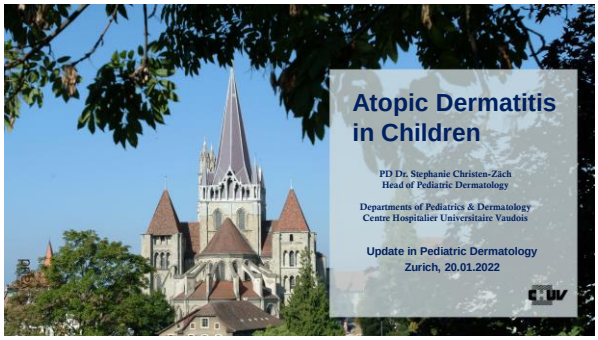
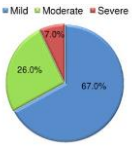


Atopic Dermatitis



Genetics

Up to 50% of offspring are affected when one parent is

Up to 80% of offspring are affected when two parents are

Epidemiology

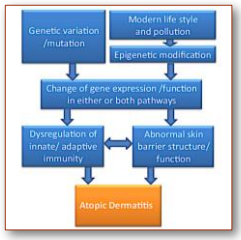
About 50 million people in Europe suffer from AD

Prevalence: 10 à 20% of children; 3 à 5% of adults

Disease onset: 45% within first 6 months of life; 85% before 5 years of age

Ring et al. Atopic eczema: burden of disease and individual suffering-results from a large EU study in adults. J Eur Acad Dermatol Venereol. 2019 Jul;33(7):1331-1340. Nutten S. Atopic dermatitis: global epidemiology and risk factors. Ann Nutr Metab. 2015;66 Suppl 1:8-16. Böhme 2008, Tab 2003, ISSAC Lancet 2006.

Atopic Dermatitis – A multifactorial disease

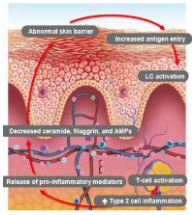


Bin L. and Leung DYM. Allergy Asthma Clin Immunol (2016) 12:52.

Atopic dermatitis – a disease of

Barrier Dysfunction

- Facilitates antigen/allergen entry and subsequent Th2 immunologic inflammation
- High risk for AD with FLG gene mutations



Th2 driven inflammation

- At immune system level, activated T cells secrete Th2 and Th22 cytokines, including IL-4, IL-5, IL-13, IL-22, IL-31
- Cytokines impair expression of barrier proteins and lipids
- Activation drives inflammation and epidermal breakdown, resulting in clinical presentation

Many of the Th2 cytokines (e.g. IL-4, IL-5, IL-13) are also associated with other atopic diseases, including asthma and chronic rhinosinusitis.

AMPs, antimicrobial peptides; LC, Langerhans cells;
1. Elias PM, Schmuth M. Curr Opin Allergy Clin Immunol. 2009;9(5):437-443; 2. Manka LA, Wrechster ME. Expert Rev Clin Immunol. 2018;14(4):295-306.

Atopic Dermatitis - Skin Dysbiosis

AD patients experience frequent cutaneous infections and *S. aureus* is commonly cultured from both lesional and nonlesional AD skin[1]

- Present on lesional skin of 80-100% of AD patients vs healthy controls[1,2]
- May be due to reduced antimicrobial peptide expression in the skin of AD patients[1]

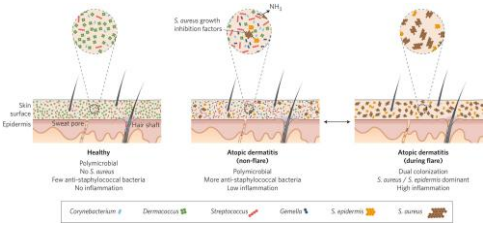
S. aureus colonization correlates with disease severity and greater type 2 immune deviation[1-3]

1. Kong HH, et al. Genome Res. 2012;22(5):850-859; 2. **Warner JA, et al. *Br J Dermatol.*** 2006;160(1):183-185; 3. **Totte JE, et al. *Br J Dermatol.* 2016;175(4):687-695.**

ATOPIC DERMATITIS FLARE

- Dysbiosis with decreased microbiome diversity
- *S epidermidis, S aureus* and *Malassezia predominate*

Severe flare = *S aureus predominates*



Normalization of microbiome => End of flare

Odell, L., Flavell, R. Microbiome: Ecology of eczema. *Nat Microbiol* **1,** 16135 (2016) doi:10.1038/nmicrobiol.2016.135

Associated atopic diseases

Food allergies[4-6]	Allergic rhino-conjonctivitis[1,6]	Asthma[1-3,6]
		
10% - 37%	34%	20% - 35%

Silverberg JI, Simpson EL. *Pediatr Allergy Immunol.* 2013;24(5):476-486. 2. van der Hulst AE, et al. *J Allergy Clin Immunol.* 2007;120(3):565-569. 3. Zheng T, et al. *Allergy Asthma Immunol Res.* 2011;3(2):67-73. 4. Maraan S, et al. *Curr Opin Allergy Clin Immunol.* 2014;14(5):423-429. 5. Eigenmann PA, et al. *Pediatrics.* 1998;101(3):E8. 6. Yang EJ, et al. *Pediatrics.* 2018;142(6):e20181102. 2. Bantz SK, et al. *J Clin Cell Immunol.* 2014;5(2

Nonatopic conditions associated with AD

Psychological disorders

In a European multicenter study of 3635 patients vs 1359 controls

AD patients suffered from

- 17.6% anxiety
- 10% depression
- 15% suicidal ideation
- 63.4% mental health burden of dermatological therapy

Brunner et al. J of Invest. Dermat. 2017; 137: 18-25. Andersen et al. Curr dermatol Rep. 2017; 6(1):35-41. Balleva FNet al. Acta Derm Venereol. 2018;98:563-569.

Patients with AD experience debilitating effects impacting on day-to-day functioning

Disease burden of moderate to severe atopic dermatitis

Pruritus	Sleep Disturbances	Flares	Skin Infections	Comorbidities	Impaired Quality of Life	Mental Health Disorders	Work Productivity
· Frequent and intense itch	· Difficulty falling asleep · Frequent awakenings	· Persistent signs and symptoms	· Bacterial, viral, fungal	· Other atopic diseases	· Daily activities and social functioning · Life-course decisions	· Anxiety · Depression	· Absenteeism · Presenteeism

Due to their AD 83% of teens avoid ≥1 everyday activity; 46% report negative effects on school performance, and 40% are teased or bullied

N=2502 patients from 8 different countries with moderate-to-severe AD (n=125 patients aged 14 years to 17 years) who responded to a phone interview.
Simpson EL, et al. Patient burden of moderate to severe atopic dermatitis (AD): insights from a phase 2b clinical trial of dupilumab in adults. *J Am Acad Dermatol.* 2016;74(3):491–98 Zuberbier T, et al. Patient perspectives on the management of atopic dermatitis. *J Allergy Clin Immunol.* 2006;118(1):226–232.
Simpson EL. Comorbidity in Atopic Dermatitis. *Curr Dermatol Rep.* 2012;1(1):29–36 Drucker AM, et al. The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. *J Invest Dermatol.* 2017;137(1):26–30; Whiteley J, et al. The burden of atopic dermatitis in US adults: results from the 2013 National Health and Wellness Survey. *Curr Med Res Opin.* 2016;32(10):1645-1651.

ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children

A Wollenberg [1], S Christen-Zäch [2], A Taieb [3], C Paul [4], J P Thyssen [5], M de Bruin-Weller [6], C Vestergaard [7], J Seneschal [8], T Werfel [9], M J Cork [10], B Kunz [11], K Fölster-Holst [12], M Traczak [13], U Darsow [14, 15], Z Szalai [16], M Deleuran [17], L von Kobyletzki [18, 19], S Barbarot [20], A Heratizadeh [21], U Gieler [22], D J Hijnen [23], S Weidinger [24], L De Raeve [25], Å Svensson [26], D Simon [27], J F Stalder [28], J Ring [14, 29], European Task Force on Atopic Dermatitis/EADV Eczema Task Force

SEVERE SCORAD >50 or persistent eczema	Hospitalization, systemic immunosuppression: cyclosporine A[C], methotrexate[C], azathioprine[C], mycophenolate mofetil[NC]
MODERATE SCORAD 25-50 or recurrent eczema	Proactive therapy with topical tacrolimus[3] or class II or III topical glucocorticosteroids[C], wet wrap therapy, UV therapy (UVB 311 nm)[A], psychosomatic counseling, climate therapy
MILD SCORAD <25 or transient eczema	Reactive therapy with topical glucocorticosteroids class II[A] or depending on local cofactors: topical calcineurin inhibitors[3], antiseptics including, silver, silver-coated textiles[A]
BASELINE Basic Therapy	Educational programs, emollients bath oils, avoidance of clinically relevant allergens (encasing, if diagnosed by allergy tests)

[A]Refer to guideline text for restrictions; [C]Licensed indication; [NC]Off-label/treatment option.

Goals for atopic dermatitis management

- Reinforce the skin barrier
- Reduce inflammation and flares
- Manage comorbidities and secondary complications
- Minimize treatment-related adverse events
- Maximize medical outcomes and psychosocial status
- Educate and empower patients

To make the right therapeutic choice
➢ **adapt it to the child's age**

ETP is more than offering information

What is Therapeutic Patient Education (TPE)?

- Interweaving of education & medical care
- Integrated & psychological approach
- To help empower patients with a chronic disease
- Self-managing, coping processes and skills
- Therapeutic effect additional to all other interventions

World Health Organization

EADV

European task force for AD

Wollenberg A, Barbarot S, Bieber T, Christen-Zaech,S et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. *J Eur Acad Dermatol Venereol.* 2018;32(5):657-682.

Basic management - Cleansing

Daily bathing or showering

- To remove bacterial contaminants and desquamated scale
- Water < 35°C, duration ~ 5 minutes
- Soap less cleanser or bath oils, without irritants or strong allergens
- +/- antiseptics such as sodium hypochlorite
- pH between 5-6 -> acid mantel
  - Improves epidermal barrier function
  - Maintains bacterial and chemical resistance
  - Proteolytic process-> skin desquamation

Wollenberg A, Christen-Zaech S, Taieb A,et al. ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. European Task Force on Atopic Dermatitis/EADV Eczema Task Force. J Eur Acad Dermatol Venereol. 2020 Dec;34(12):2717-2744.

Basic management - Emollients

Emollients have a definite place in secondary and tertiary AD prevention

Cochrane review including 77 studies (6603 participants, mean age: 18.6 years)

- Compared moisturizer containing emollients versus no moisturizer
  - Beneficial effect in reducing SCORAD
  - Leading to fewer flares
  - Reduced use of corticosteroids
  - Did not find reliable evidence that one moisturizer is better than another

Emolliants should be applied daily and liberally

- Basic treatment of the disturbed skin barrier function
- 100 g per week in young children and up to 500 g in adults as
- Moisturizers with a hydrophylic formula in summer and higher lipid content in winter

Discuss treatment cost to assure compliance

van Zuuren EJ et al Cochrane Database of Systematic Reviews 2017

Basic management - Emollients plus

Emollients with non-medicated, active ingredients

- Neither fulfilling the definition of nor needing a licence as a topical drug
- These products, referred to as 'emollients plus' by the European guideline
- May contain, flavonoids, saponins and riboflavins from protein-free oat plantlet extracts, or bacterial lysates from Aquaphilus dolomiae or Vitreoscilla filiformis species or endobioma (endolysin).
- They improve AD lesions and influence the skin microbiome
- In vitro and clinical research data from different laboratories have provided some background information on molecular targets and possible mode of action of these active emollients plus

Wollenberg A, Christen-Zaech S, Taieb A,et al. ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. European Task Force on Atopic Dermatitis/EADV Eczema Task Force. J Eur Acad Dermatol Venereol. 2020 Dec;34(12):2717-2744.

Basic management - Trigger avoidance

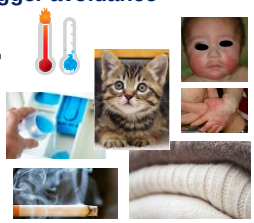
Climate
- Winter: overdressing, low humidity and indoor heating
- Humidifiers -> exposure to mold allergens if not cleaned often
- Summer: Sweat retention and increased vasodilatation

Saliva
- Teething, eating in infants -> major irritant
- Lip-licker's dermatitis in older children

Clothing
- Soft cotton, no wool, no harsh materials (take of labels)
- Avoid fabric softeners and all products with fragrances

Passive smoking
- Increases dermatitis and risk for asthma

Avoid allergens if proven



Counsel patients to identify and avoid triggers of disease flares as much as possible.

Basic management - Trigger avoidance

10-37% of children with moderate to severe AD have a food allergy

- Most commonly to milk, eggs, soy, wheat and peanuts
- No restrictive diets without clear diagnosis of food allergy!
- Low accuracy of food allergy testing
- Food may be an irritant or histamine liberator

Cat exposure during infancy -> increases risk of developing AD

Cat exposure of AD children -> increases risk of developing asthma

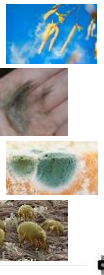
Spergel JM et al Pediatrics. 2015;136(6); Epstein TG et al. J Pediatr. 2011 F;158(2):265-71

Basic management - Trigger avoidance

Test children with moderate to severe AD

<5 years of age
- not responding to topical treatment
- with urticaria and gastrointestinal symptoms
- test for food allergies
- milk, egg, peanut, wheat and soy

> 5 years of age
- with persistent skin involvement over time
- with signs of rhino-conjunctivitis, asthma, contact allergy
- test for aeroallergens
- house-dust mites, grass pollens, animal dander and molds



Spergel JM et al Pediatrics. 2015 ;136(6)

Topical antiinflammatory treatment

- Topical corticosteroids
- Topical calcineurin inhibitors
- Topical phosphodiesterase 4 inhibitors
- Upcoming topical treatments

Topical corticosteroids (TCS)

Factors to consider
- Severity and localization of the dermatitis
- Age of pediatric patient
- Potency and galenic formulation

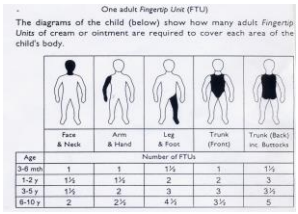
Chose least potent preparation that adequately controls AD

Mild to moderate disease
- Intermittent use of low to mid-potency (class I-II) TCS

Moderate to severe disease
- Mid-potency to potent (class II-III) TCS for acute flares
- Followed by proactive treatment
  - TCS or calcineurin-inhibitors 2x/week

Hanifin J et al. Br J Dermatol. 2002;147(3):528-37; Breneman D et al. J Am Acad Dermatol. 2008;58(6):990-9; Paller AS et al. Pediatrics. 2008 ;122(6)

Topical corticosteroids - quantity



Cave
- increased body surface area-to-weight ration in infants
- occlusion increases potency 10-100x

Topical calcineurin-inhibitors

Tacrolimus (Protopic®) 0.03% (>2 yr), 0.1% ointment (>16 yr)
Pimecrolimus (Elidel®) 1% cream (>3 month)

Inhibit calcineurin-dependent T-cell activation, impeding the production of proinflammatory cytokines and mediators.

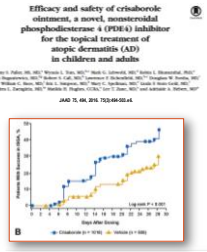
After treating acute flares with TCS switching to TCI or as proactive therapy

Advantages
- No steroid side effects
- Safely used around eyes, face, neck & intertriginous areas
- No systemic immunosuppression
- No increased cutaneous infections
- No evidence of increased risk of skin cancer or lymphoma

Disadvantages
- Burning or stining sensation with application

Paller AS J Pediatr. 2001;138(2):163-8; Kolavala M et al. Am J Clin Dermatol. 2011;1(12):15-24. Ho VC et al. J Pediatr. 2003;142(2):135-42; Patel RR et al. Arch Dermatol. 2003;139(9):1184-5. Paller A et al. J Am Acad Dermatol. 2001;44(l Suppl):S47-57; Harper J, et al. Br J Dermatol. 2001;144(4):781-7. Berger TG et al. J Am Acad Dermatol. 2006 ;55(2):271; Arellano FM et al. J Allergy Clin Immunol. 2009 ;123(5):1111-6

Topical PDE4 Inhibitor – Crisaborole 2% ointment



2 double-blind, vehicle-controlled phase III trials
- **1'500 patients with mild to moderate AD**
- **2 years old and older (mean 12 years)**
- **Study drug was applied 2x/day for 28 days**

Significant improvement on ISGA score and of pruritus

Adverse events
- **rarely local burning sensations**

Aapproved in USA, Canada, Australia, Israel and Hong Kong
-> Patients ≥2 years old with mild-to-moderate AD
-> twice daily to affected areas

Approved in Europe in 2020
-> but not commercialized on the European market

When is it time for systemic therapy?

Does the patient have moderate-to-severe atopic dermatitis?

- Has adequate patient education been provided?
- Have alternative diagnoses been considered?
- Has intensive topical therapy been given an adequate trial?

Does the patient still have persistent moderate-to-severe disease/impaired QoL despite intensive topical therapy?

Discuss systemic therapy with the patient/caregiver

Conventional systemic treatments			Biologics	JAK-Inhibitors
Ciclosporin Licensed > 16 years 2.5-5 mg/kg/day in two doses Response 1-2 wk	**Methotrexate** Off-label 0.3-0.4 mg/kg/wk Response 8-12 wk	**Azathioprine** Off-label 1-3 mg/kg/day Response 8-12 wk	**Dupilumab** Licensed > 12 years <60kg init. 400mg s.c. then 200mg Q2W >60kg init. 600mg s.c. then 300mg Q2W Response 4-6 wk	**Upadacinib** Licensed >12 years > 30kg: 15mg/day Response 1-2 wk

Wollenberg A, Christen-Zaech S, Taieb A,et al. J Eur Acad Dermatol Venereol. 2020 Dec;34(12):2717-2744.

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