON ATOPIC ECZEMA**

Version 2.2, October 2023

**EUROPEAN  
CENTRE FOR  
GUIDELINES  
DEVELOPMENT**



**European  
Dermatology  
Forum**

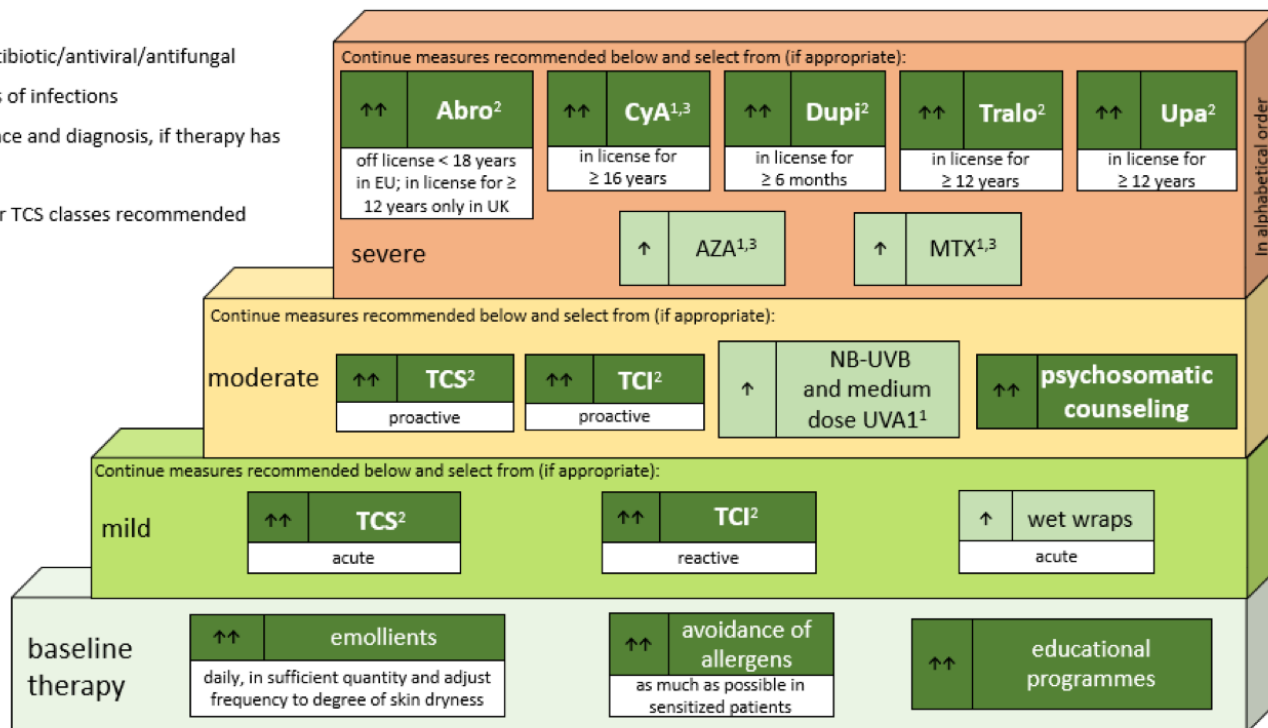


A Wollenberg<sup>1,2</sup>, M Kinberger<sup>3</sup>, B Arents<sup>4</sup>, N Aszodi<sup>1</sup>, G Avila Valle<sup>3</sup>, S Barbarot<sup>5</sup>, T Bieber<sup>6</sup>, HA Brough<sup>7</sup>, P Calzavara Pinton<sup>8</sup>, S Christen-Zäch<sup>9</sup>, M Deleuran<sup>10</sup>, M Dittmann<sup>3</sup>, C Dressler<sup>3</sup>, AH Fink-Wagner<sup>11</sup>, N Fosse<sup>12</sup>, K Gáspár<sup>13</sup>, L Gerbens<sup>14</sup>, U Gieler<sup>15</sup>, G Girolomoni<sup>16</sup>, S Gregoriou<sup>17</sup>, CG Mortz<sup>18</sup>, A Nast<sup>3</sup>, U Nygaard<sup>19</sup>, M Redding<sup>20</sup>, EM Rehbinder<sup>21</sup>, J Ring<sup>22</sup>, M Rossi<sup>23</sup>, C Roxburgh<sup>20</sup>, E Serra-Baldrich<sup>24</sup>, D Simon<sup>25</sup>, ZZ Szalai<sup>26</sup>, JC Szepietowski<sup>27</sup>, A Torrelo<sup>28</sup>, T Werfel<sup>29</sup>, C Flohr<sup>30,31</sup>



## EuroGuiDerm Guideline on Atopic Eczema Stepped-care plan for children and adolescents with atopic eczema

- Add antiseptic/antibiotic/antiviral/antifungal treatment in cases of infections
- Consider compliance and diagnosis, if therapy has insufficient effect
- Refer to table 3 for TCS classes recommended



<sup>1</sup> refer to guideline text for restrictions, <sup>2</sup> licensed indication, <sup>3</sup> off-label treatment

↑↑ (dark green) strong recommendation for the use of an intervention / ↑ (light green) weak recommendation for the use of an intervention

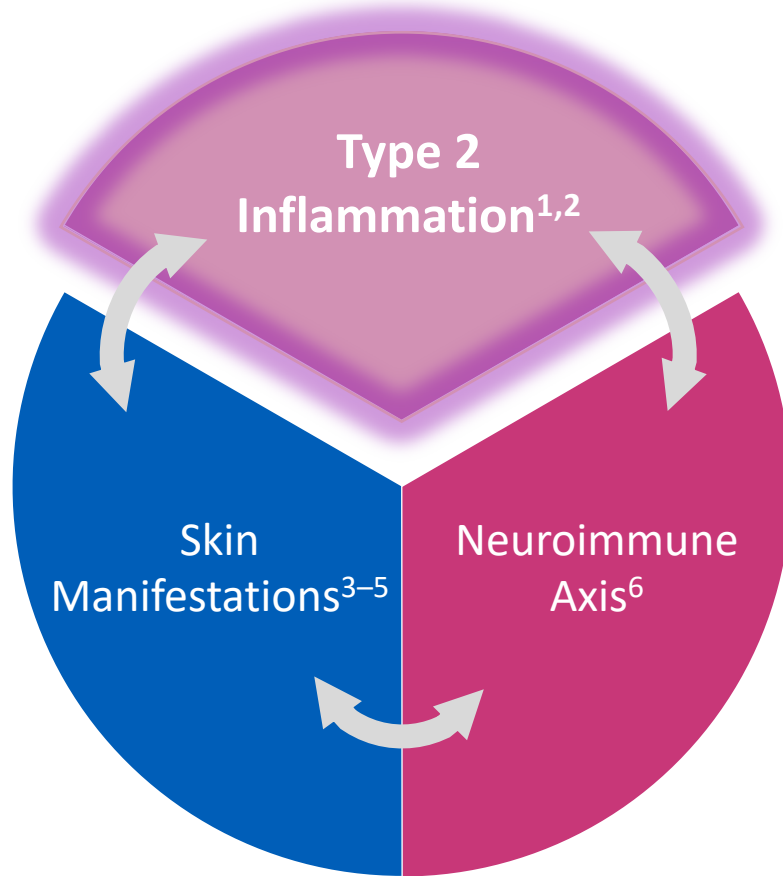
For definitions of disease severity, acute, reactive, proactive see section 'VII' and section 'Introduction to systemic treatment' of the EuroGuiDerm Atopic Eczema Guideline

AZA=azathioprine; CyA=ciclosporin; Dupi=dupilumab; MTX=methotrexate; TCI=topical calcineurin inhibitors; TCS= topical corticosteroids; Upa=upadacitinib; UVA1=ultraviolet A1; NB-UVB=narrow-band ultraviolet B



>75%  
12/15

# Type 2 Inflammation



Type 2 inflammation, via the actions of cytokines and cytokine receptors on immune, neural, and skin cells, mediates associated dermatologic diseases such as AD.<sup>1,2,6</sup>

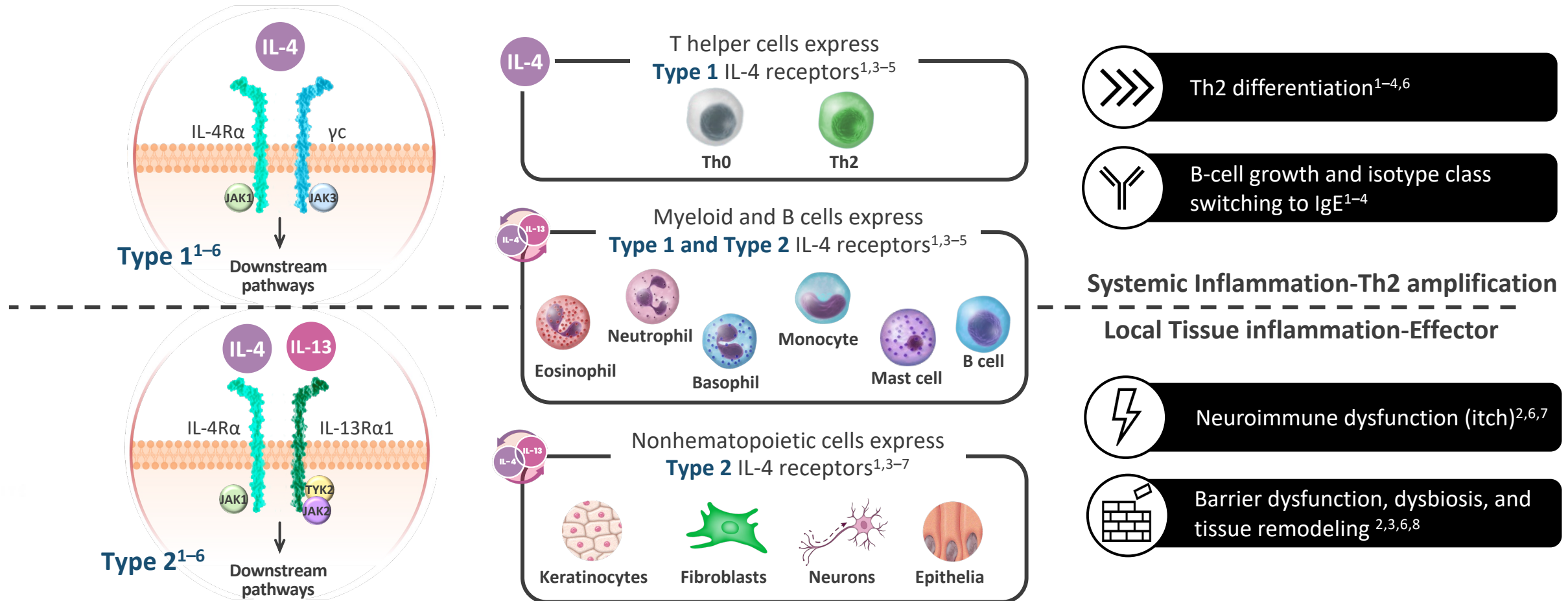
Type 2  
inflammation



AD, atopic dermatitis; CSU, chronic spontaneous urticaria; PN, prurigo nodularis.

1. Haddad EB, et al. *Dermatol Ther (Heidelb)*. 2022;12:1501–1533. 2. Ingrassi G, et al. *Exp Dermatol*. 2021;30:1208–1217. 3. Beck LA, et al. *JID Innov*. 2022;2:100131. 4. Weigelt N, et al. *J Cutan Pathol*. 2010;37:578–586. 5. Wernersson S, Pejler G. *Nat Rev Immunol*. 2014;14:478–494. 6. Garcovich S, et al. *Vaccines (Basel)*. 2021;9:303.

# IL-4 and IL-13 Signaling Is Mediated by Type 1 IL-4 Receptor and Type 2 IL-4 Receptor Complexes

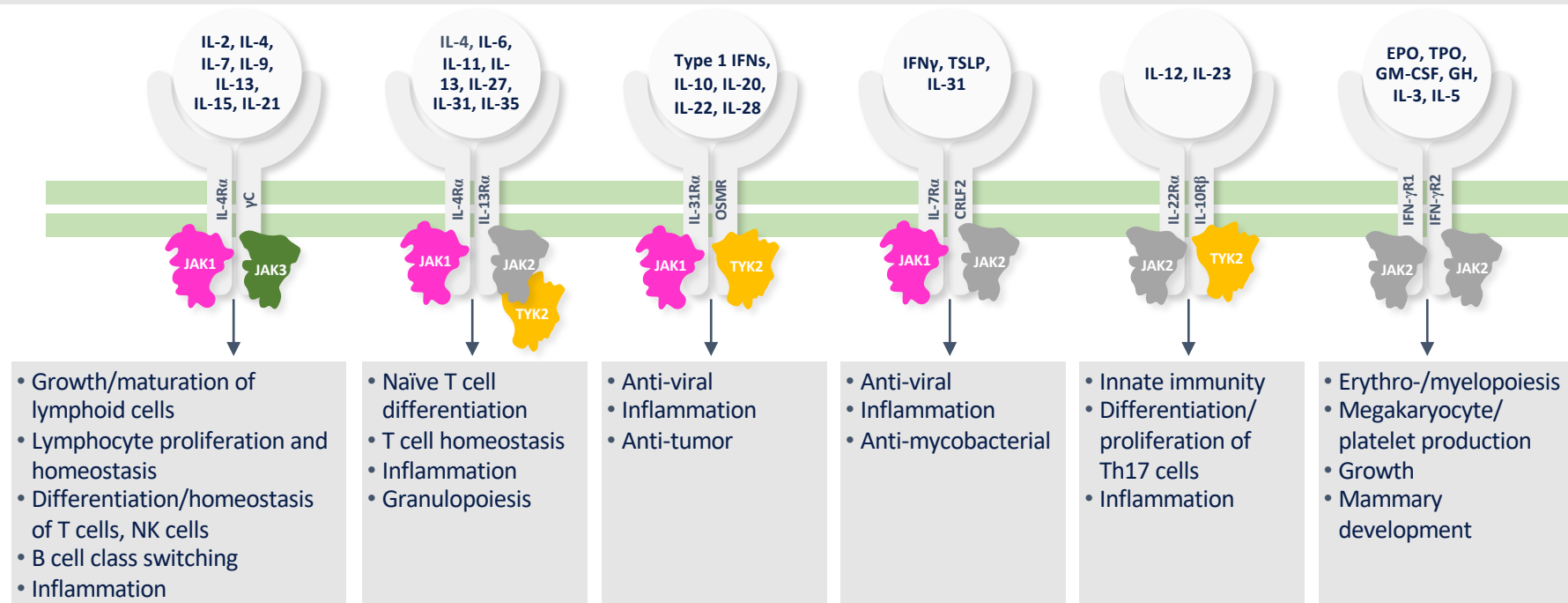


AD, atopic dermatitis; CSU, chronic spontaneous urticaria; γc, gamma chain; JAK, Janus kinase; Ig, immunoglobulin; IL, interleukin; IL-4Rα, interleukin-4 receptor alpha; IL-13Rα1, interleukin-13 receptor alpha type 1; PN, prurigo nodularis; STAT, signal transducer and activator of transcription; Th, helper T cell. 1. Romeo MJ, et al. *J Allergy Clin Immunol.* 2014;133:952–960. 2. Paller AS, et al. *J Allergy Clin Immunol.* 2017;140:633–643. 3. Haddad EB, et al. *Dermatol Ther (Heidelb).* 2022;12:1501–1533. 4. Wills-Karp M, Finkelman FD. *Sci Signal.* 2008;1:pe55. 5. Junttila IS. *Front Immunol.* 2018;9:888. 6. Furue M. *J Clin Med.* 2020;9:3741. doi: 10.3390/jcm9113741. 7. Oetjen LK, et al. *Cell.* 2017;171:217–228.e13. 8. Beck LA, et al. *JID Innov.* 2022;2:100131.

# The novel treatments

# JAKs are intracellular signaling molecules that work in pairs and play a role in a diverse range of biologic functions<sup>1-6</sup>

The JAK family consists of four structurally-related isoforms that transmit cytokine or growth factor signals to the nucleus



γC, gamma chain; CRLF2, cytokine receptor-like factor; EPO, erythropoietin; GH, growth hormone; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFNγ, interferon gamma; IL, interleukin; JAK, Janus kinase; NK, natural killer; OSMR, oncostatin M receptor; Th, T helper cell; TPO, thrombopoietin; TSLP, thymic stromal lymphopoietin; TYK, tyrosine kinase

1. Clark JD, et al. J Med Chem 2014;57:5023-38; 2. Cornelissen C, et al. Eur J Cell Bio 2012;91:552-66; 3. Lou H, et al. J Immunol 2017;198:2543-55; 4. Klonowska J, et al. Int J Mol Sci 2018;19:3086; 5. Bieber T, et al. Nat Rev Drug Discov 2021;20:1-20; 6. Wolk K, et al. J Interferon Cytokine Res 2010;30:617-28

# Comparison of different JAK inhibitors


Received: 27 January 2022 | Revised: 6 June 2022 | Accepted: 12 June 2022

DOI: 10.1111/dth.15636

REVIEW ARTICLE

DERMATOLOGIC  
THERAPY | WILEY

## Comparative efficacy and safety of abrocitinib, baricitinib, and upadacitinib for moderate-to-severe atopic dermatitis: A network meta-analysis

Huiying Wan<sup>1</sup> | Haiping Jia<sup>2</sup> | Tian Xia<sup>3</sup>  | Dingding Zhang<sup>4</sup>

- upadacitinib 30mg was superior to all regimens
- upadacitinib 15mg was better than remaining regimens except for abrocitinib 200mg in terms of IGA and EASI response
- abrocitinib 200 mg was superior to abrocitinib 100 mg, baricitinib 1mg, 2mg, and 4mg for clinical efficacy
- upadacitinib 30mg caused more TEAEs
- abrocitinib, baricitinib, and upadacitinib were consistently effective therapies in adult and adolescent patients with AD
- upadacitinib 30mg may be the optimal option in short-term studies
- more efforts should be done to reduce the risk of TEAEs caused by upadacitinib 30mg

Clinical Trial > [N Engl J Med. 2021 Mar 25;384\(12\):1101-1112. doi: 10.1056/NEJMoa2019380.](#)

## Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis

Thomas Bieber<sup>1</sup>, Eric L Simpson<sup>1</sup>, Jonathan I Silverberg<sup>1</sup>, Diamant Thaçi<sup>1</sup>, Carle Paul<sup>1</sup>, Andrew E Pink<sup>1</sup>, Yoko Kataoka<sup>1</sup>, Chia-Yu Chu<sup>1</sup>, Marco DiBonaventura<sup>1</sup>, Ricardo Rojo<sup>1</sup>, Jeremias Antinew<sup>1</sup>, Ileana Ionita<sup>1</sup>, Rodney Sinclair<sup>1</sup>, Seth Forman<sup>1</sup>, Jacek Zdybski<sup>1</sup>, Pinaki Biswas<sup>1</sup>, Bimal Malhotra<sup>1</sup>, Fan Zhang<sup>1</sup>, Hernan Valdez<sup>1</sup>, JADE COMPARE Investigators

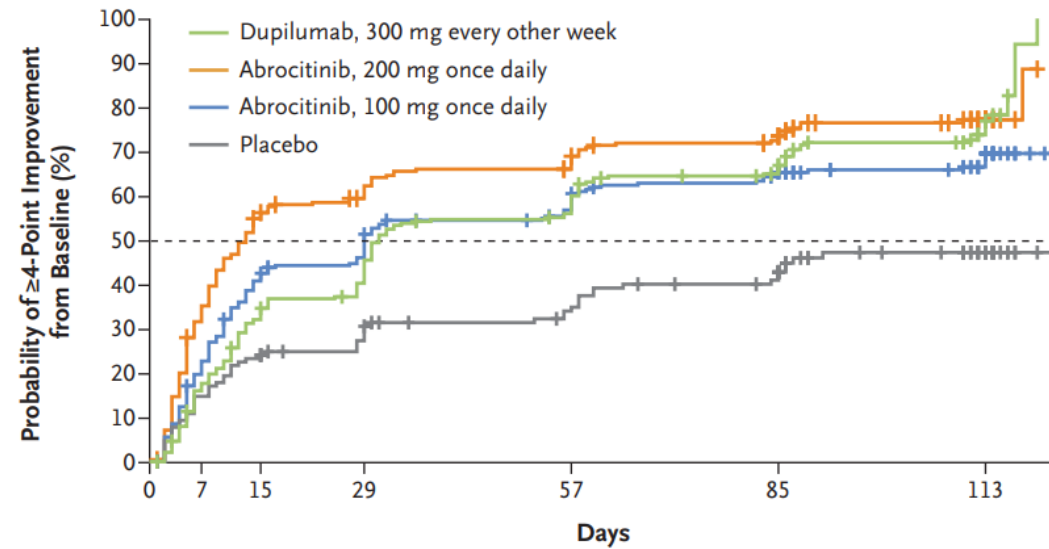
Collaborators, Affiliations + expand

PMID: 33761207 DOI: 10.1056/NEJMoa2019380

### Abstract

#### CONCLUSIONS

In this trial, abrocitinib at a dose of either 200 mg or 100 mg once daily resulted in significantly greater reductions in signs and symptoms of moderate-to-severe atopic dermatitis than placebo at weeks 12 and 16. The 200-mg dose, but not the 100-mg dose, of abrocitinib was superior to dupilumab with respect to itch response at week 2. Neither abrocitinib dose differed significantly from dupilumab with respect to most other key secondary end-point comparisons at week 16. (Funded by Pfizer; JADE COMPARE ClinicalTrials.gov number, NCT03720470.)



**No. at Risk**

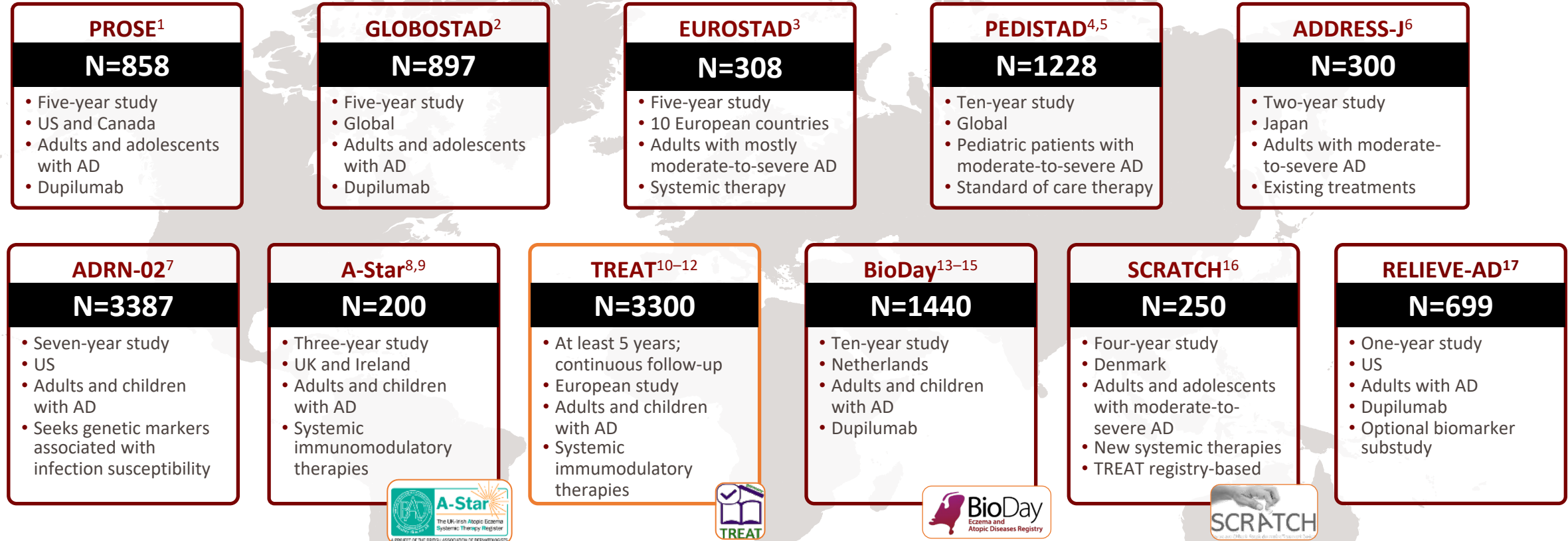
Dupilumab, 300 mg every other week	240	199	160	137	99	73	42
Abrocitinib, 200 mg once daily	226	153	100	86	70	53	24
Abrocitinib, 100 mg once daily	236	187	137	122	93	74	44
Placebo	130	110	99	89	76	65	29

**Figure 1. Median Time to Itch Response.**

Itch response was defined as an improvement from baseline of at least 4 points in the score on the Peak Pruritus Numerical Rating Scale, on which scores range from 0 to 10, with higher scores indicating greater severity of pruritus.



# Real-World and Registry Studies in AD Provide Data on Effectiveness and Safety of Dupilumab in Clinical Practice



AD, atopic dermatitis.  
 1. <https://clinicaltrials.gov/ct2/show/NCT03428646>. Accessed February 2023. 2. <https://clinicaltrials.gov/ct2/show/NCT03992417>. Accessed February 2023. 3. de Bruin-Weller M, et al. *J Dermatolog Treat.* 2021;32:164–173. 4. <https://clinicaltrials.gov/ct2/show/NCT03687359>. Accessed February 2023. 5. Sanofi and Regeneron Data on File. 2023. 6. Katoh N, et al. *J Dermatol.* 2019;46:290–300. 7. <https://clinicaltrials.gov/ct2/show/NCT01494142>. Accessed February 2023. 8. <https://astar-register.org/>. Accessed February 2023. 9. <https://doi.org/10.1186/ISRCTN11210918>. Accessed February 2023. 10. <https://treat-registry-taskforce.org/projects/#national>. Accessed June 2022. 11. <https://clinicaltrials.gov/ct2/show/NCT03621137>. Accessed February 2023. 12. <https://clinicaltrials.gov/ct2/show/NCT03057860>. Accessed February 2023. 13. <https://www.bioday.nl/focus-areas/>. Accessed February 2023. 14. <https://clinicaltrials.gov/ct2/show/NCT03549416>. Accessed February 2023. 15. Ariëns LFM, et al. *J Am Acad Dermatol.* 2021;84:1000–1009. 16. Larsen HP, et al. *Acta Dermato-Venereologica.* 2022;102:adv00760. 17. Strober B, et al. *JAMA Dermatol.* 2022;158:142–150.

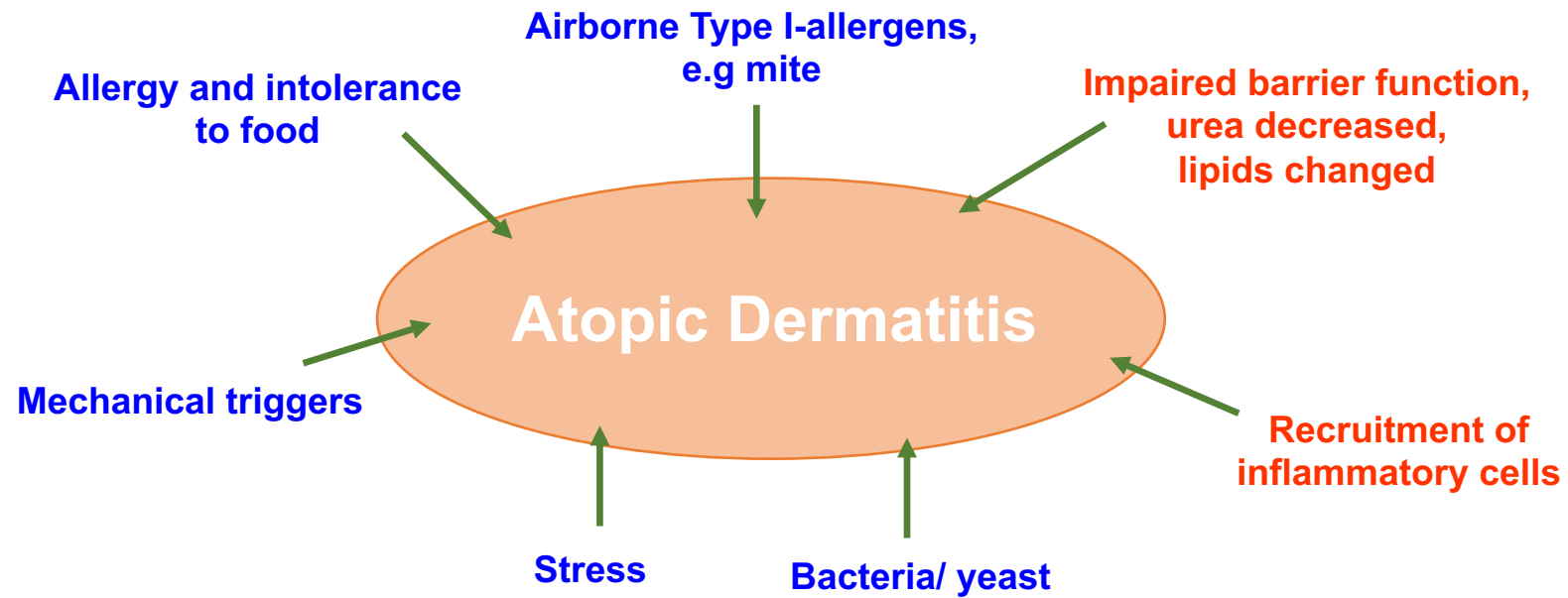
# The patient centered approach



IgE > 100 ku/l for Dpt 1



## AD: **Causes** and **Triggers**



**Good topical skin care is needed**

# The Social Function of the Skin



<http://www.weltderwunder.de/imperia/md/images/mensch/verhalten/sexualitaet/5.jpg>



Source: Sanosan Brand



<http://www.just4wellness.de/j4gKlassischeMassagej4w6.aspx>

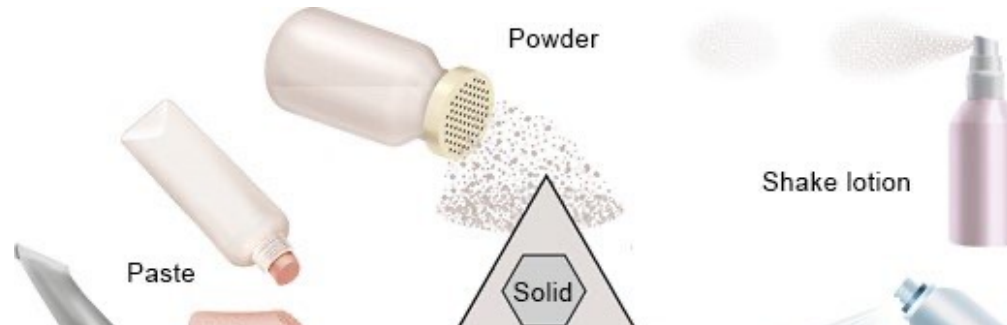
## Challenges based on living environment:

- Climate
- Pollution
- Hard water
- Cultural expectations on clothing and food
- Too much or too little hygiene

## Optimal topical treatment...

- ...varies in skin areas
  - ...depends on healthiness of skin
  - ...depends on clothing
  - ...on specific ingredients
- 
- ❖ For example plant derived oil: native oil contains allergenic protein only purified or hydrolyzed products may be used
  - ❖ Never use greasy ointment on oozing skin





## New:

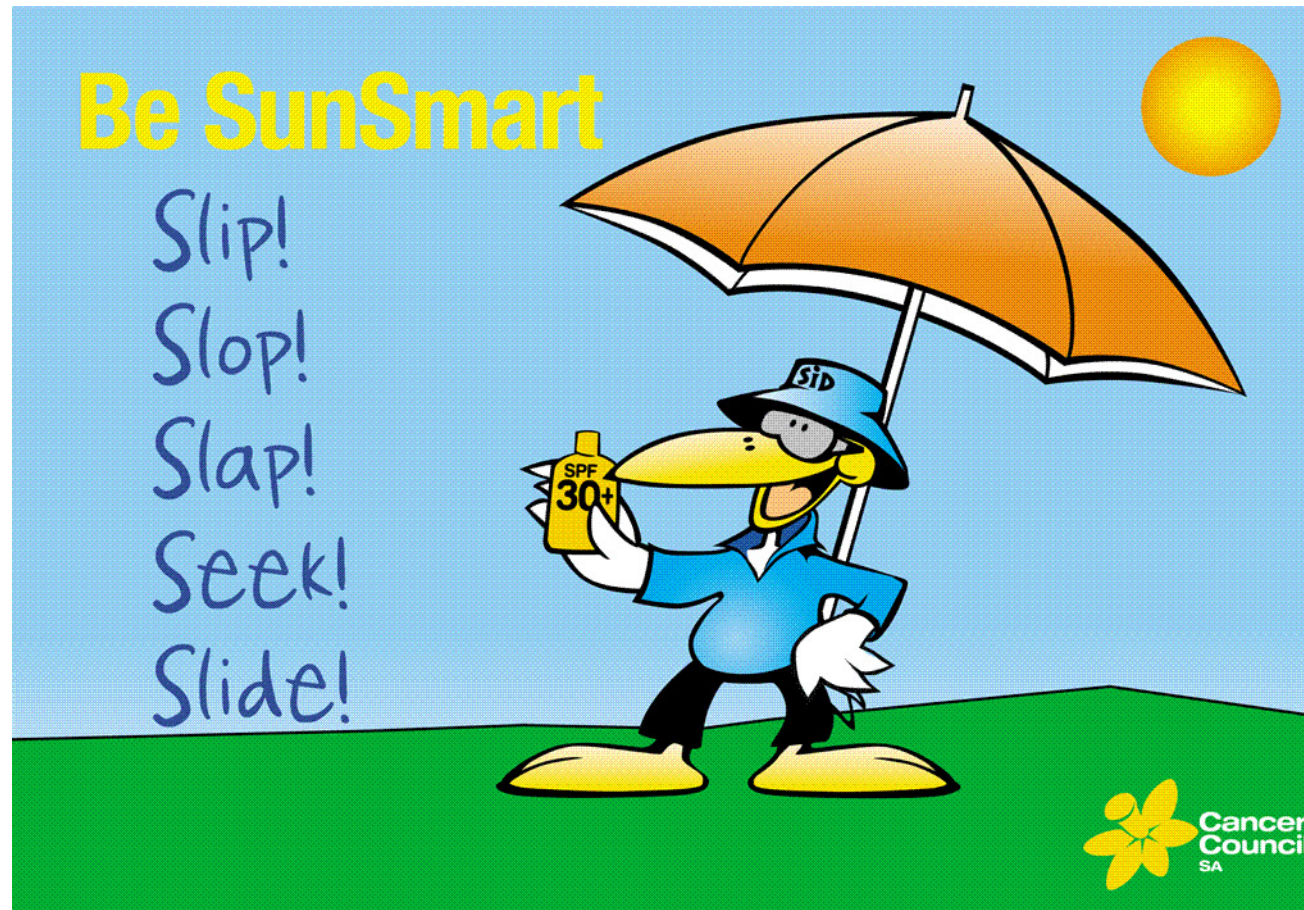
Modern technology and ingredients become more important  
e.g. Licochalcone A or TRPM8-Agonists like Menthoxypropanediol (MPD )



**Role of doctors as professional advisors becomes more important for the individual health!**

# Communication needs to be easy to remember

*“Slip on a shirt, slop on the 30+ sunscreen, slap on a hat, seek shade or shelter, slide on some sun glasses!”*



*For a better life with  
allergies*

