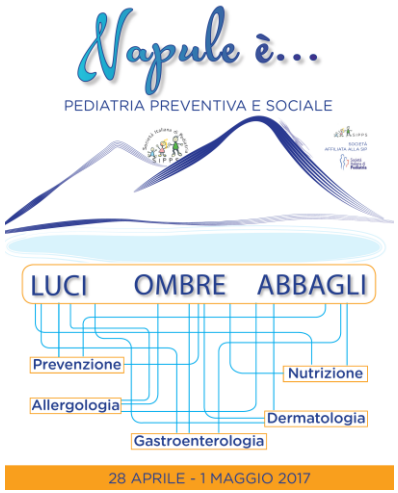
La gestione della dermatite atopica

Diego Peroni

Universita' di Pisa

- ✓ **Introduction**
- ✓ **Topical treatment**
  - ✓Emollients
  - ✓Anti-inflammatory
  - ✓New treatment
- ✓ **Conclusions**



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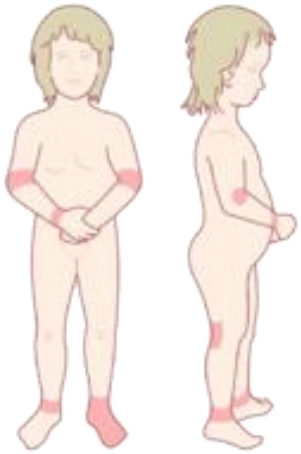
Usually facial lesions
Patchy elsewhere

Infant



Lesions settling into elbow and knee flexures. Also on wrists and ankles

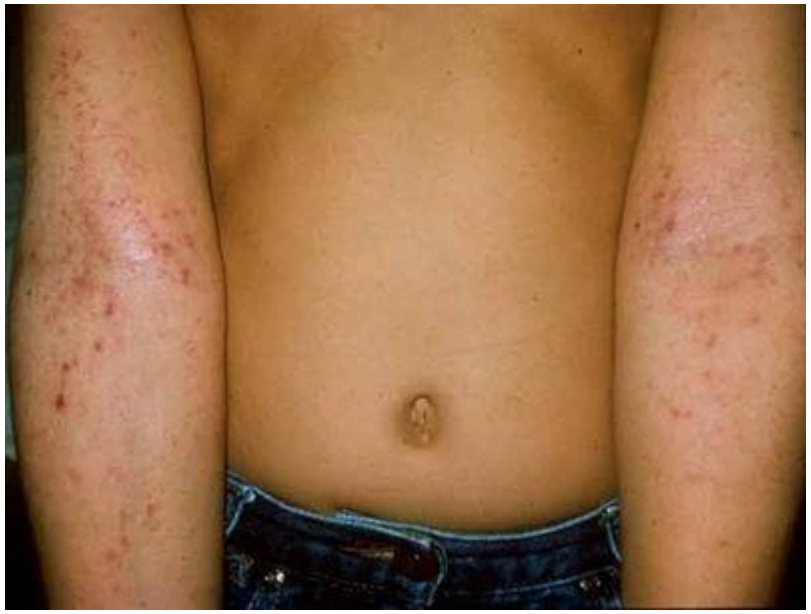
Older child

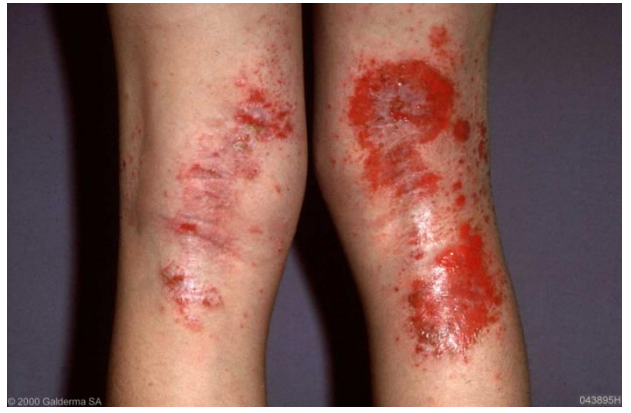
Options include

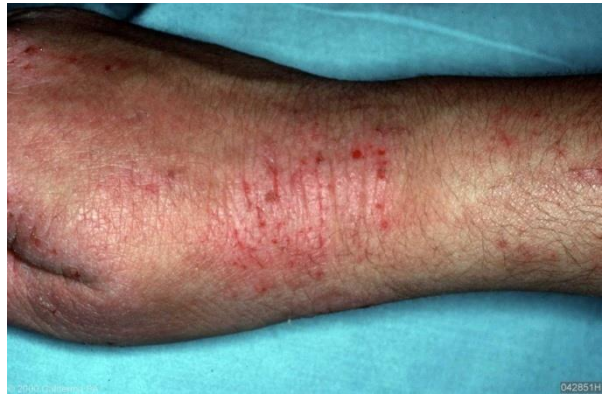
- Remains clear
- Localized hand eczema provoked by irritants
- Generalized low-grade eczema
- Eczema stays confined to limb flexures

Mid-teens

May clear, persist or change pattern

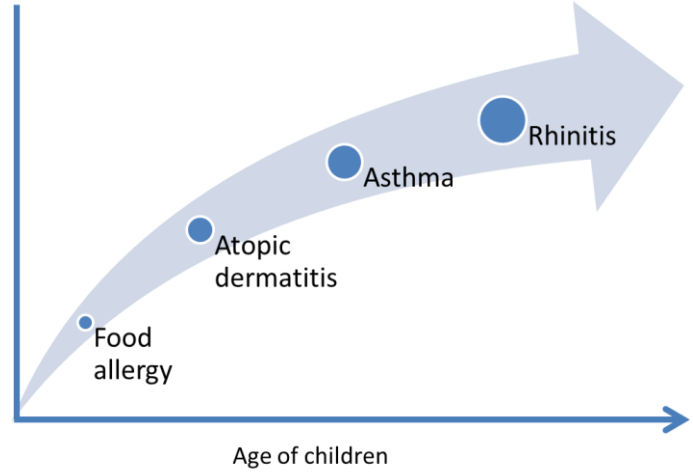






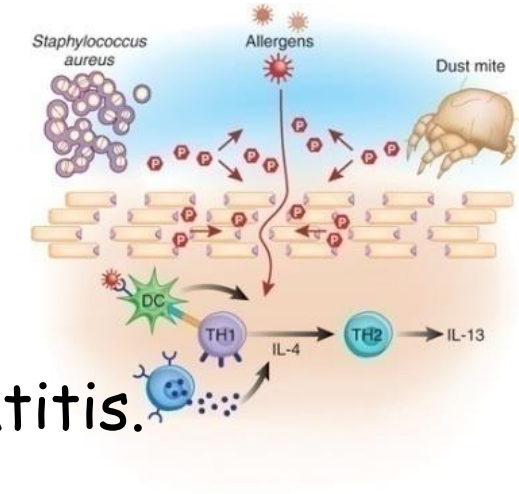
Atopic Dermatitis: Development

- There are at least two theories proposed to explain the development of this common disorder.



1) For years, the major theory was that patients had an aberrant and robust Th2 adaptive immune response to largely innocuous environmental antigens.

2) Recent research highlights the importance of skin barrier abnormalities and an inadequate host response to common cutaneous microbes as other highly plausible mechanisms that might predispose individuals to develop atopic dermatitis.



Deciphering the complexities of atopic dermatitis: Shifting paradigms in treatment approaches. D Leung, JACI 2014: 134;769

	Clinical features	Biophysical features
AD_{FLG}	Palmar hyperlinearity	Severe decrease in NMF
	More persistent	pH
	↑ Allergic sensitization	IL-1β
	↑ Risk of asthma	Type 1 interferon–mediated stress response
	↑ Severity of AD	
	↑ Eczema herpeticum	
$AD_{NON\text{-}FLG}$	No palmar hyperlinearity	Mild decrease in NMF
	Less persistent	pH lower compared with patients with AD_{FLG}
	Less allergic sensitization	IL-1β low compared with patients with AD_{FLG}
	Lower risk of asthma	Dysregulation of lipid metabolic processes

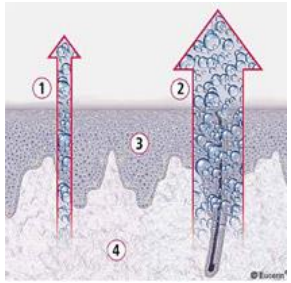
NMF, Natural moisturizing factor.

Trigger factors aggravating pruritus perception in AD

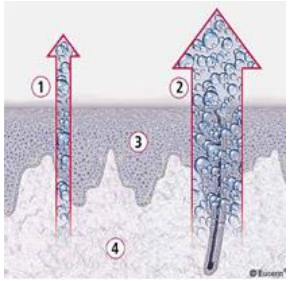
Epidermal barrier

Xerosis, a common problem of the skin of patients suffering from AD, results in an increased transepidermal water loss and a decreased ability of the stratum corneum to bind water

a disturbed epidermal barrier constitutes an activator of pruritus.



scratching behaviour and induction of pruritus are triggered by water content below 10%



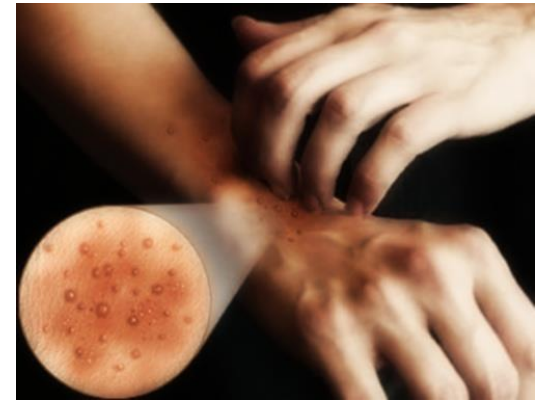
Buddenkotte J, Allergy. 2010;65:805-21.

THE ROLE OF PRURITUS IN ATOPIC DERMATITIS PATHOGENESIS

- neuropeptides,
- proteases,
- IL-31,
- kallikrein 7;
- ……..?

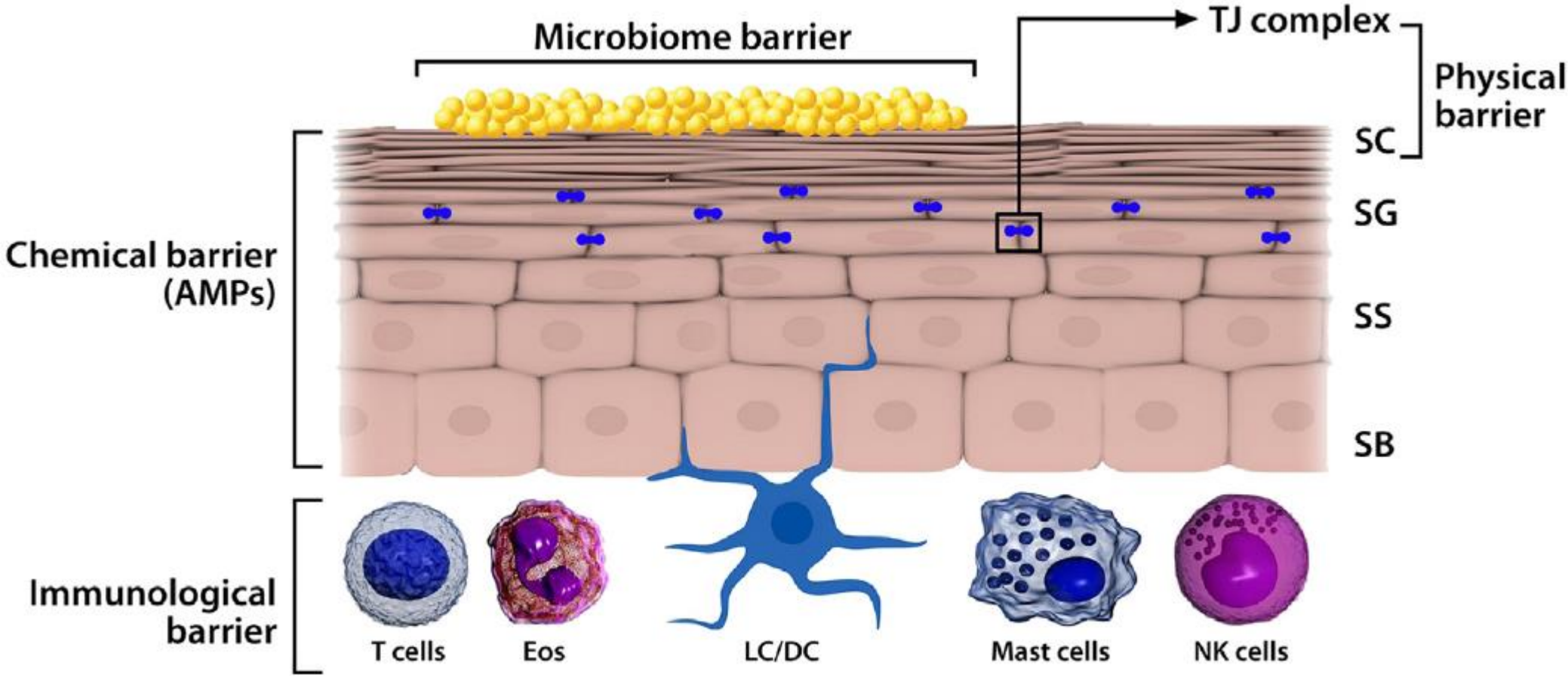
Pruritus is an unpleasant sensation provoking the desire to scratch and constitutes an essential feature of atopic dermatitis

pruritus



Jung T, JACI 2008;122:1074

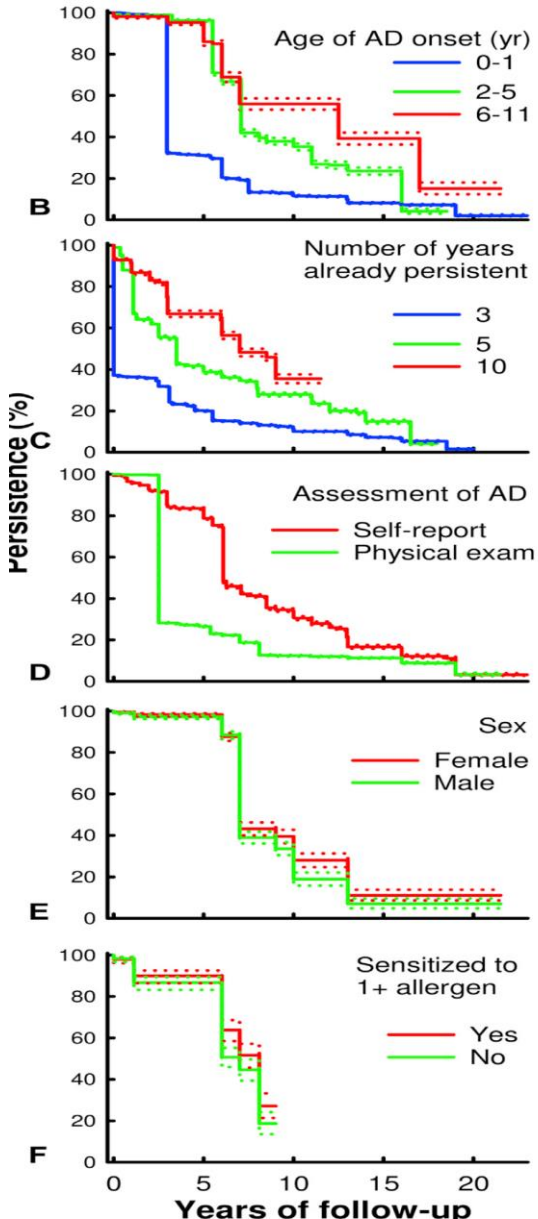
Deciphering the complexities of atopic dermatitis: Shifting paradigms in treatment approaches. D Leung, JACI 2014: 134;769



The skin as a multitiered barrier. The stratum corneum (SC) is the first physical barrier protecting the skin from the environment. Gene mutations (eg, filaggrin-null mutations) or cytokines (eg, IL-4, IL-13, IL-25, and IL-33) downregulating epidermal proteins, including filaggrin, leads to allergen or microbial penetration through this barrier.

Persistence of atopic dermatitis (AD): A systematic review and meta-analysis.

Kim, J Am Acad Dermatol 2016



CAPSULE SUMMARY

- Previous studies have reported conflicting results regarding the persistence of childhood atopic dermatitis into adulthood.
- Only 1 in 5 children with atopic dermatitis had disease persistence beyond 8 years. Children with already persistent disease, later onset, and more severe disease were more likely to have disease persist into adolescence and adulthood.
- These risk factors may be useful to predict which children will have persistent atopic dermatitis.

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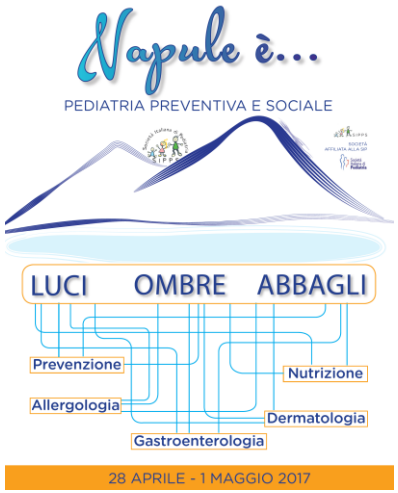

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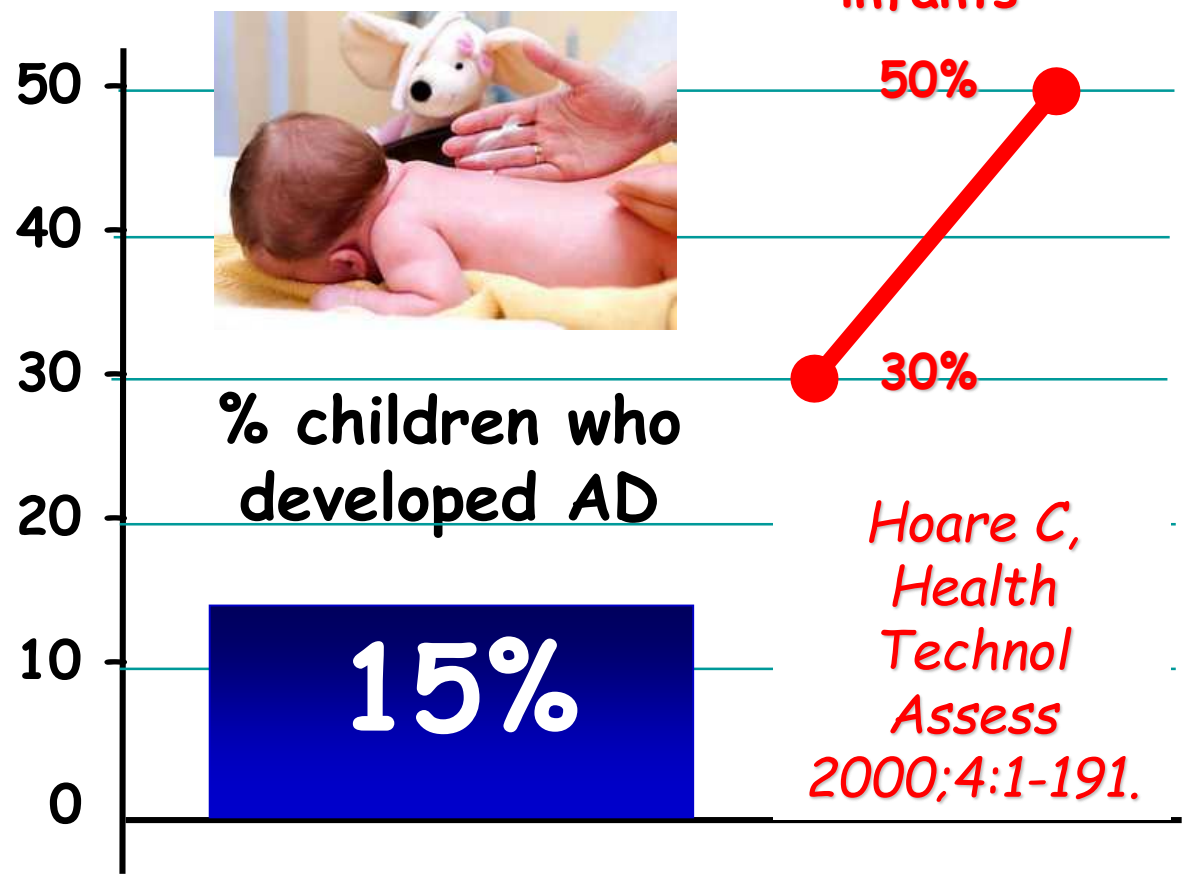
A pilot study of emollient therapy for the primary prevention of atopic dermatitis.

Simpson EL, J Am Acad Dermatol. 2010;63:587-93.

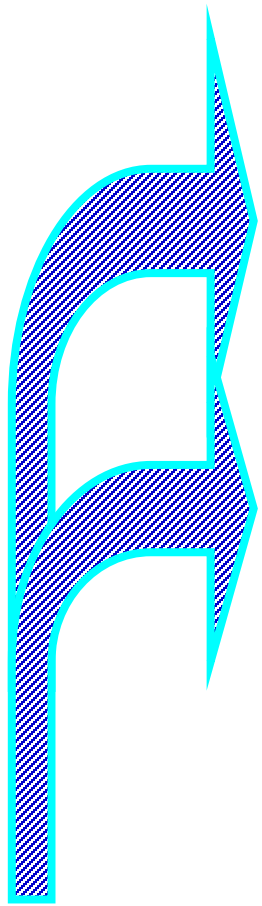
- ✓22 neonates at high risk for developing AD
- ✓emollient therapy from birth.
- ✓followed up mean time of 547 days



Barrier repair therapy in atopic dermatitis: an overview.

Hon KL, Am J Clin Dermatol. 2013;14(5):389-99.

- ✓12 randomized trials
- ✓11 cohort studies
- ✓natural moisturizing factors, ceramides,



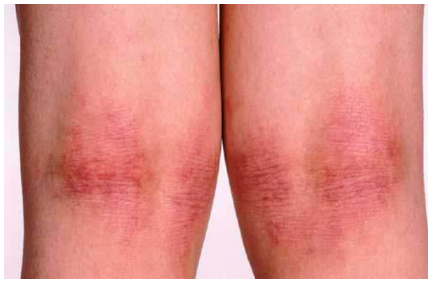
Proper moisturizer therapy can reduce:

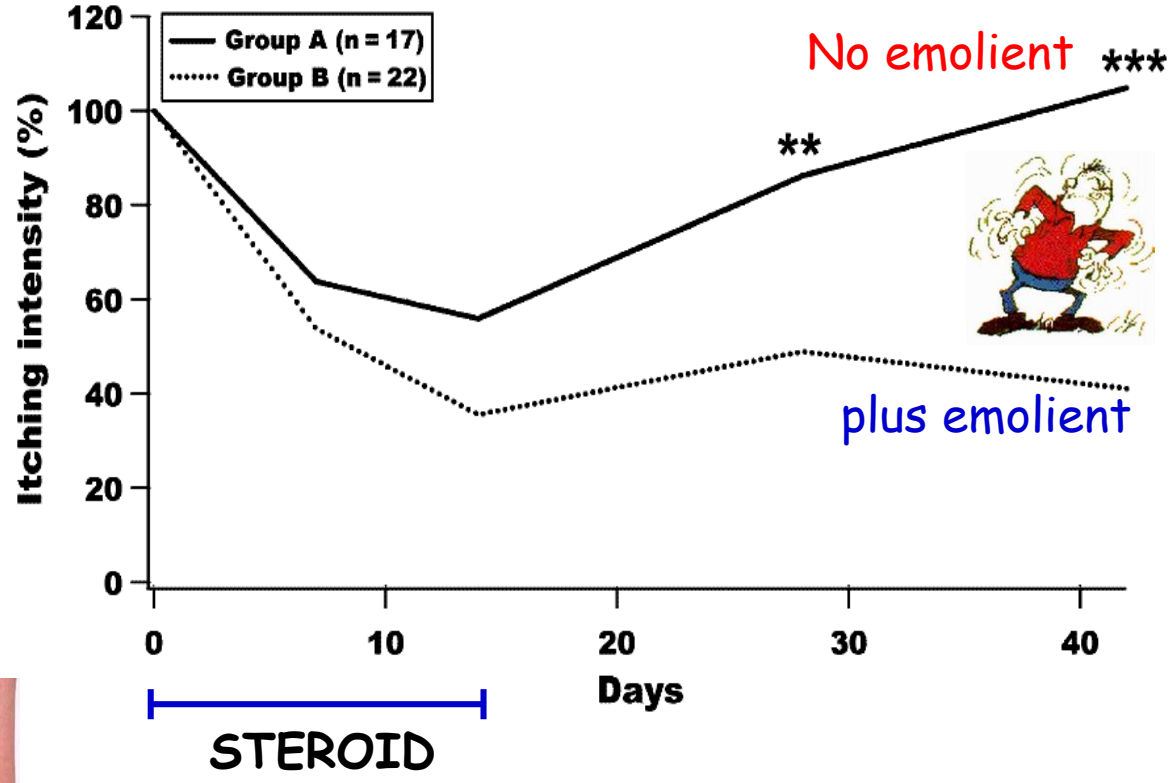
1) the frequency and intensity of flares, as well as
2) the need for topical corticosteroids or topical calcineurin inhibitors

Emollients Improve Treatment Results with Topical Corticosteroids in Childhood Atopic Dermatitis: a Randomized Comparative Study

Szczepanowska Ped All Immunol 2008;19:614

- ✓ 52 ch with AD (2-12 yrs).
- ✓ 26 ch received a steroid cream for 2 weeks (+4 weeks follow-up with no treatment) (Group A).
- ✓ 26 ch received steroid cream for 2 weeks + emolients for 6 weeks (Group B).





* p=0.004 ** p=0.01 ***p<0.001

Classification of moisturizers

Class	Mode of action	Biological similarity	Some examples
Humectants	Attract and bind water from deeper epidermis to SC	NMF in corneocytes	Glycerin
			Alpha hydroxy acids
			Hyaluronic acid
			Sorbitol
			Urea
Occlusives	Form a hydrophobic film to retard TEWL of SC	Intercellular lipid bilayers	Carnauba wax
		- Ceramide	Lanolin
		- Cholesterol	Mineral oils
		- Free fatty acids	Olive oil
			Petrolatum
			Silicone
Emollients	Smoothens skin by filling the cracks between desquamating corneocytes	Natural lipids found on skin and sebum	Collagen
			Colloidal oatmeal
			Elastin
			Glyceryl stearate
			Isopropyl palmitate
			Shea butter
			Stearic acid

SC, subcutaneous layer; NMF, natural moisturizing factor; TEWL, transepidermal water loss.

A review on the role of moisturizers for atopic dermatitis.

Giam, As Pac Allergy 2016

Some of the newer anti-inflammatory agents have been added into the moisturizer formulations in order to alleviate mild-to-moderate AD. These anti-inflammatory agents include:

glycyrrhetinic acid, palmitoylethanolamine, telmesteine, Vitis vinifera, ceramide-dominant barrier repair lipids and filaggrin breakdown products (e.g., ceramide precursor/pseudoceramide, 5-sphingosine-derived sphingolipid, niacinamide, vitamin B3, pyrrolidone carboxylic acid, and arginine)

These active agents are combined with emollients or humectants, which may provide additional barrier repair and control of xerosis

Treatment of Pruritus in Mild-to-Moderate Atopic Dermatitis With a Topical Non-Steroidal Agent

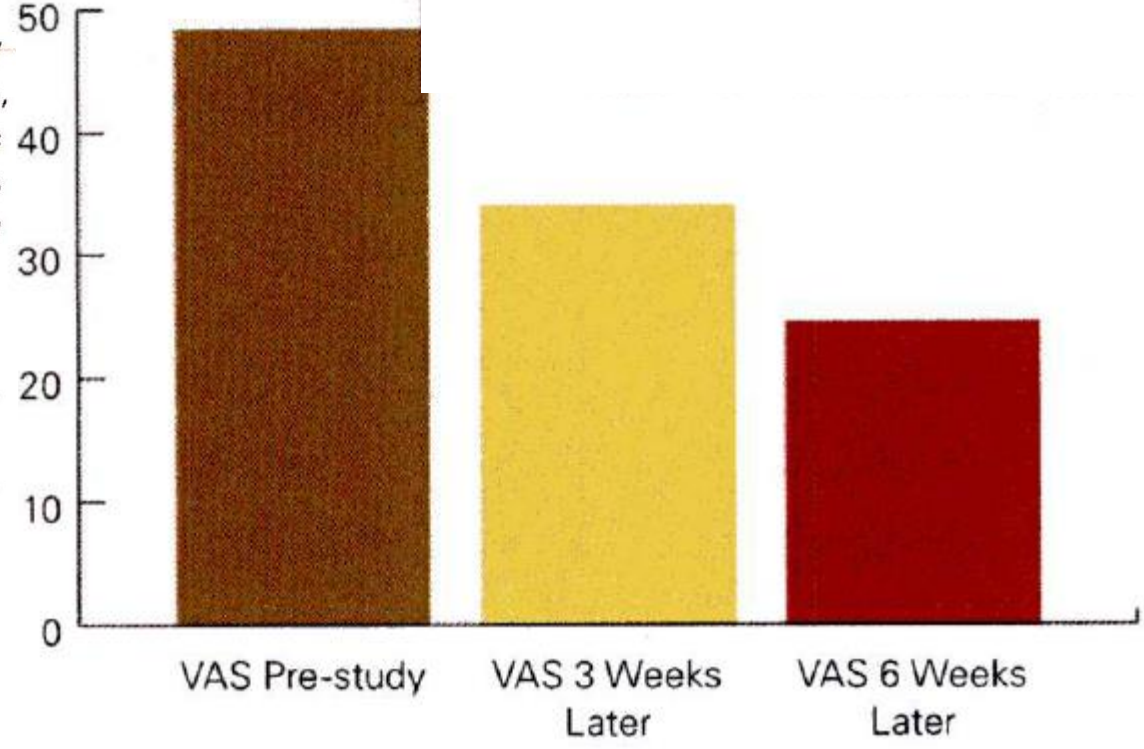
Stefano Veraldi MD PhD[a], Paolo De Micheli MSc[b], Rossana Schianchi MD[b], Luisa Lunardon MD[a]

Atopiclair® is a topical non-steroidal anti-inflammatory agent for the treatment of allergic diseases of the skin, such as irritant/allergic contact dermatitis and atopic dermatitis (AD). The three main ingredients contained in this product are glycyrrhetinic acid, telmesteine and *Vitis vinifera*

Patients were examined after three (T1) and six weeks of treatment (T2). Primary objective of the study was the evaluation of pruritus after three and six weeks of treatment. Pruritus severity was evaluated by means of a 0-100 mm Visual Analogue Scale (VAS).[9]

RESULTS

Eighty-nine Caucasian patients with mild-to-moderate AD were enrolled: 38 males (42.7%) and 51 females (57.3%), with an age ranging from 18 to 42 years (average age: 19.9 years).



Changes in VAS

A randomised, double-blind, vehicle-controlled study to evaluate the efficacy and safety of MAS063D (Atopiclair®), in the treatment of mild to moderate atopic dermatitis.

Belloni, Eur J Dermatol 2005; 15: 31

MAS063D (Atopiclair®) is a hydrolipidic cream that has been developed for the management of atopic dermatitis (AD). The putative active ingredients of MAS063D are hyaluronic acid, telmesteine, *Vitis vinifera*, glycyrrhetinic acid. A five-week study in 30 adult patients with mild to moderate AD

MAS063D improved

- the total body area affected (17.2%→13.2%, $p < 0.001$),
- itch score (2.7→1.3 on a 10-point scale, $p = 0.001$) and
- EASI score (28.3 → 24.3, $p = 0.024$)

after 22 days treatment compared to baseline

A randomised, double-blind, vehicle-controlled study to evaluate the efficacy and safety of MAS063D (Atopiclair®), in the treatment of mild to moderate atopic dermatitis.

Belloni, Eur J Dermatol 2005; 15: 31

Outcome	Change in MAS063D group (mean ± SD, n = 15)	Change in control group (mean ± SD, n = 15)	P (Wilcoxon Rank Sum Test) for MAS063D
Affected area	4.0 ± 3.0	0.5 ± 1.5	$p < 0.001$
Itch score (also significant at visit 3)	1.3 ± 0.5	0.5 ± 0.6 ($p = 0.025$, *table 3*)	$p = 0.001$
EASI	4.0 ± 3.9	0.7 ± 2.6	$p = 0.024$
Grading of severity of atopic dermatitis	0.5 ± 0.7	0.2 ± 0.6	$p = 0.08$
Quality of sleep	0.0 ± 0.0	–0.1 ± 0.4	$p = 0.15$

MAS063D (Atopiclair®) is a hydrolipidic cream that has been developed for the management of atopic dermatitis (AD).

The putative active ingredients of MAS063D are hyaluronic acid, telmesteine, *Vitis vinifera*, glycyrrhetinic acid.

A five-week study in 30 adult patients with mild to moderate AD

MAS063DP is Effective Monotherapy for Mild to Moderate Atopic Dermatitis in Infants and Children: A Multicenter, Randomized, Vehicle-Controlled Study.

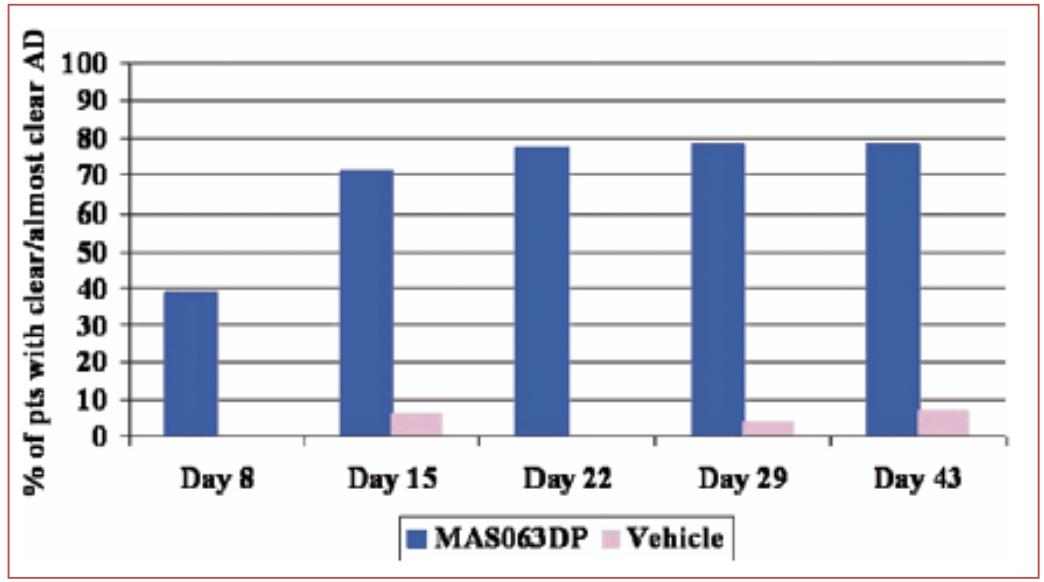
Boguniewicz, J Ped 2008; 152:854

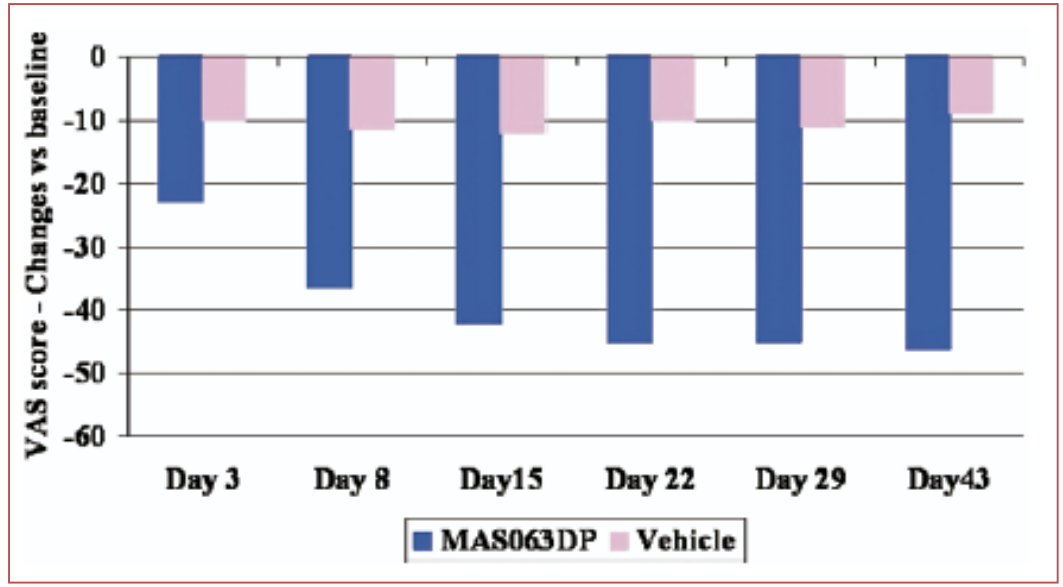
142 pts (6 mo.to 12 yrs)

MAS063DP (n 72) or vehicle (n 70) cream

3 times per day to affected areas and sites prone to develop AD.

The primary endpoint for efficacy was the nvestigator's Global Assessment at day 22





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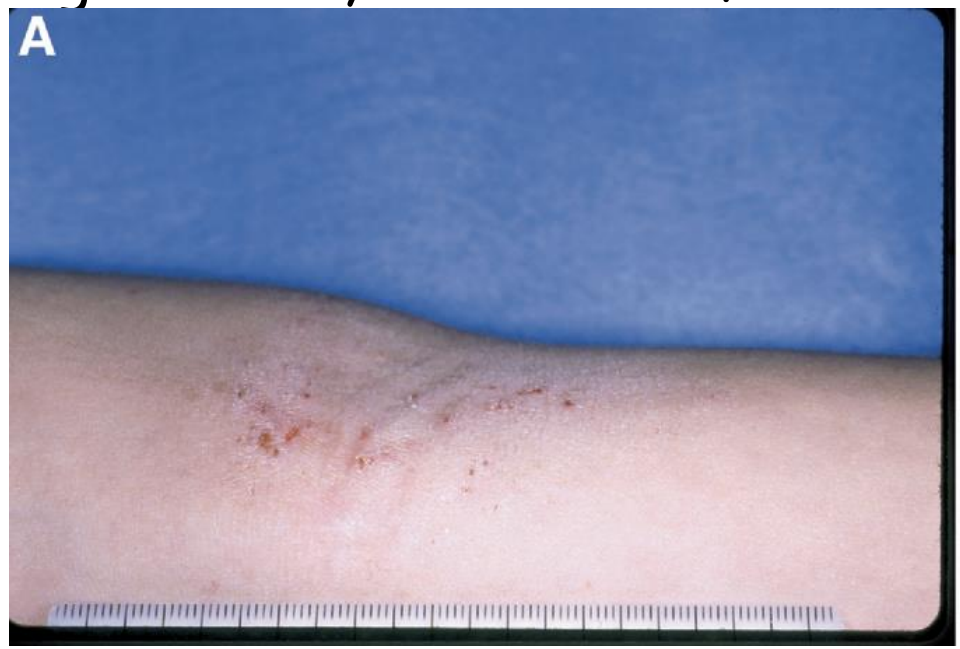

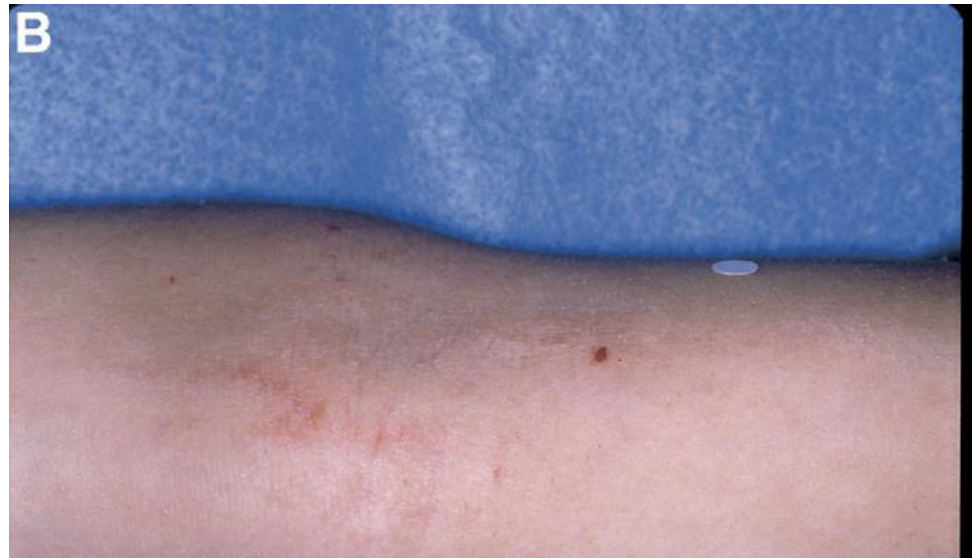

Representative atopic dermatitis skin lesions at day 1 **(A) and day 8 (B) of treatment with MAS063DP.**

MAS063DP is Effective Monotherapy for Mild to Moderate Atopic Dermatitis in Infants and Children: A Multicenter, Randomized, Vehicle-Controlled Study.

Boguniewicz, J Ped 2008; 152:854

MAS063DP cream is effective and safe as monotherapy for the treatment of symptoms of mild to moderate atopic dermatitis in infants and children

Repres
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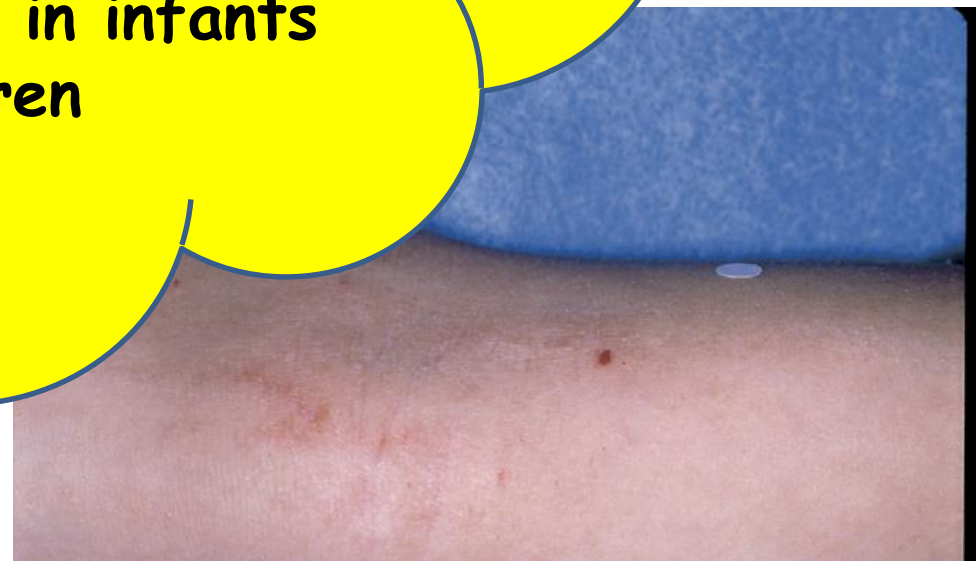
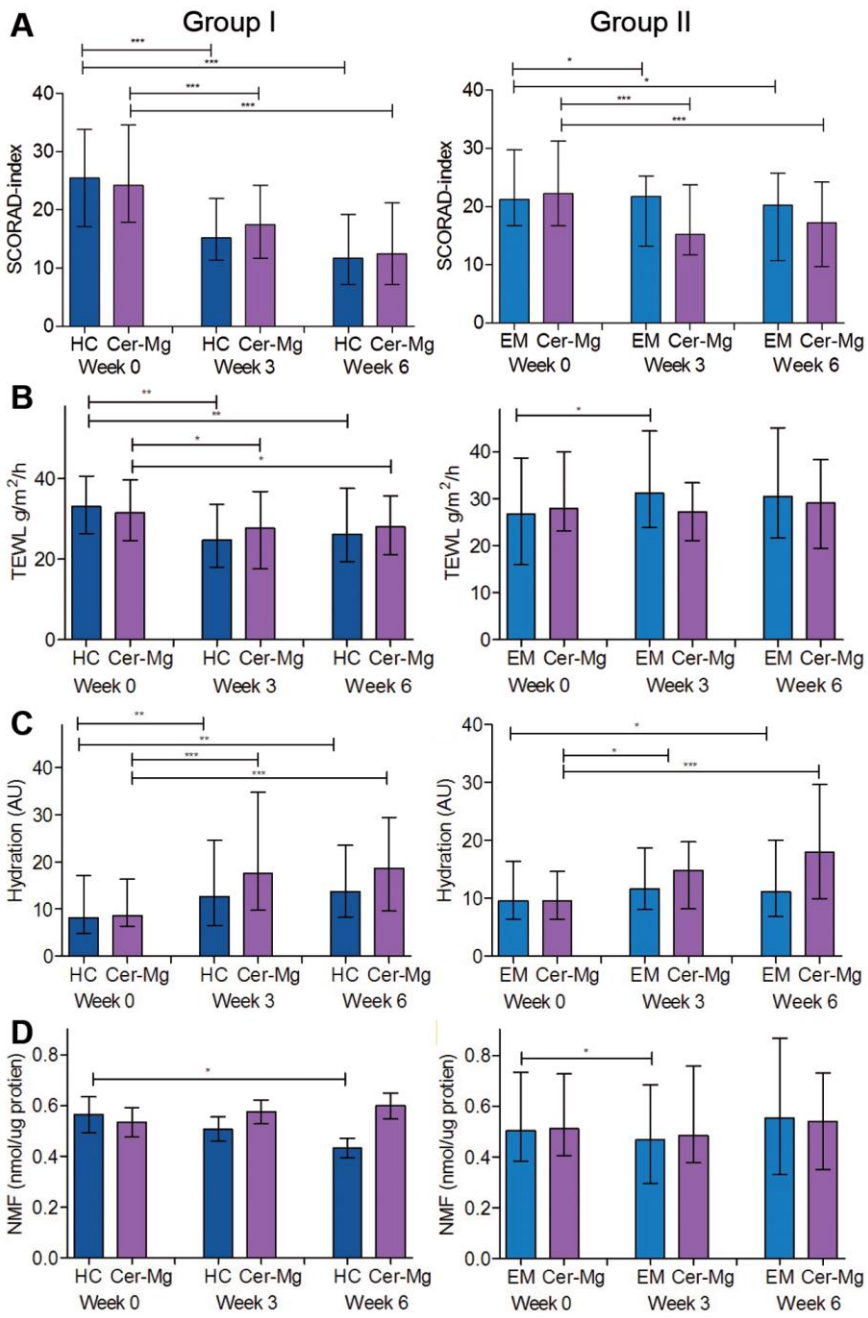




Efficacy of a Cream Containing Ceramides and Magnesium in the Treatment of Mild to Moderate Atopic Dermatitis: A Randomized, Double-blind, Emollient- and Hydrocortisone-controlled Trial.

Koppes , Acta Derm Ven 2016

After 6 weeks, group I showed comparable significant improvement in SCORAD and TEWL, while in group II, the decrease in SCORAD and TEWL was significantly greater after Cer-Mg compared with emollient.

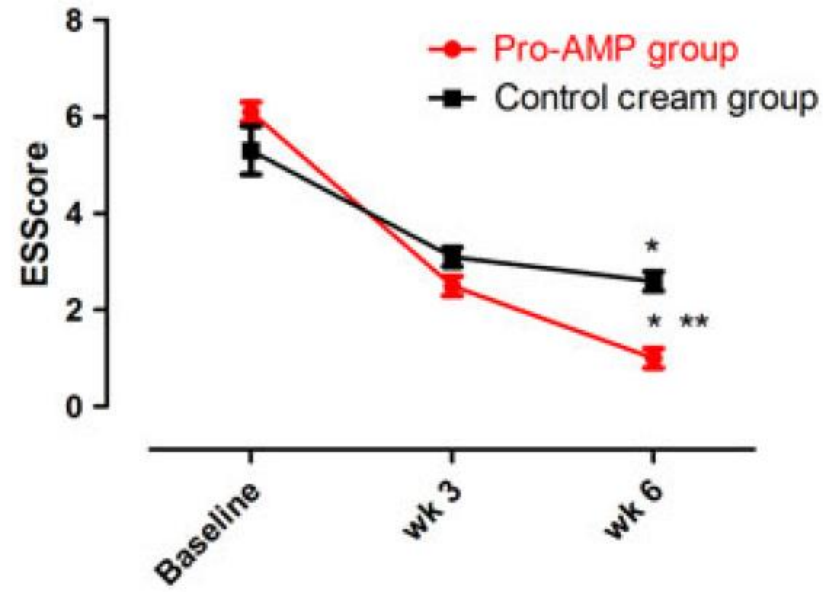
Finally, Cer-Mg cream was more effective in improving skin hydration and maintenance of levels of NMF than hydrocortisone and emollient.

Local rhamnosoft, ceramides and L-isoleucine in atopic eczema: a randomized, placebo controlled trial

Marseglia A. PAI,2014; 25:271-275

- ✓ A non-steroidal, anti-inflammatory moisturizing cream containing rhamnosoft, ceramides, and L-isoleucine (ILE) (pro-AMP cream)
- ✓ 107 children (72 allocated to pro-AMP cream and 35 allocated tocontrol group) with mild-to-moderate chronic AE of the face
- ✓ Treatments were applied twice daily for a 6-week period.

Evolution of Eczema severity Score from baseline to week 3 and week 6 in the two study groups.



*p < 0.001 vs baseline
**p > 0.001 vs control cream

Emollient Therapy

1. The direct use of emollients on inflamed skin may be poorly tolerated and it is better to treat the acute flare first.

2. Emollients are the mainstay of maintenance therapy.

3. Hydration of the skin is usually maintained by at least twice daily application of moisturizers.

4. The cost of high-quality (low in contact allergens) emollient therapies often restrict their use because such therapies are considered to be non-prescription drugs and the quantities required are usually high (150–200 g per week in young children, up to 500 g in adults).

Guidelines for treatment of atopic eczema (atopic dermatitis) Part I
J. Ring, JEADV 2012, 26, 1045–1060

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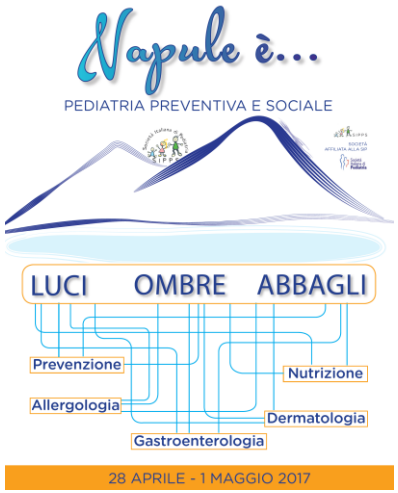

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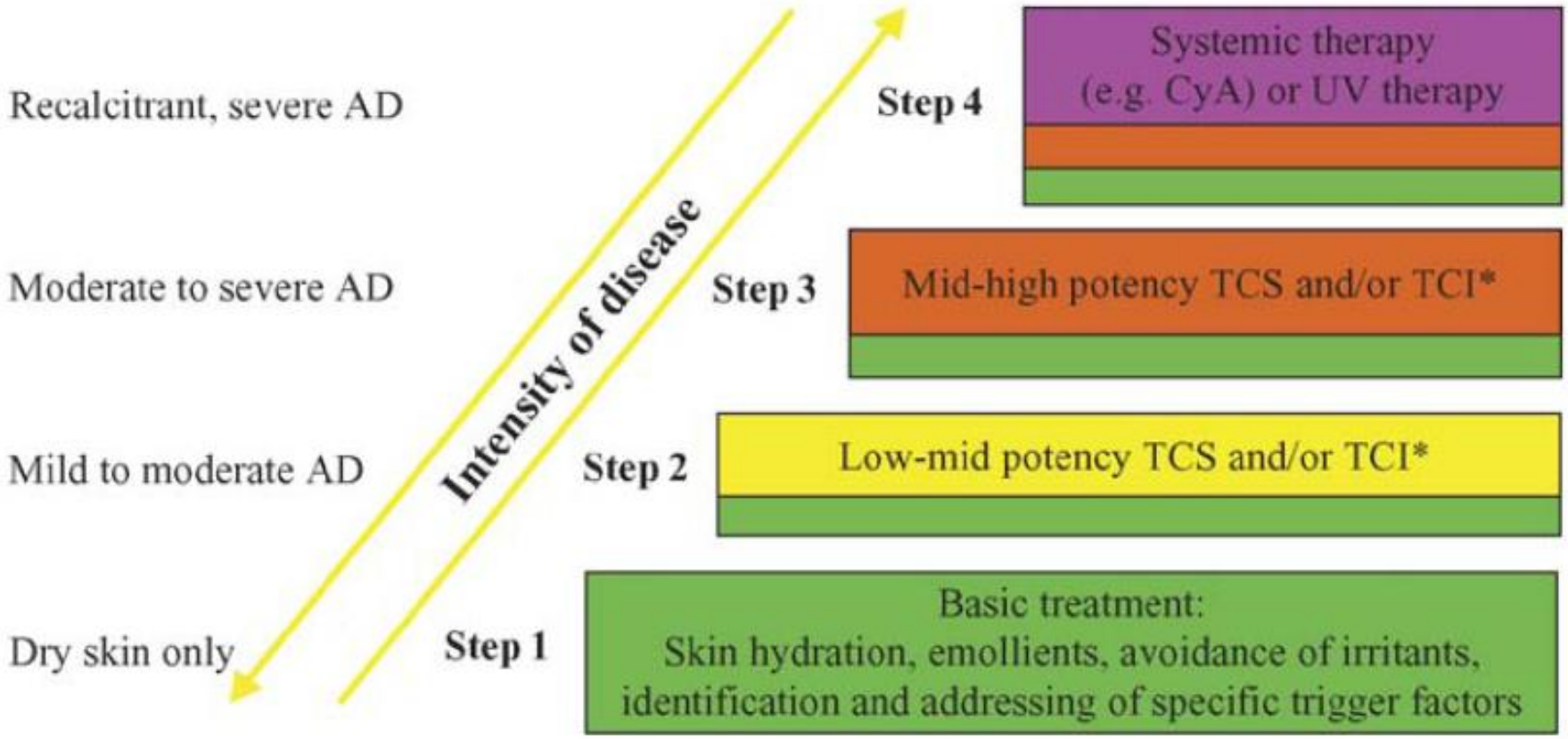
Stepwise management of patients with AD



TCS = Topical corticosteroids, TCI = Topical calcineurin inhibitors, CyA = Cyclosporine A
* Over the age of 2 years

Akdis CA, Practal JACI 2006;118:152

Update on topical glucocorticoid use in children.

K. Morley, Curr Opin Pediatr 2012, 24:121

Immunologic effects	Metabolic effects
↑ Anti-inflammatory genes [lipocortins which inhibit phospholipase A2 (PLA2), inhibitory cytokines]	↑ Blood sugar levels
↑ Collagen breakdown	↑ Glycogen synthesis, gluconeogenesis
↑ Eosinophil apoptosis	↑ Insulin resistance
↑ Degradation of inflammatory mRNA transcripts	↑ Protein catabolism
↑ Sequestration of lymphocytes in lymphoid tissue	↑ Sodium retention via intrinsic mineralocorticoid activity
↑ Neutrophil count in circulation, ↓ count at sites of inflammation	↑ Hepatic amino acid uptake
↓ Pro-inflammatory gene transcription (NFκB, PLA2, adhesion molecules)	↑ Hepatic RNA and protein synthesis
↓ Influx, maturation, and differentiation of leukocytes	↑ Lipid mobilization
↓ Protein synthesis in lymphatic tissues (complement and IgG)	↑ Lung surfactant production
↓ Capillary permeability and dilation	↑ Gastric acid secretion
↓ Phagocytosis	↑ Growth hormone (GH) production acutely, ↓ GH synthesis chronically
↓ Mast cell sensitization	↑ Memory acutely, ↓ memory chronically
	↑ Osteoclast activity, ↓ osteoblast activity
	↓ GLUT 4 expression and translocation to the membrane [6]

Update on topical glucocorticoid use in children.

K. Morley, Curr Opin Pediatr 2012, 24:121

KEY POINTS

- Glucocorticoids are well tolerated and effective in children.
- Correct glucocorticoid selection minimizes side effects.
- Vehicle selection, especially use of gels, may improve patient compliance.

Prescribing Topical Corticosteroids in Atopic Dermatitis

Type of Preparation

- **Ointment** bases are more occlusive than creams and result in better penetration and an increased hydrating effect on the skin. Because preservatives are not required in ointments, they are associated with a lower incidence of hypersensitivity reactions.

- **Creams**, however, can be more cosmetically acceptable on the face and are preferable in moist, hairy areas.

- **Lotions**, **gels**, and **mousses** are useful on the scalp but often contain alcohol, which may cause a stinging or burning sensation on inflamed skin.

Charman C. Clin Dermatol. 2003:21:193-200.

Expert consensus: time for a change in the way we advise our patients to use topical corticosteroids. A. Bewley, BJD, 2008 158, 917

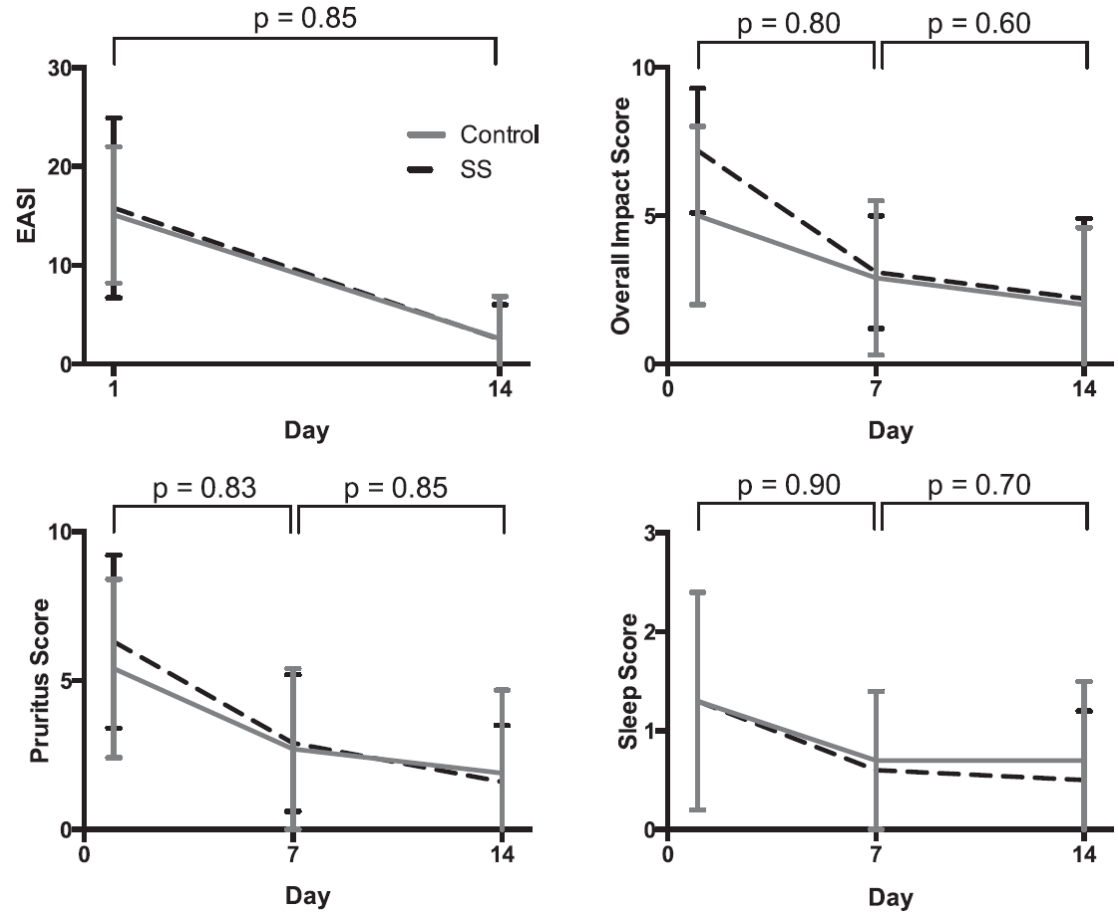
Examples of data to include in information leaflets for patients prescribed topical corticosteroids

Maximum fingertip units per week
How long a prescribed tube of cream/ointment should last
Stepping up or stepping down treatment potency
Instructions on duration of course of treatment and when to re-treat
Realistic goals: e.g. 'continue until affected skin is completely flat'
Time frames for review, if goals not achieved
Possible side-effects — what to look out for, when to stop treatment, when to seek advice, etc.
Precautions with pregnancy or breast-feeding (if any)
Useful local/national support groups (with contact details)

A randomized, controlled trial comparing topical steroid application to wet versus dry skin in children with atopic dermatitis.

Kohn, J Am Acad Dermatol 2016;75:306

Patients were randomized to apply TCS either via Soak and Smear (n = 22) or to dry skin (n = 23) for 14 days.
The primary outcome was an improvement in the Eczema Area and Severity Index score.
Secondary outcomes included assessments of disease burden, pruritus, and sleep

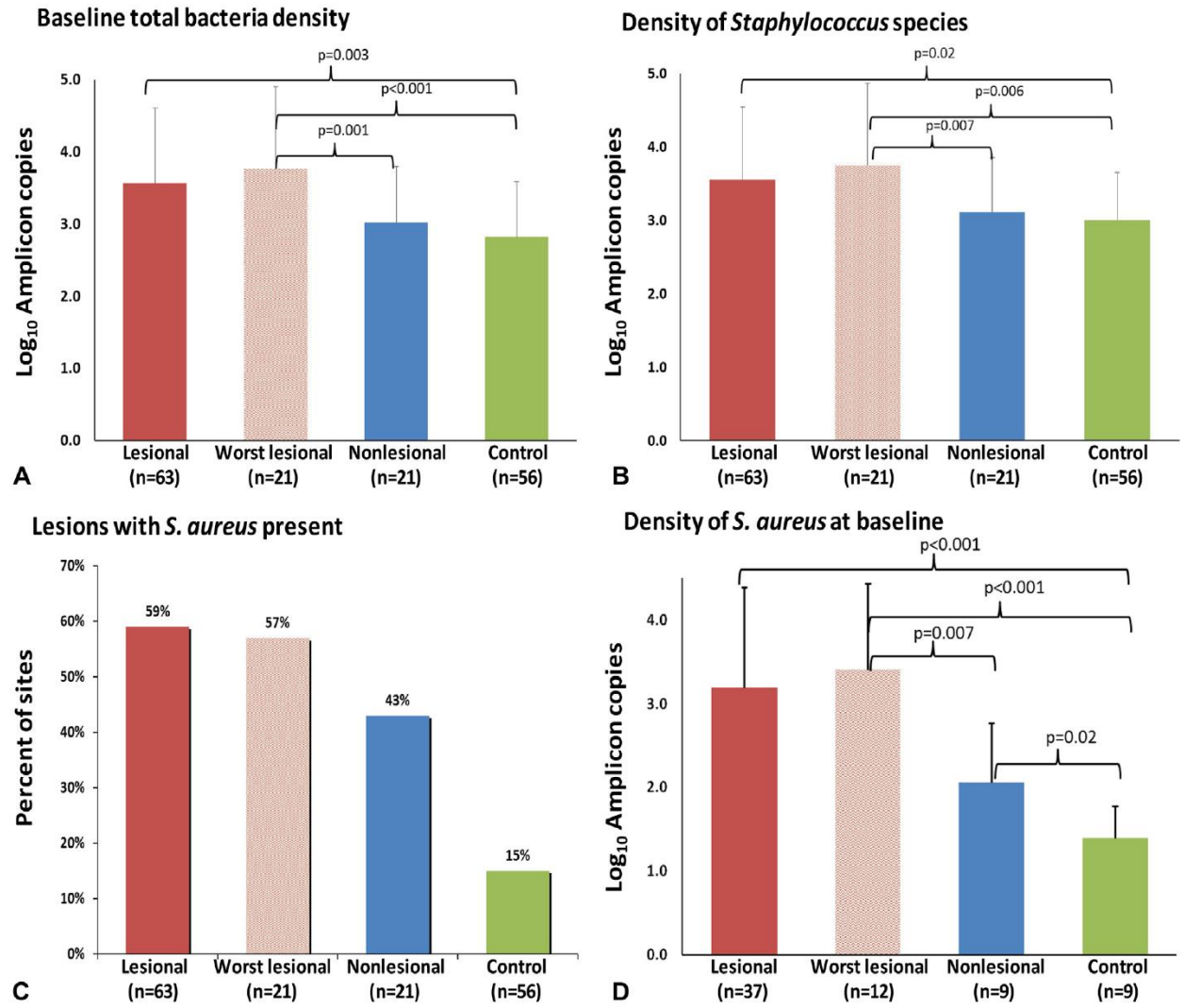


We did not find that application of TCS to presoaked skin works better than application to dry skin for the treatment of AD in children.

Cutaneous microbiome effects of fluticasone propionate cream and adjunctive bleach baths in childhood atopic dermatitis.

Gonzales, J Am Acad Dermatol 2016;75:481

In a randomized, placebo-controlled, single-blinded clinical trial in 21 children with AD and 14 healthy children, lesional and nonlesional AD skin was examined at baseline and after 4-week treatment with TCS alone or TCS plus bleach bath. Microbial DNA was extracted for quantitative polymerase chain reaction of predominant genera and 16S rRNA sequencing



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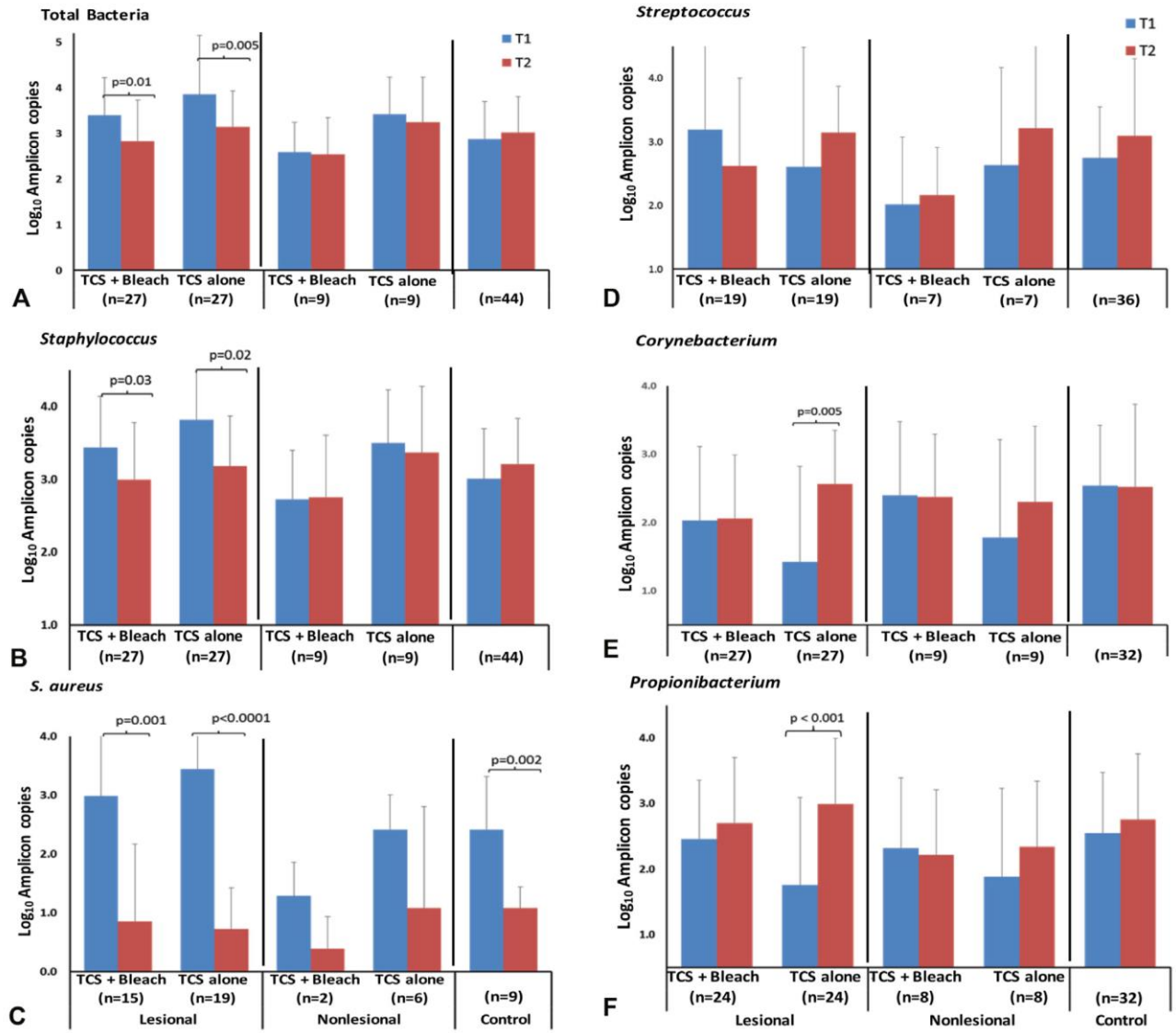
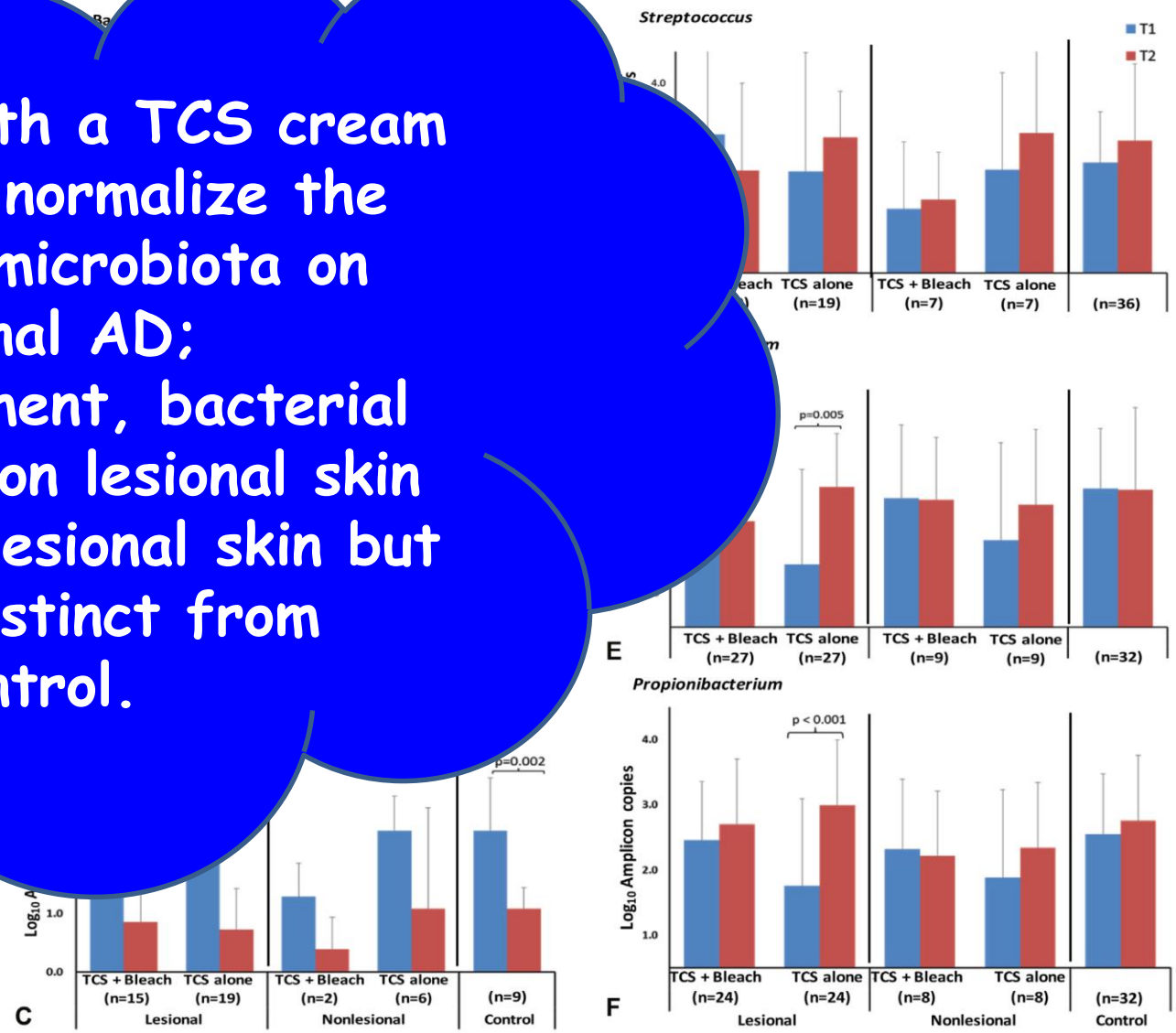


Cutaneous microbiome effects of fluticasone propionate cream and adjunctive bleach baths in childhood atopic dermatitis.

Gonzales. J Am Acad Dermatol 2016;75:481

In a randomized, placebo-cor… single-bli… trial in … AD and … chil… no… ex… afte… with… plus… Micr… extracted … quantitative … chain reaction of predominant genera and 16S rRNA sequencing

Treatment with a TCS cream suffices to normalize the cutaneous microbiota on lesional AD; after treatment, bacterial communities on lesional skin resemble nonlesional skin but remain distinct from control.



Potenza degli steroidi topici

Abbreviazioni:
c:crema, p=pomata, u=unguento, lp= lipocrema, l= lozione, e= emulsione, s=soluzione, sch= schiuma, g= gel

STEROIDI TOPICI SUPERPOTENTI (GRADO I)	
Clobetasolo propionato 0,05% p. u. s. sch.	*Clobesol; Olux sch*

STEROIDI TOPICI MOLTO POTENTI (GRADO II)	
Alcinonide 0,1% c.	*Halciderm*
Amcinonide 0,1% p.	*Amcinil*
Betametasone dipropionato 0,05% u c	*Diprosone; Betamesol; Betametasone dipropionato*
Diflucortolone valerato 0,3% c. p. u.	*Nerisona forte, Temetex forte, Cortical, Dervin*
Fluocinonide 0,05% p. g. l.	*Flu 21, Topsyn*

STEROIDI TOPICI POTENTI A (GRADO III)	
Betametasone dipropionato 0,05% c. u. s.	*Diprosone, Betamesol, Betanesone dipropionato Sandoz*
Betametasone valerato 0,1% c. u. e. s.	*Ecoval 70, Bettamousse, Betesil cerotti*
Desossimetasone 0,025% e.	*Flubason*
Diflucortolone valerato 0,1% c. u. s.	*Nerisona, Temetex, Dermaval, Cortical 0,2, Flu-cortanest*
Fluticasone propionato 0,05% c.; 0,005% u.	***Flixoderm*** *crema e unguento*
Metilprednisolone aceponato 0,1% c. u .s.	*Advantan, Avancort*
Mometasone furoato 0,1% c. u .s.	***Altosone, Elocon***

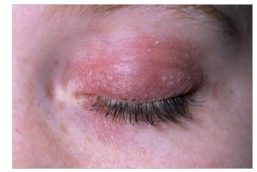
STEROIDI TOPICI POTENTI B (GRADO IV)	
Alclometasone dipropionato 0,1% c. u. l.	*Legederm*
Beclometasone dipropionato 0,025% c.	*Menaderm simplex; Beclometasone Doc*
Betametasone benzoato o,1% c. l. g.	***Beben***
Budesonide 0,025 c. u.	*Bidien; Preferid*

STEROIDI TOPICI DI MEDIA POTENZA (GRADO V)	
Betametasone benzoato 0,025% c.	***Beben*** *crema dermica*
Betametasone valeroacetato 0,05% p. u. l.	*Beta 21, Gentalyn Beta, Ecoval*
Desonide 0,05% c. e. l.	*Sterades; Reticus*
Idrocortisone butirrato 0,1% c. p. l. e.	***Locoidon***
Fluocinolone acetonide 0,025% p.l. c.	*Localyn; Fluocit; Fluovitef; Omniderm; Sterolone; Ultraderm; Boniderma; Dermolin; Fluvean*
Triamcitolone Acetonide 0,1% c	***Ledercort A10, Aureocort***
STEROIDI TOPICI DI POTENZA MINIMA A (GRADO VI)	
Clobetasone butirrato 0,05% c.	*Eumovate*
Fluocinolone acetonide 0,01% glicole	Localyn glicole
Fluocortin butilestere 0,02% c. p.	Vaspit
STEROIDI TOPICI DI POTENZA MINIMA B (GRADO VII)	
Idrocortisone da 0,05 a 1% c. p.	*Lenirit; Dermirit; Cortidro; Dermadex c*
Fluocinolone acetonide 0,01% glicole	*Localyn glicole*
Fluocortin butilestere 0,02% c. p.	*Vaspit*
Desametasone 0,2% c. u.	*Dermadex; Soldesam*
Flumetasone	Solo in associazione
Metiprednisolone	Solo in associazione

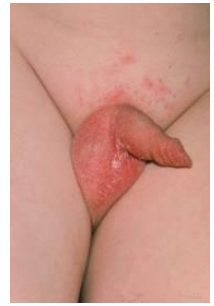
Topical anti-inflammatory therapy

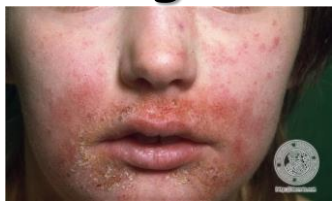
Topical Calcineurin Inhibitors

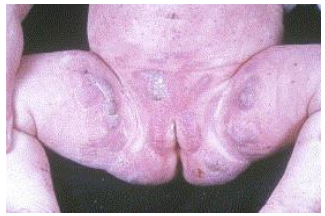
- The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a corticosteroid with intermediate activity, while the latter is clearly more active than 1.0% pimecrolimus cream.



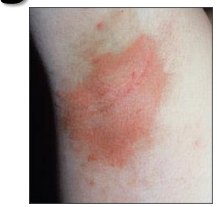
- **TCI do not induce skin atrophy**. This favours their use over topical corticosteroids in delicate body areas such as the **eyelid** region, the **perioral** skin, the **genital** area, the **axilla** region or the **inguinal fold** and for topical **long-term management**.







Severe granuloma gluteale infantum



Guidelines for treatment of atopic eczema (atopic dermatitis) Part I
J. Ring, JEADV 2012, 26, 1045-1060

Safety and Efficacy of Pimecrolimus in Atopic Dermatitis: A 5-Year Randomized Trial. Bardur Sigurgeirsson, Pediatrics 2015; 135:597

2418 infants were enrolled in this 5-year open-label study. Infants were randomized to PIM (n = 1205; with short-term TCSs for disease flares) or TCSs (n = 1213).

The primary objective was to compare safety

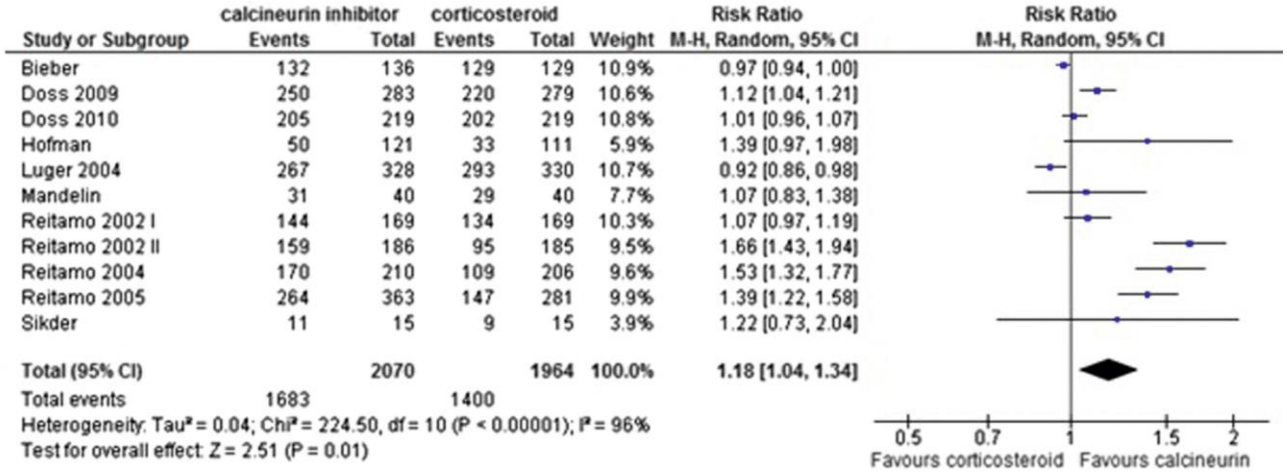
the secondary objective was to document PIM's long-term efficacy.

Both PIM and TCSs had a rapid onset of action with 50% of patients achieving treatment **success by week 3**.

After 5 years, 85% and 95% of patients in each group **achieved overall and facial treatment success**, respectively.

The **PIM group** required substantially **fewer steroid days** than the TCS group (**7 vs 178**). The profile and frequency of adverse events was similar in the 2 groups; in both groups, there was no evidence for impairment of humoral or
cellular immunity

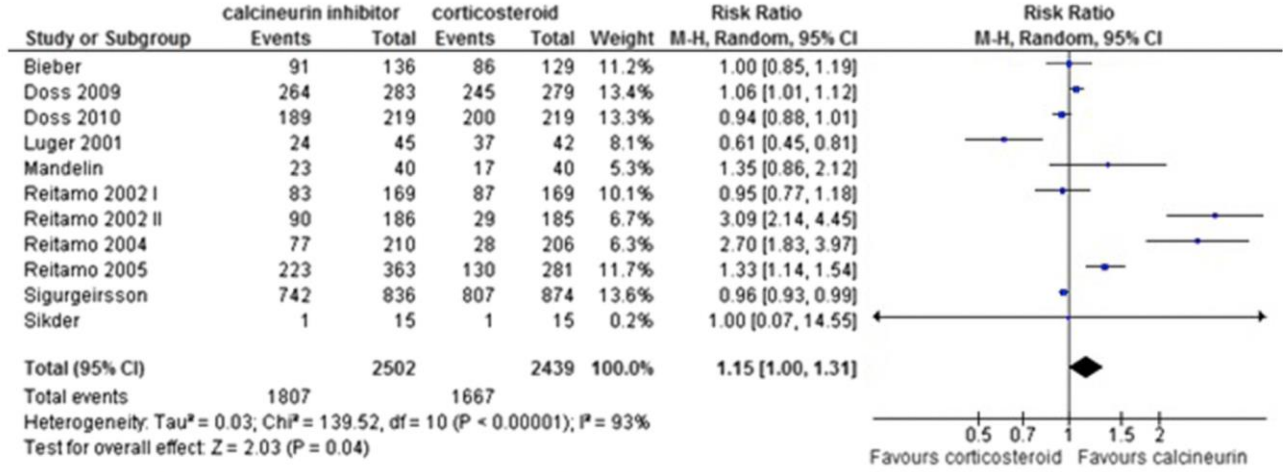
Systematic review and meta-analysis of randomized clinical trials (RCTs) comparing topical calcineurin inhibitors with topical corticosteroids for atopic dermatitis. Broeders, J Am Ac Dermatol 2016;75:41



Study or Subgroup	calcineurin inhibitor Events	Total	corticosteroid Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bieber	132	136	129	129	10.9%	0.97 [0.94, 1.00]
Doss 2009	250	283	220	279	10.6%	1.12 [1.04, 1.21]
Doss 2010	205	219	202	219	10.8%	1.01 [0.96, 1.07]
Hofman	50	121	33	111	5.9%	1.39 [0.97, 1.98]
Luger 2004	267	328	293	330	10.7%	0.92 [0.86, 0.98]
Mandelin	31	40	29	40	7.7%	1.07 [0.83, 1.38]
Reitamo 2002 I	144	169	134	169	10.3%	1.07 [0.97, 1.19]
Reitamo 2002 II	159	186	95	185	9.5%	1.66 [1.43, 1.94]
Reitamo 2004	170	210	109	206	9.6%	1.53 [1.32, 1.77]
Reitamo 2005	264	363	147	281	9.9%	1.39 [1.22, 1.58]
Sikder	11	15	9	15	3.9%	1.22 [0.73, 2.04]
Total (95% CI)		2070		1964	100.0%	1.18 [1.04, 1.34]
Total events	1683		1400			

Heterogeneity: Tau² = 0.04; Chi² = 224.50, df = 10 (P < 0.00001); I² = 96%
Test for overall effect: Z = 2.51 (P = 0.01)

Fig 2. Improvement of dermatitis. Please see Table I for reference citations. *CI*, Confidence interval; *M-H*, Mantel-Haenszel.



Study or Subgroup	calcineurin inhibitor Events	Total	corticosteroid Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bieber	91	136	86	129	11.2%	1.00 [0.85, 1.19]
Doss 2009	264	283	245	279	13.4%	1.06 [1.01, 1.12]
Doss 2010	189	219	200	219	13.3%	0.94 [0.88, 1.01]
Luger 2001	24	45	37	42	8.1%	0.61 [0.45, 0.81]
Mandelin	23	40	17	40	5.3%	1.35 [0.86, 2.12]
Reitamo 2002 I	83	169	87	169	10.1%	0.95 [0.77, 1.18]
Reitamo 2002 II	90	186	29	185	6.7%	3.09 [2.14, 4.45]
Reitamo 2004	77	210	28	206	6.3%	2.70 [1.83, 3.97]
Reitamo 2005	223	363	130	281	11.7%	1.33 [1.14, 1.54]
Sigurgeirsson	742	836	807	874	13.6%	0.96 [0.93, 0.99]
Sikder	1	15	1	15	0.2%	1.00 [0.07, 14.55]
Total (95% CI)		2502		2439	100.0%	1.15 [1.00, 1.31]
Total events	1807		1667			

Heterogeneity: Tau² = 0.03; Chi² = 139.52, df = 10 (P < 0.00001); I² = 93%
Test for overall effect: Z = 2.03 (P = 0.04)

Fig 3. Treatment success. Please see Table I for reference citations. *CI*, Confidence interval; *M-H*, Mantel-Haenszel.

Calcineurin inhibitors were associated with higher costs and had more adverse events (74% vs 64%; RR 1.28; 95% CI 1.05-1.58; P = .02) including a higher rate of skin burning (30% vs 9%; RR 3.27; 95% CI 2.48-4.31; P <.00001) and pruritus (12% vs 8%; RR 1.49; 95% CI 1.24-1.79; P\.00001).

There were no differences in atrophy, skin infections

Systematic review and meta-analysis of randomized clinical trials (RCTs) comparing topical calcineurin inhibitors with topical corticosteroids for atopic

matol 2016;75:41

Calcineurin inhibitors were associated with higher medication costs in the first RCT (V101 vs V15). The second RCT reported higher total medical costs compared with corticosteroids as well, both for patients with moderate (£527 vs £177) and severe (£621 vs £215) atopic dermatitis

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vs 9%; RR 3.27;
P <.00001) and
% vs 8%; RR 1.49; 95%
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There were no differences in atrophy, skin infections

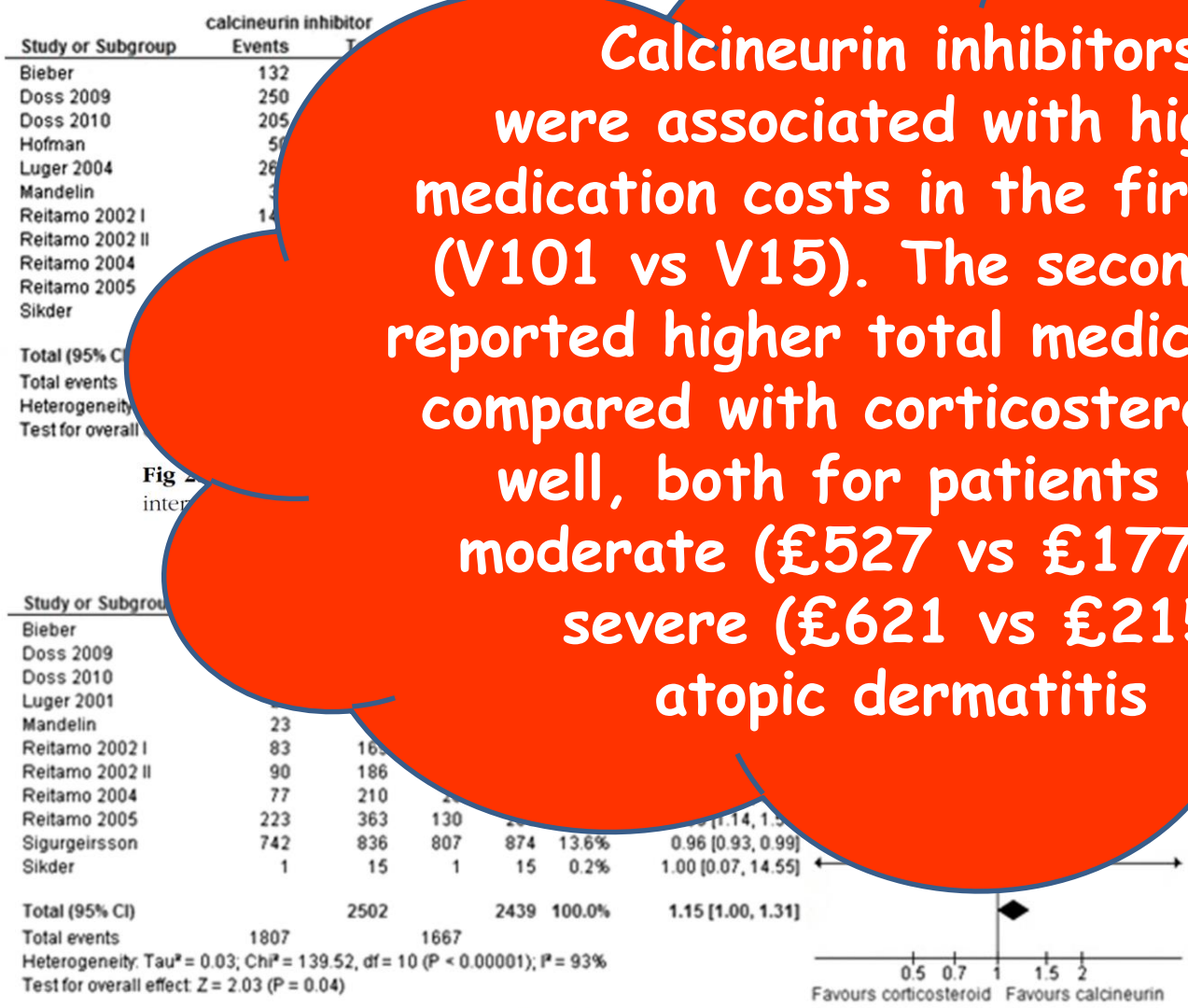
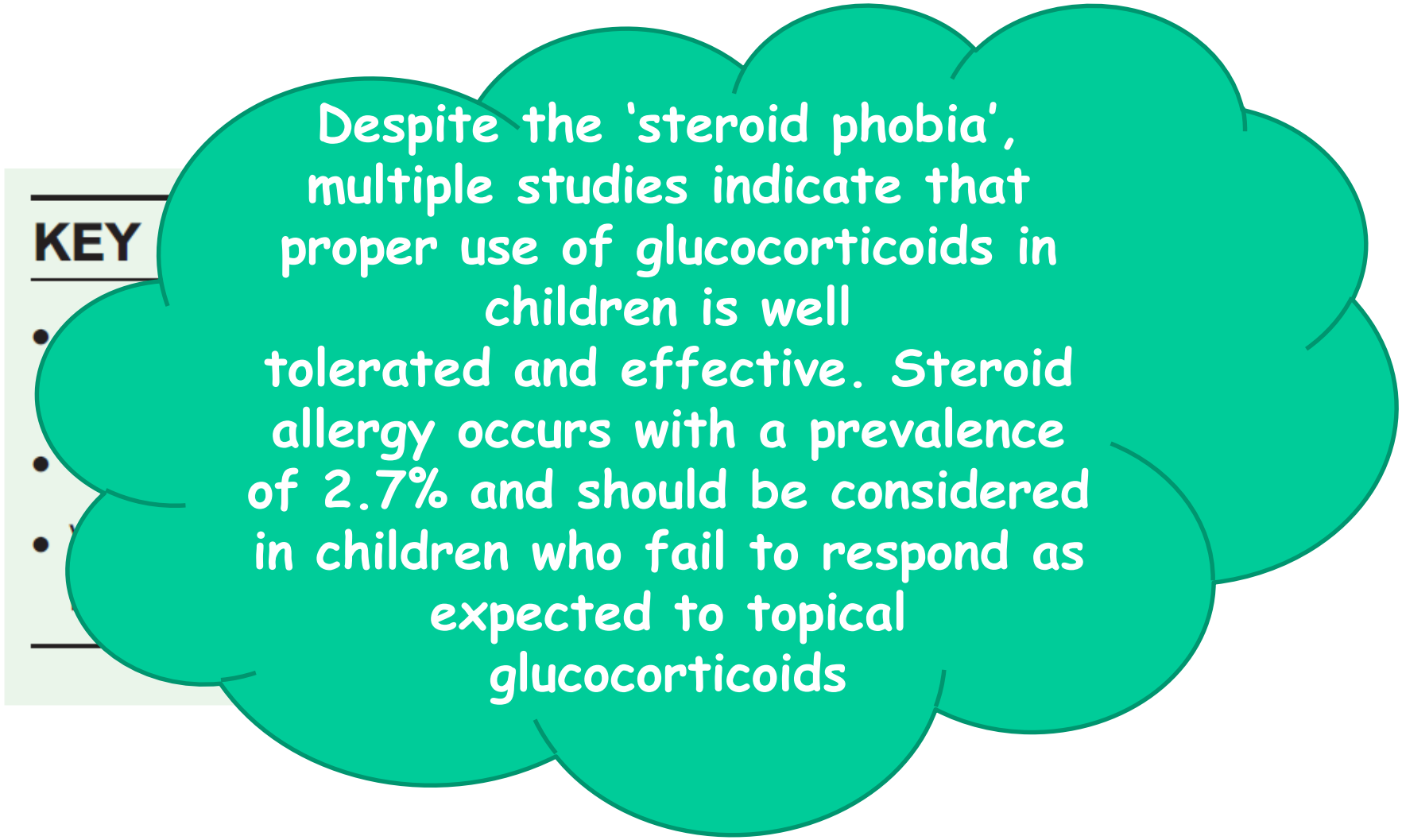


Fig 3. Treatment success. Please see Table I for reference citations. *CI*, Confidence interval; *M-H*, Mantel-Haenszel.

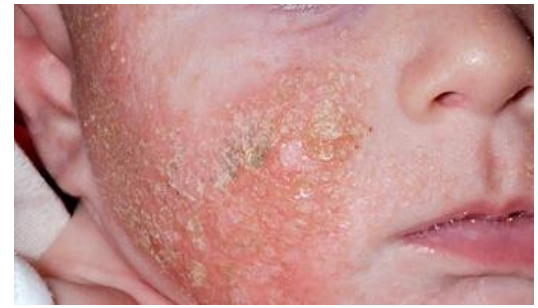
Update on topical glucocorticoid use in children.
K. Morley, Curr Opin Pediatr 2012, 24:121



Despite the 'steroid phobia', multiple studies indicate that proper use of glucocorticoids in children is well tolerated and effective. Steroid allergy occurs with a prevalence of 2.7% and should be considered in children who fail to respond as expected to topical glucocorticoids

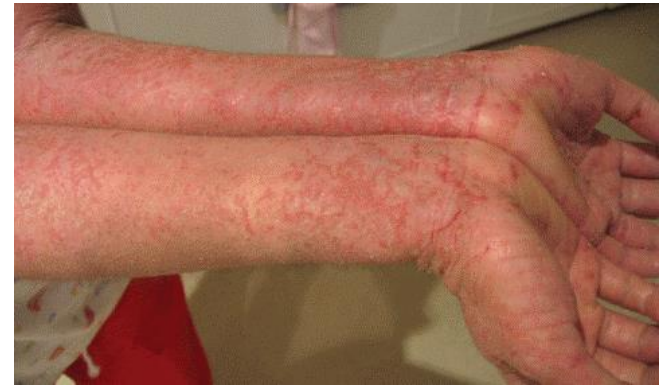
Topical anti-inflammatory therapy and wet wraps

- Patients with acute, oozing and erosive lesions, and children in particular, sometimes do not tolerate standard topical application, and may first be treated with **'wet wraps'** until the oozing stops.



- They are highly effective in acute eczema and improve tolerance.

- The use of wetwrap dressings with diluted corticosteroids for up to 14 days (usual is up to 3 days) is a safe crisis intervention treatment of severe and/or refractory AE



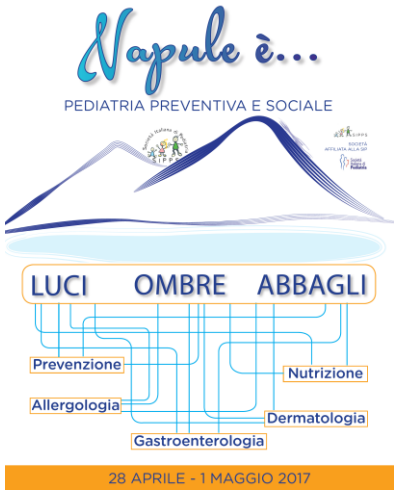
Guidelines for treatment of atopic eczema (atopic dermatitis) Part I
J. Ring, JEADV 2012, 26, 1045–1060

La gestione della dermatite atopica

Diego Peroni

Universita' di Pisa

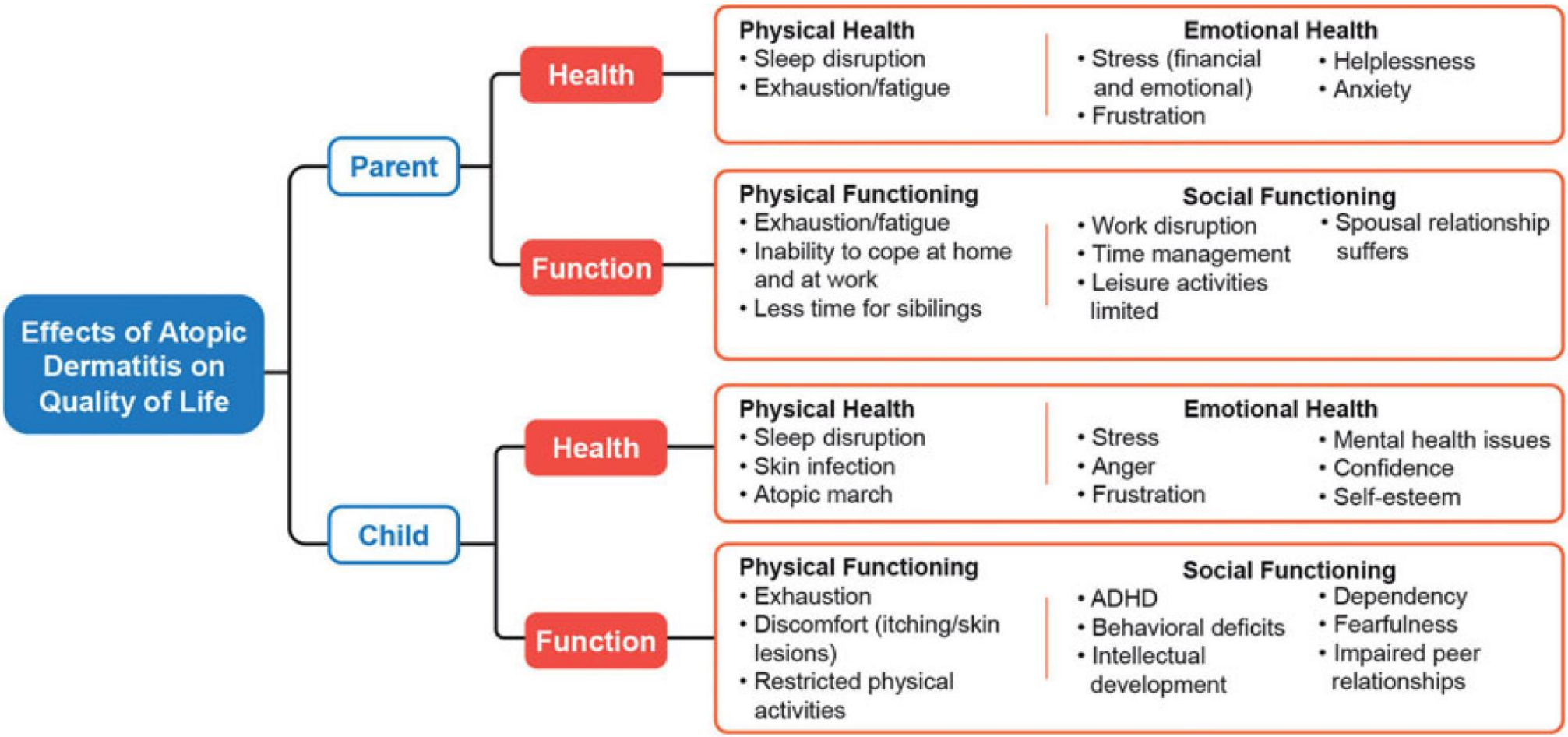
- ✓ Introduction
- ✓ Topical treatment
  - ✓Emollients
  - ✓Anti-inflammatory
  - ✓New treatment
- ✓ Conclusions



diego.peroni@unipi.it

Addressing treatment challenges in atopic dermatitis with novel topical therapies.

Silverberg, J Dermatol Treat 2016

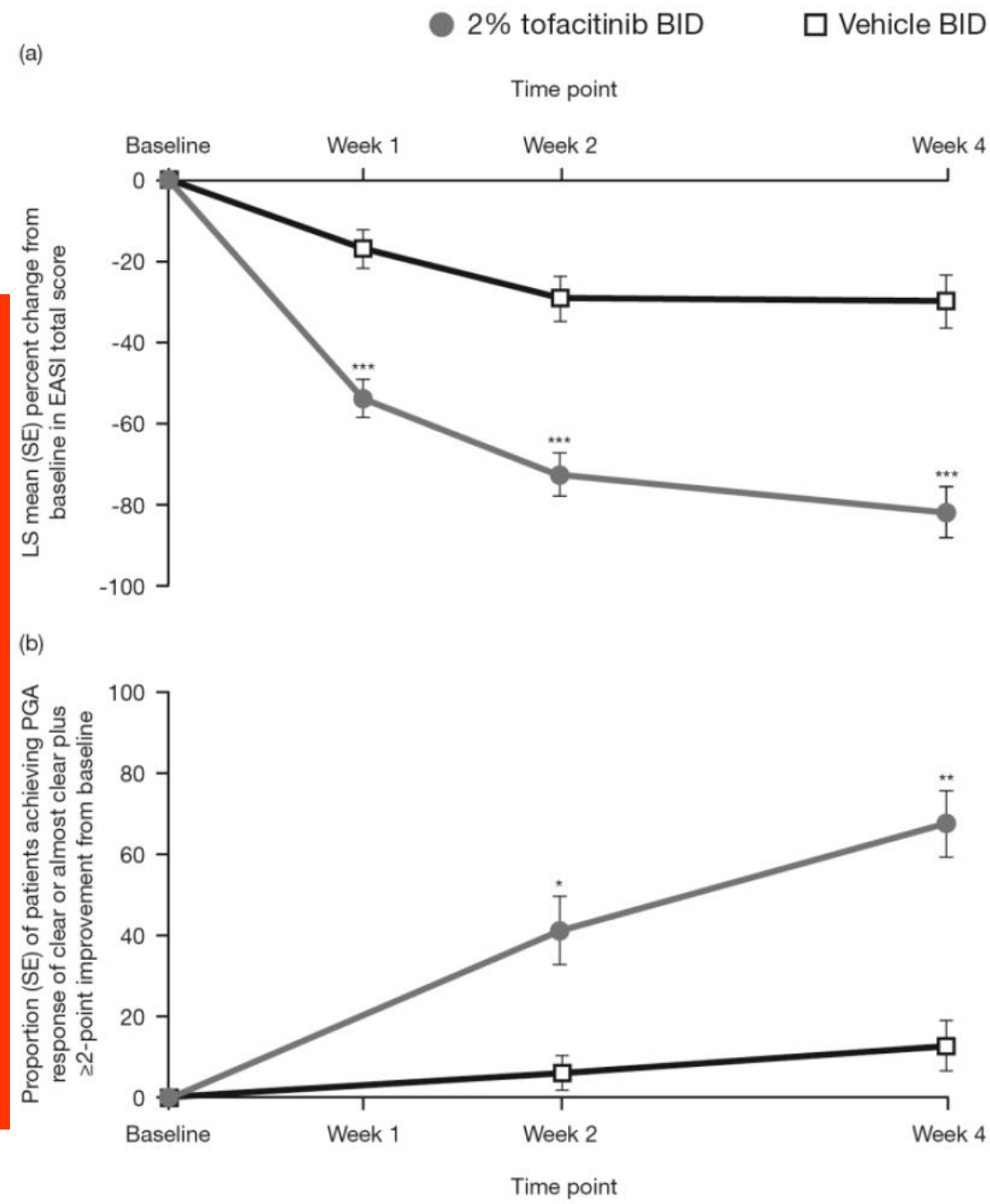


Topical tofacitinib for atopic dermatitis: A Phase 2a randomised trial.

Bisonnette, Br J Dermatol 2016

Despite substantial unmet medical need, it has been 15 years since a new AD drug with a novel mechanism of action has been approved, highlighting the need for other effective agents.

Recent clinical and non-clinical data support potential therapeutic benefit of Janus kinase (JAK) inhibition in treating AD.

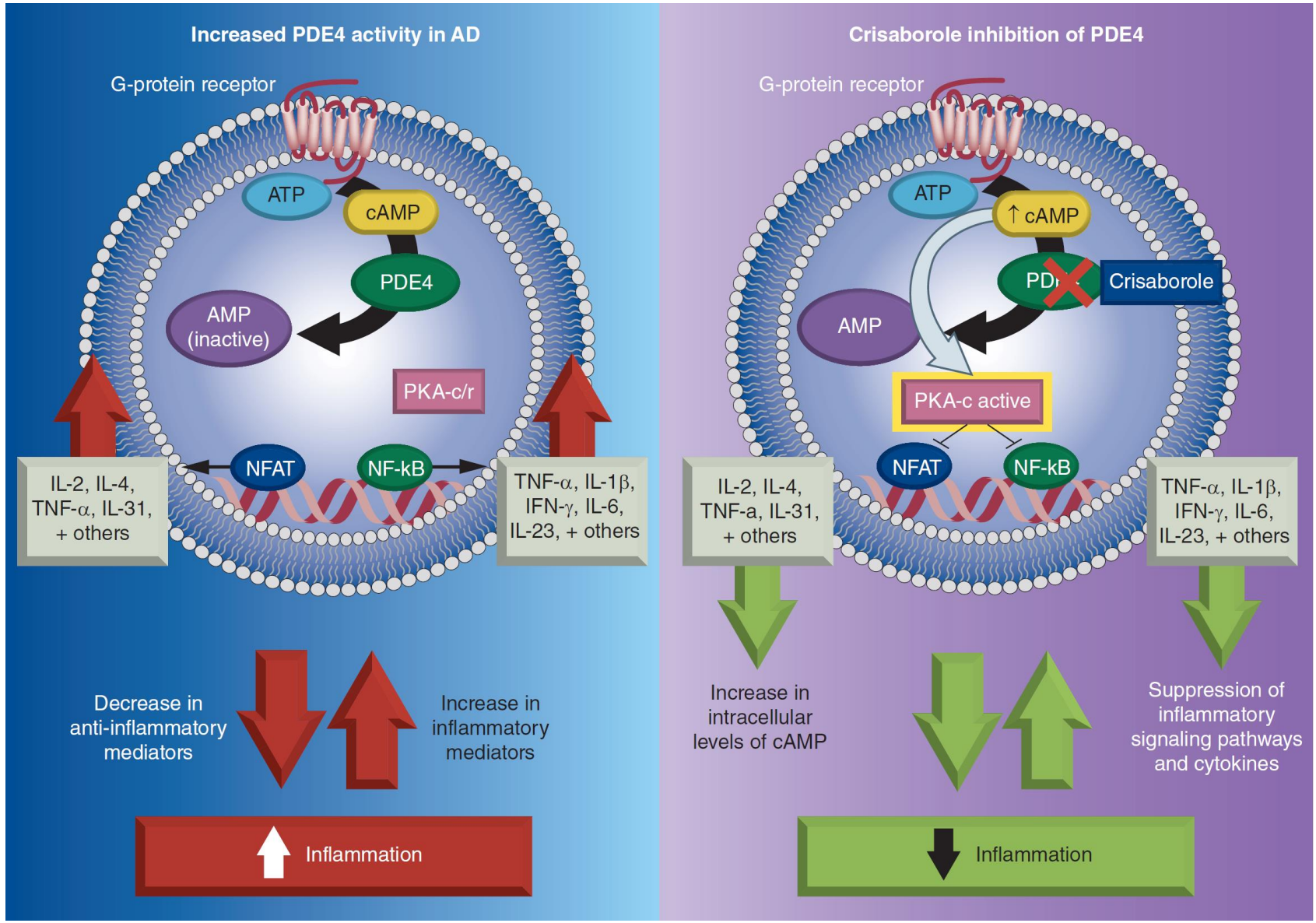


Addressing treatment challenges in atopic dermatitis with novel topical therapies.

Silverberg, J Dermatol Treat 2016

Topical therapy	Mechanism of action	Trial	Phase	Patients
Crisaborole/AN2728	PDE4 inhibitor	AD-303 (long-term safety extension study)		• Enrollment: TBD from AD-301 and AD-302 • Patients ≥2 years of age • AD involvement ≥5% treatable BSA • ISGA score of mild (2) or moderate (3)
		NCT02118792 (AD-302)	3	• Enrollment: 750 • Patients ≥2 years of age • AD involvement ≥5% treatable BSA • ISGA score of mild (2) or moderate (3)
		NCT02118766 (AD-301)	3	• Enrollment: 750 • Patients ≥2 years of age • AD involvement ≥5% treatable BSA • ISGA score of mild (2) or moderate (3)
		NCT01602341 (AD-204)	2	• Enrollment: 86 • Male and female patients between 12 and 17 years of age • BSA ≤35% • Presence of 2 comparable lesions
		NCT01301508 (AD-202)	II	• Enrollment: 46 • Male and female patients between 18 and 75 years of age • AD clinically stable for ≥1 month • 2 or more comparable lesions
		NCT01652885 (AD-203)	1 & 2	• Enrollment: 23 • Male and female patients between 12 and 17 years of age • AD involvement ≥10% and ≤35% treatable BSA
		MUSE Trial (AD-102)	1b	• Enrollment: 34 • Male and female patients between 2 and 17 years of age • ISGA score of mild (2) or moderate (3) at baseline
DRM02	PDE4 inhibitor	NCT01993420	2	• Estimated enrollment: 21 • Male and female patients between 18 and 70 years of age • Stable AD • 2 lesions of similar size with an identical EASI score of ≥5 and ≤9
E6005	PDE4 inhibitor	NCT01461941	2	• Enrollment: 78 • Male and female patients between 20 and 64 years of age • Outpatients diagnosed with AD
		NCT02094235	1 & 2	• Enrollment: 62 • Male and female patients between 2 and 15 years of age • Mild-to-moderate symptoms of AD at baseline with evaluable skin lesions

Crisaborole and its potential role in treating atopic dermatitis: overview of early clinical studies. Zane Immunotherapy (2016) 8(8), 853



Crisaborole and its potential role in treating atopic dermatitis: overview of early clinical studies. Zane Immunotherapy (2016) 8(8), 853

Table 1. Study design and outcomes for Phase I and Phase II clinical trials.

Study number	Study description	Primary end point	Key secondary end points	Cohort age range, years	AD assessment	
					Efficacy at day 29	Pruritus (pooled analysis)
102	Phase Ib, Open-label, maximal-use study, n = 34, whole body assessment	PK plasma profile and safety	Treatment success at day 29; improvement from baseline in individual AD signs and symptoms at day 29; change from baseline in treatable%BSA at day 29	2–17	47.1% Crisaborole Topical Ointment, 2%-treated patients achieved treatment success	Significant reduction in mean pruritus severity scores by day 8*
203	Phase IIa, open-label, safety, tolerability and PK study, n = 23, whole body assessment	PK plasma profiles of crisaborole and its oxidative metabolites AN7602 and AN8323 on days 1 and 8	Treatment success at days 8, 15, 22 and 29; ISGA score of clear (0) or almost clear (1) and ≥2-grade improvement from baseline at days 8, 15, 22 and 29	12–17	34.8% Crisaborole Topical Ointment, 2%-treated patients achieved treatment success‡	
202	Phase IIa, vehicle-controlled, proof-of-concept study, n = 25, target lesion assessment	Change in ADSI score from baseline at day 28	Change from baseline in ADSI score at days 14 and 42	18–75	68.0% vs 20.0% achieved treatment success, (Crisaborole Topical Ointment, 2% vs vehicle)	Significant reduction in mean pruritus severity scores by day 15*
204	Phase II, bi-lateral, dose-finding study, n = 86, target lesion assessment	Change in ADSI score from baseline at days 8, 15, 22 and 29	Proportion of target lesions achieving total or partial clearance (ADSI ≤2)	12–17	Crisaborole Topical Ointment, 2% twice daily achieved greatest improvement from baseline ADSI score	

Acta Derm Venereol 2016; 96: 792–796

CLINICAL REPORT

Anti-pruritic Effect of Sertaconazole 2% Cream in Atopic Dermatitis Subjects: A Prospective, Randomized, Double-blind, Vehicle-controlled, Multi-centre Clinical Trial of Efficacy, Safety and Local Tolerability

Sonja STÄNDER[1], Martin METZ[2], Mac H. RAMOS F.[3], Marcus MAURER[2], Nicole SCHOEPKE[2], Athanasios TSIANAKAS[1], Claudia ZEIDLER[1] and Thomas A. LUGER[1]

[1]Competence Center Chronic Pruritus, Department of Dermatology, University Hospital Münster, Münster, [2]Allergie-Centrum-Charité, Department of Dermatology and Allergy, Charité –Universitätsmedizin, Berlin, Germany, and [3]Galderma-Spirig, Egerkingen, Switzerland

	Active		Vehicle	
Characteristic	ITT	PP	ITT	PP
Total, *n*	32	24	38	29
Female, *n* (%)	16 (50)	13 (54)	24 (63)	17 (59)
Age, mean (SD)	37 (16.3)	36.7 (16.1)	31.7 (12.8)	31.7 (13.1)
AD family history, *n* (%)	16 (50)	10 (42)	20 (53)	16 (55)
Asthma as child, *n* (%)	8 (25)	6 (25)	16 (42)	11 (38)
Chronic pruritus, *n* (%)	32 (100)	24 (100)	38 (100)	29 (100)
Allergic rhinitis, *n* (%)	21 (66)	17 (71)	24 (63)	20 (69)
Xerosis/dry skin, *n* (%)	32 (100)	24 (100)	37 (97)	28 (97)
Mycological evaluation, positive, *n*	0	0	1	0
Age at first appearance, mean (SD)[a]	9 (19.1)	6.9 (17.8)	6.8 (15.5)	5.7 (14.8)
AD relapses during the last year, mean (SD)	7.6 (5.7)	6.3 (4.9)	9.1 (8.2)	10 (8.9)

[a]Age of the subject at first appearance of atopic dermatitis symptoms.
SD: standard deviation; ITT: intention-to-treat population; PP: per-protocol population.

The study failed to demonstrate the anti-pruritic effect of sertaconazole 2% cream vs. vehicle in subjects with AD who had severe, chronic pruritus

La gestione della dermatite atopica

Diego Peroni

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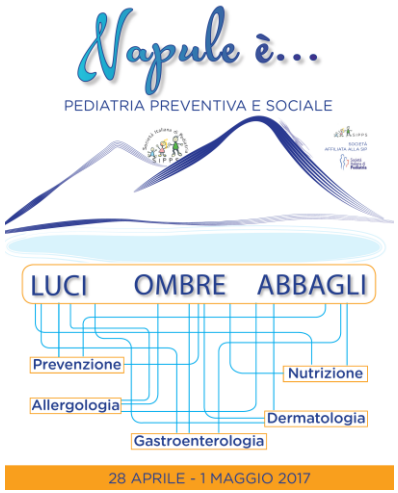
- ✓ Introduction
- ✓ Topical treatment
  - ✓Emollients
  - ✓Anti-inflammatory
  - ✓New treatment
- ✓ Conclusions



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Addressing treatment challenges in atopic dermatitis with novel topical therapies.

Silverberg. J Dermatol Treat 2016

Although topical therapies are central to the treatment of AD, options are limited. While TCSs and TCIs are somewhat effective, a number of concerns are associated with their use, particularly for the long-term treatment of AD. These safety concerns often lead to hesitancy in prescribing TCSs and TCIs as well as reduced adherence to treatment. Consequently, there is a significant need for novel topical treatment options that can rapidly improve the signs

Topical therapy	Mecha	Ph	Patients
Crisaborole/AN2728	PDE		TBD from AD-301 and AD-
			ears of age >5% treatable BSA) or moderate (3)
			ble BSA derate (3)
			e BSA derate (3)
			ween 12
			n 18
			ween 12
			≤35%
			ale patients between 2 ars of age e of mild (2) or moderate (3)
			ed enrollment: 21 nd female patients between 18 70 years of age table AD 2 lesions of similar size with an identi-cal EASI score of ≥5 and ≤9
Ec		2	• Enrollment: 78 • Male and female patients between 20 and 64 years of age • Outpatients diagnosed with AD
		4235 1 & 2	• Enrollment: 62 • Male and female patients between 2 and 15 years of age • Mild-to-moderate symptoms of AD at baseline with evaluable skin lesions

REVIEW Open Access

Consensus Conference on Clinical Management of pediatric Atopic Dermatitis

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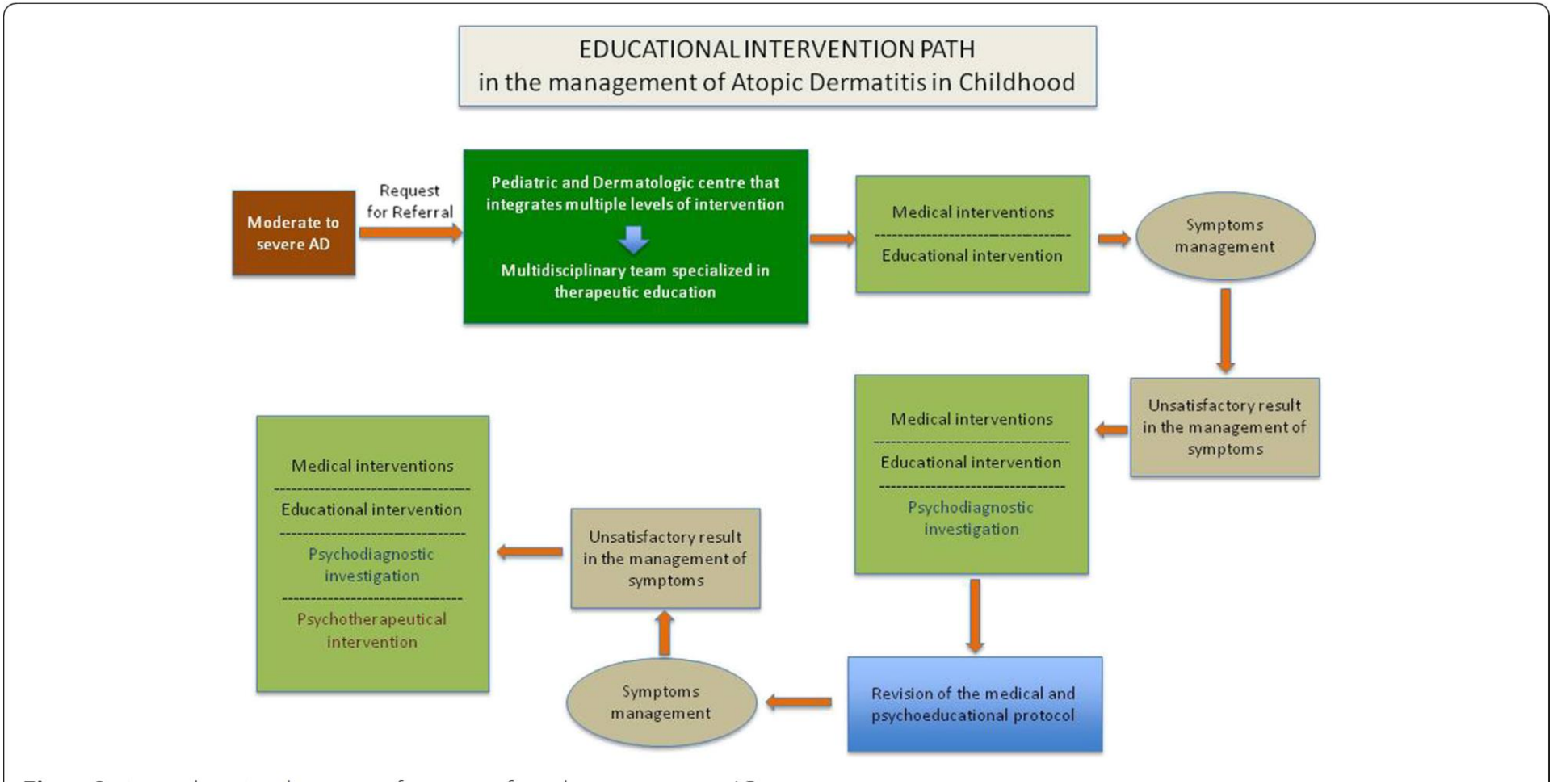

A patient-centered approach

- The need for moisturizers should be stressed.
- Time should be taken during clinic visits to discuss.
- Instructional leaflets may be provided,
- Specific environmental triggers should be evaluated and detected to prevent future flare-ups and unnecessary dietary modification.
- All creams should be introduced to the patient (such as in a booklet), along with an explanation of how, and how much, should be applied.
- A Fingertip Unit chart can be used as guide.
- The patient's personal preference should be considered.
- Patients should be informed of the cost of creams and other treatments and less expensive creams should be selected, especially if cost is an issue