

Napule è...

PEDIATRIA PREVENTIVA E SOCIALE



LUCI OMBRE ABBAGLI

Prevenzione

Allergologia

Gastroenterologia

Nutrizione

Dermatologia

25 - 28 APRILE 2019

Hotel Royal Continental, Napoli

***Pruritus in pediatric patients
with atopic dermatitis:
multidisciplinary approach***

Iride Dello Iacono

PEDIATRIA ED ALLERGOLOGIA

Ospedale Fatebenefratelli Benevento

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In press

***Summary document of an
italian expert group.***

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**** SIPPS**

Atopic dermatitis (AD) is a chronic multifactorial disorder that requires multidisciplinary management and affecting 2-20% of the general population with age and ethnic differences.



Approximately 80% of AD patients exhibit elevated levels of serum IgE. In contrast to normo-IgE and non allergic intrinsic AD patients, extrinsic AD patients with hyper IgE levels are associated with increased disease severity, mutation in the FLG gene and impaired skin barrier function.

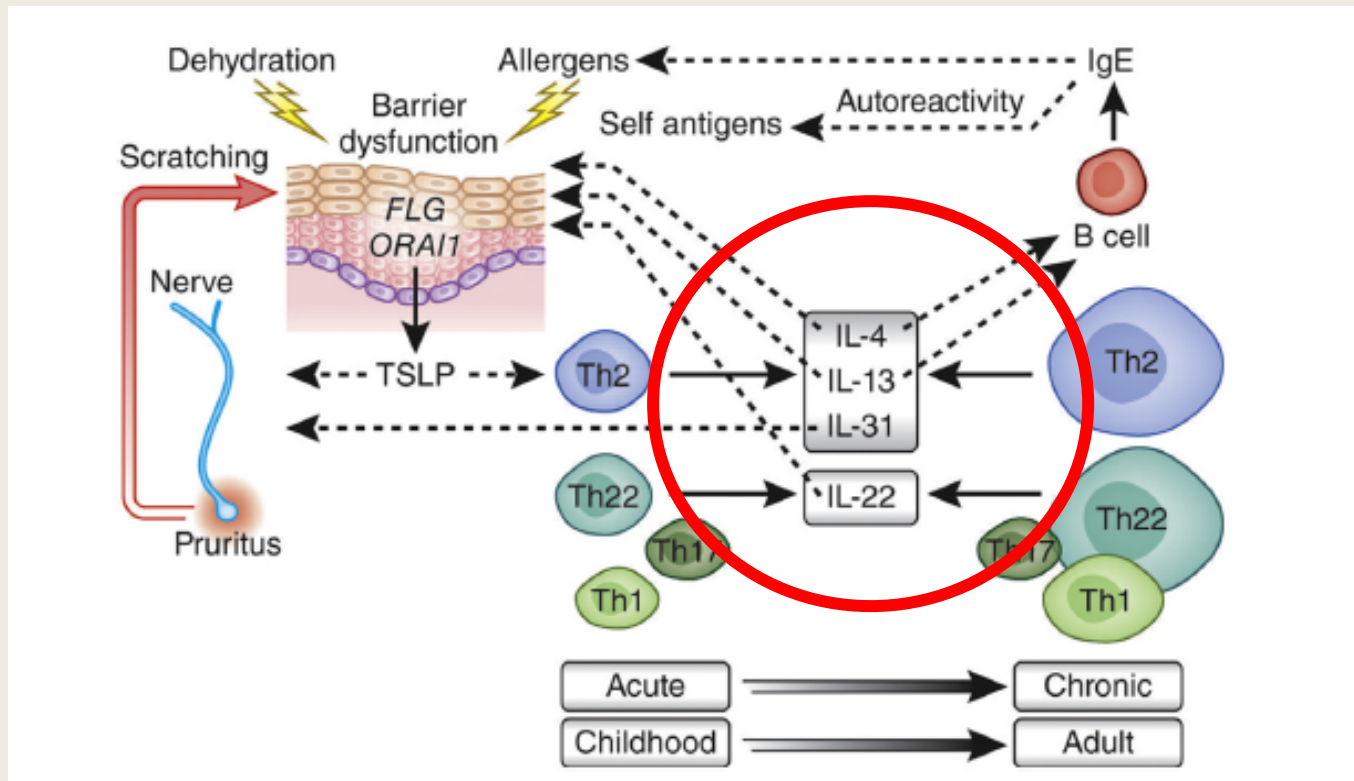


With regards to immune abnormalities, AD is currently considered as a biphasic T cell-mediated disease. A Th2 signal predominates in the acute phase, whereas a Th2 to Th1 switch promotes disease chronicity.



PATHOGENESIS OF ATOPIC DERMATITIS

Immune deviation towards Th2 and T22 expansion in AD

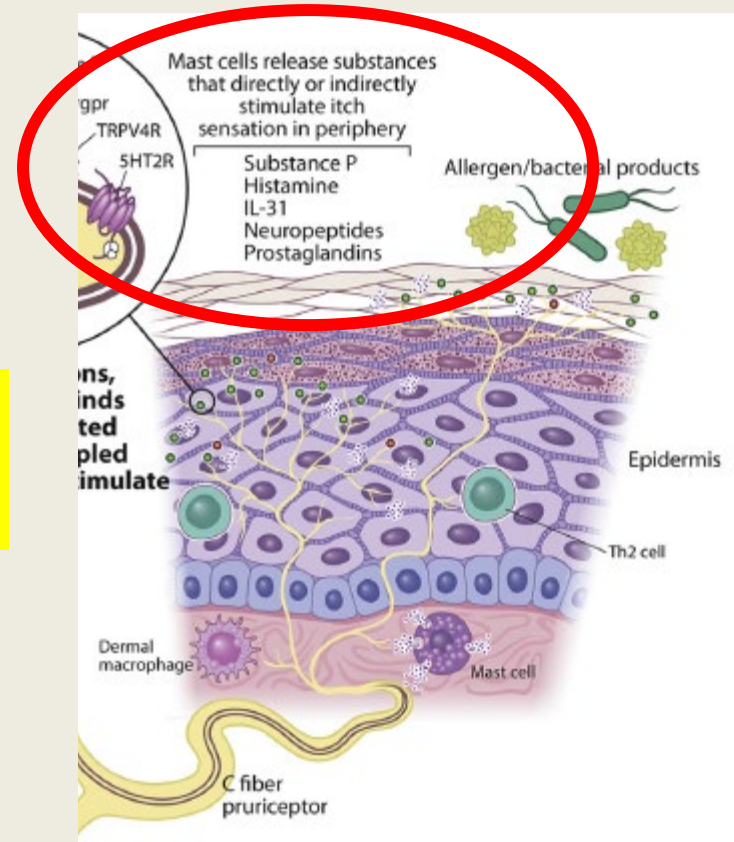


Pruritus in pediatric patients with atopic dermatitis: a multidisciplinary approach, summary

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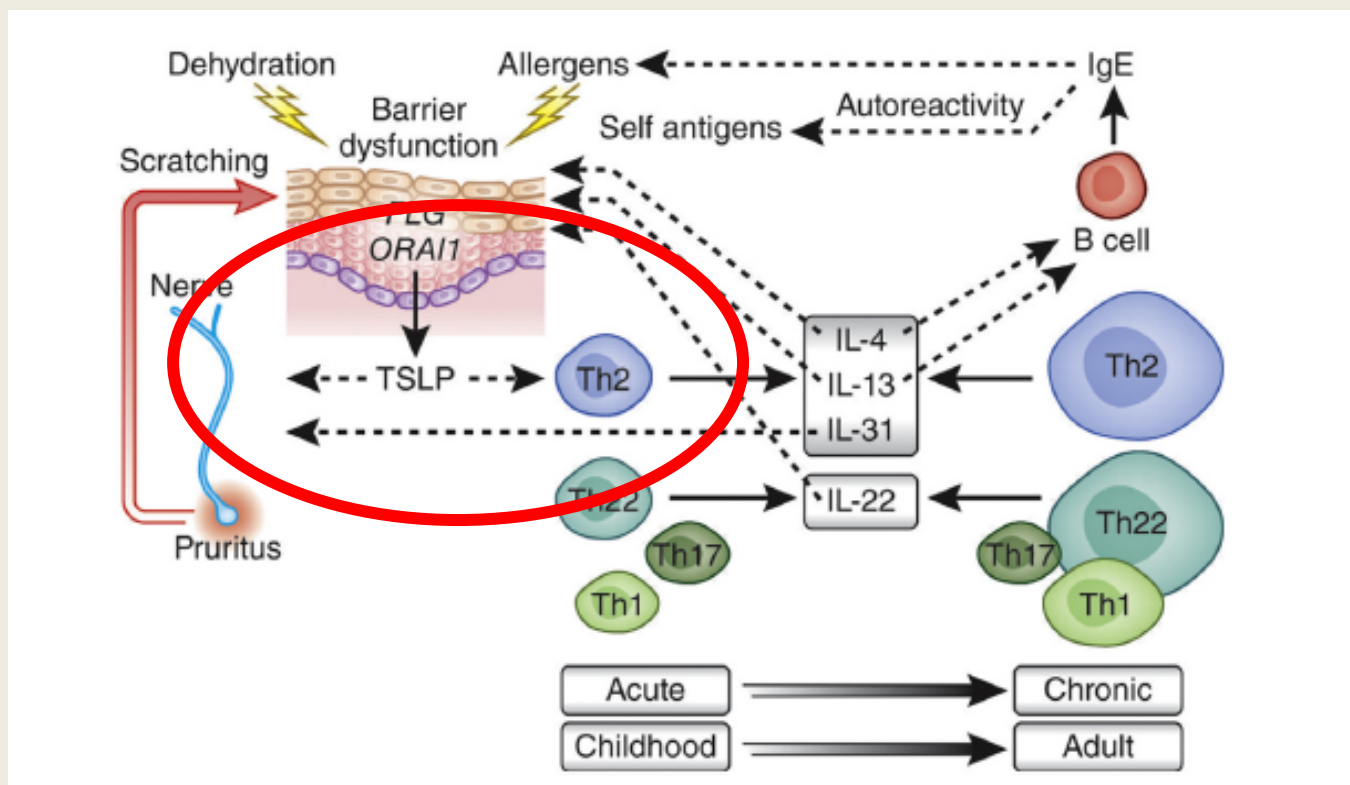
In press

Recently, a role of IL-31 produced by Th2 cells has been recognized in inducing itch.



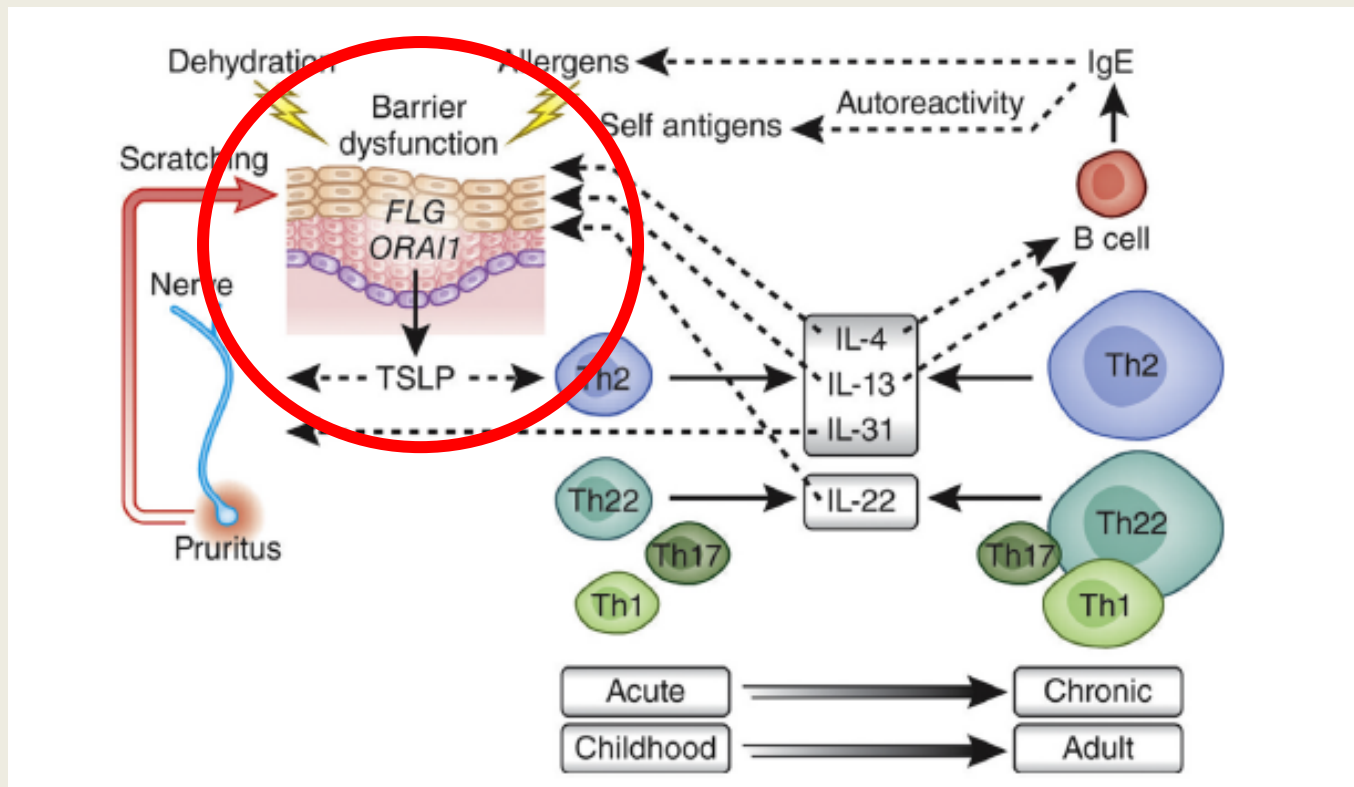
Skin thymic stromal lymphopoietin initiates Th2 responses through an orchestrated immune cascade

Juan Manuel Leyva-Castillo¹, Pierre Hener¹, Paula Michea^{2,3}, Hajime Karasuyama^{4,5}, Susan Chan¹, Vassili Soumelis^{2,3} & Mei Li^{1,6,7}



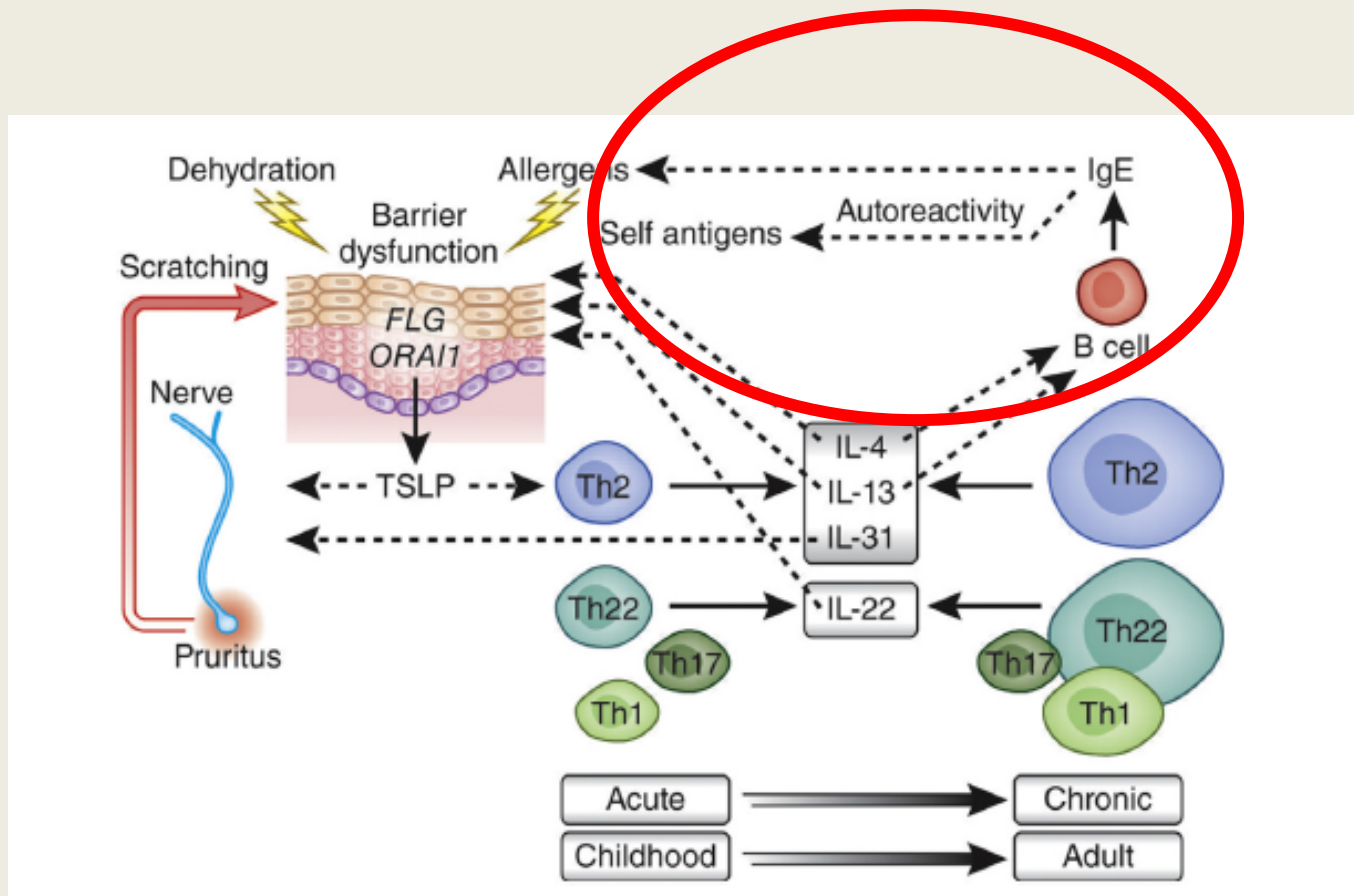
PATHOGENESIS OF ATOPIC DERMATITIS

Disruption of barrier proteins by IL-4, IL-13 and IL-22



PATHOGENESIS OF ATOPIC DERMATITIS

IgE autoreactivity in AD



CLINICAL FEATURES

AD is most common during childhood. The diagnosis of AD is generally easy and based on clinical features that vary upon patient age and disease severity.

Table 1. Characteristic features of atopic dermatitis by age. Modified from Ref. [1].

AD	Infant	Childhood	Adolescent or Adult
Lesions	Exudative erythematous weepy papules and plaques	Weepy erythematous papules and plaques intermixed with lichenified plaques, particularly in flexural areas	Erythematous papules and plaques with xerotic scale and crust Lichenified plaques in flexural areas
Distribution	Scalp, face (without perioral and periorbital involvement) trunk, extensor surfaces	Flexural surfaces, including antecubital and popliteal fossa, wrist, and neck	Hands, flexural surfaces, upper trunk

CLINICAL FEATURES

In addition, other signs and symptoms may be associated and are helpful to confirm the diagnosis in some patients.

Table 2. Associated features of atopic dermatitis. Modified from Ref. [1].

Pityriasis alba: Hypopigmented patches on face, upper trunk, upper extremities

Keratosis pilaris: Follicular hyperkeratosis of outer arms, lateral cheeks, buttocks, thighs

Dennie-Morgan fold (atopic pleat): Extra line on lower eyelid

Allergic shiners: Violaceous to gray color of infraorbital area

Hyperlinear palms: Increased and exaggerated skin markings on palms

Ichthyosis vulgaris: Scaling of extensor extremities, fish-scale appearance of extensor leg

Hertoghe sign: Loss of lateral eyebrows

White dermatographism: Blanching of skin after stroking

Circumoral pallor: Pallor of perioral area

Nummular dermatitis: Sharply circumscribed thick coin-shaped scaly plaques

New pathways for itching in patients with atopic dermatitis?



Jennifer Heimall, MD, and Jonathan M. Spergel, MD, PhD *Philadelphia, Pa*

J ALLERGY CLIN IMMUNOL
AUGUST 2017

Atopic dermatitis has been described **as the itch that rashes**. Indeed, the itching associated with the condition is often considered to be the most challenging feature of the disease to control. In addition, itching has been cited as the symptom most associated with effect on quality of life in patients with atopic dermatitis.



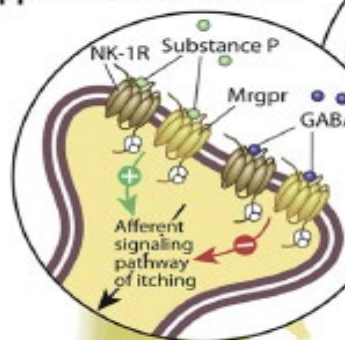
New pathways for itching in patients with atopic dermatitis?



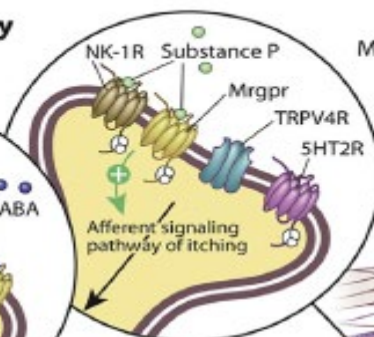
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GABA acts as an inhibitory neurotransmitter to suppress itch sensation



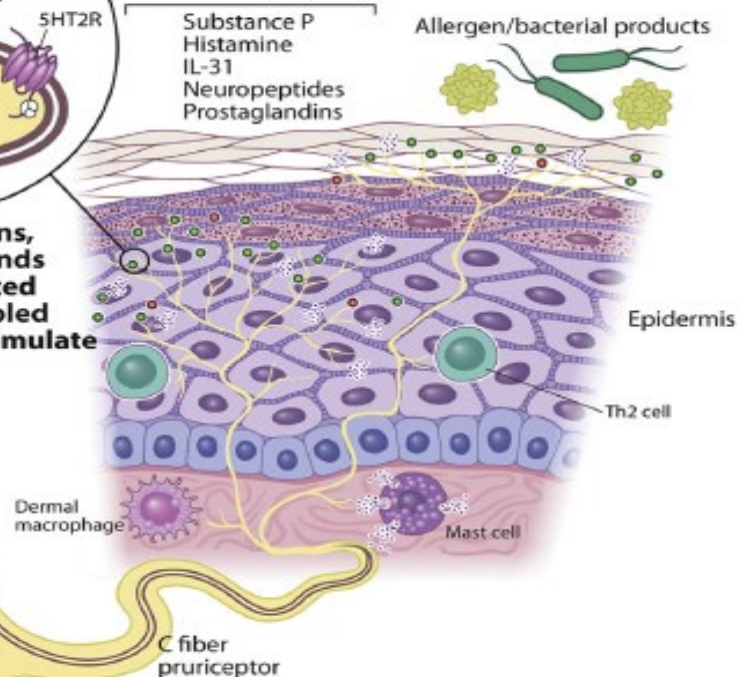
In both locations, Substance P binds NK-1/Mas-related G-Protein-coupled receptors to stimulate itch sensation



Mast cells release substances that directly or indirectly stimulate itch sensation in periphery

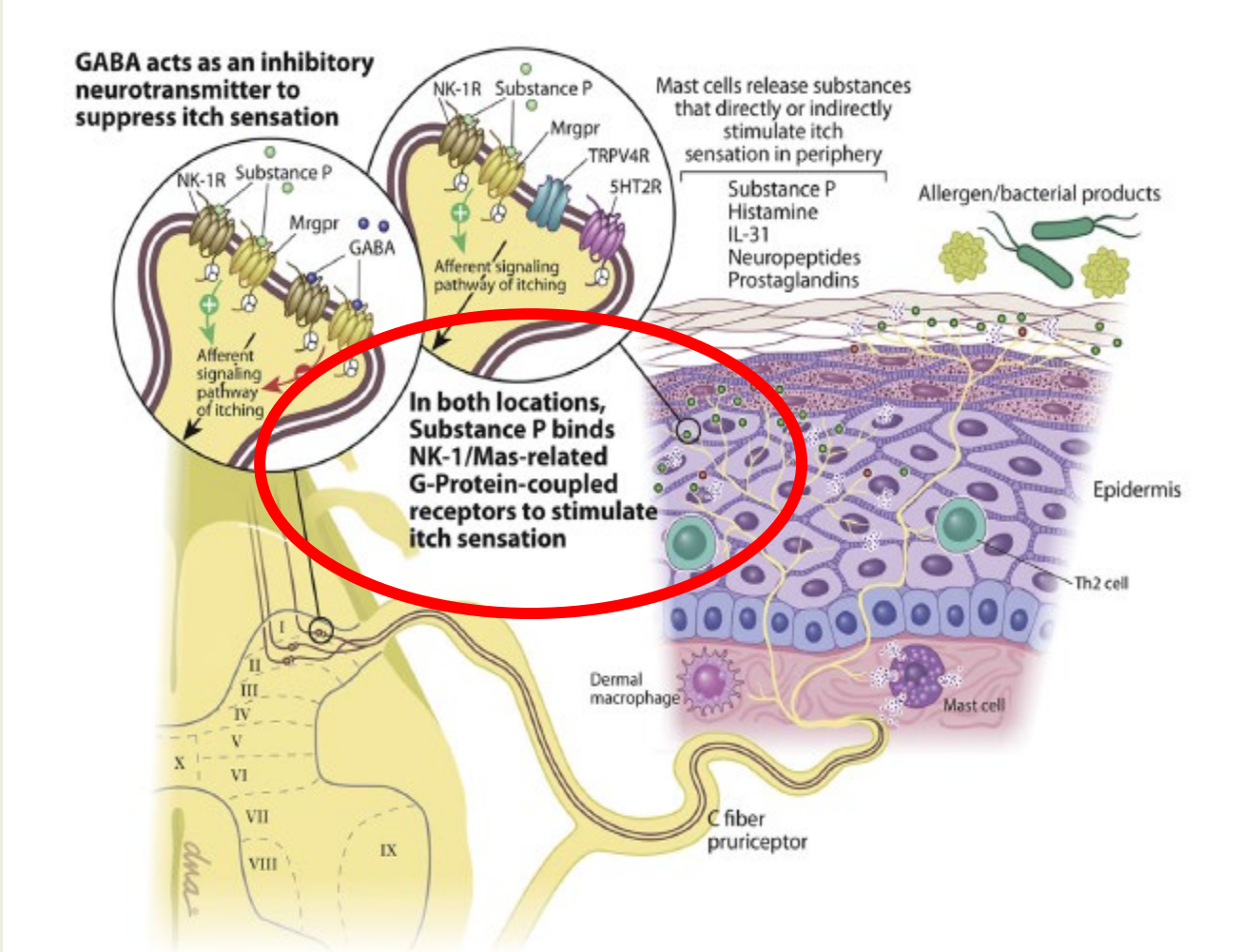
Substance P
Histamine
IL-31
Neuropeptides
Prostaglandins

Allergen/bacterial products



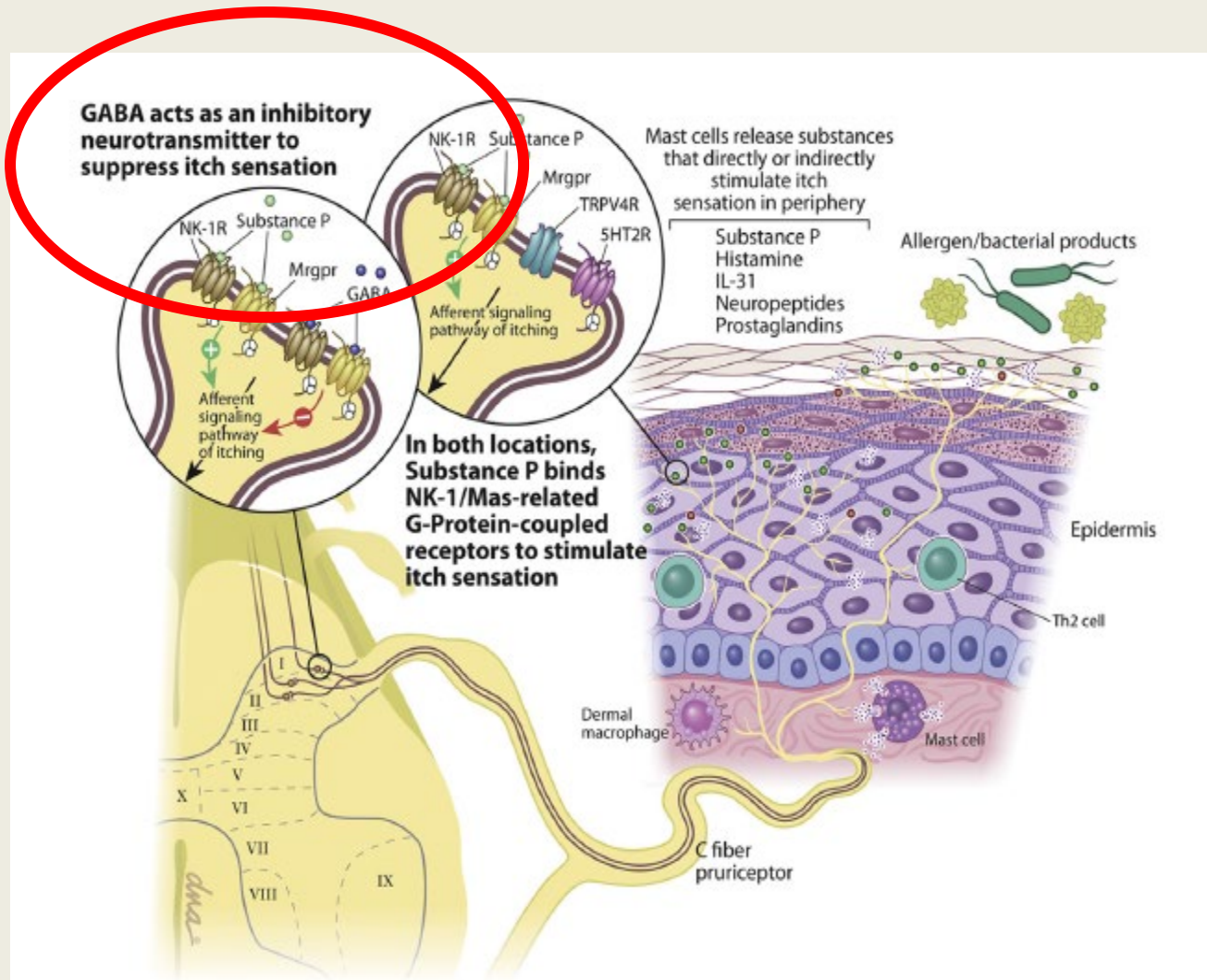
Substance P-mediated activation of Mas-related G protein-coupled receptors (Mrgprs)

Azimi et al. J Allergy Clin Immunol 2017; 140: 447-53



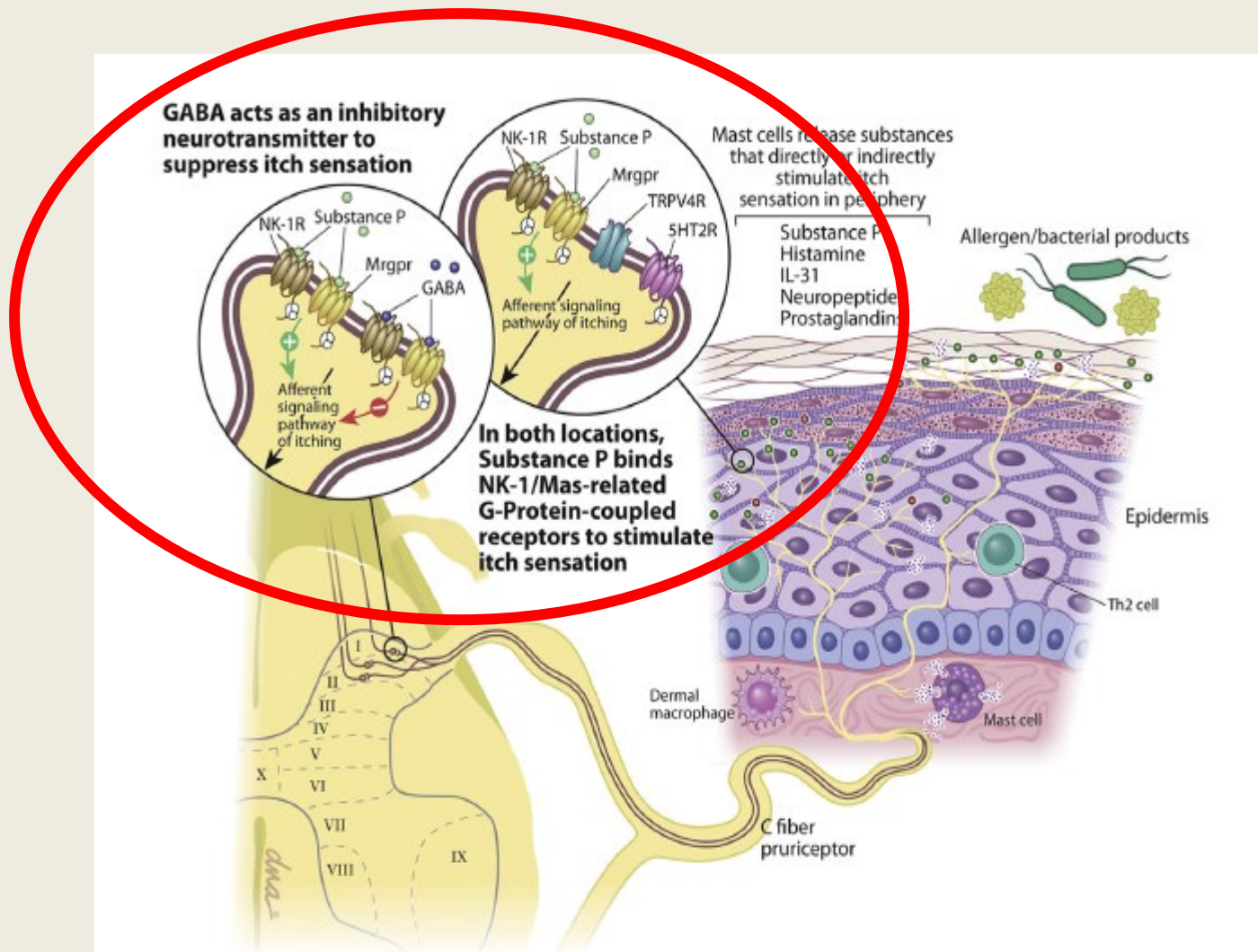
Activation of GABA pathway

Cevikbas F et al. J Allergy Clin Immunol 2017; 140: 454-64



Activation of TRPV4 receptor on the skin

Luo J et al. J Allergy Clin Immunol 2017

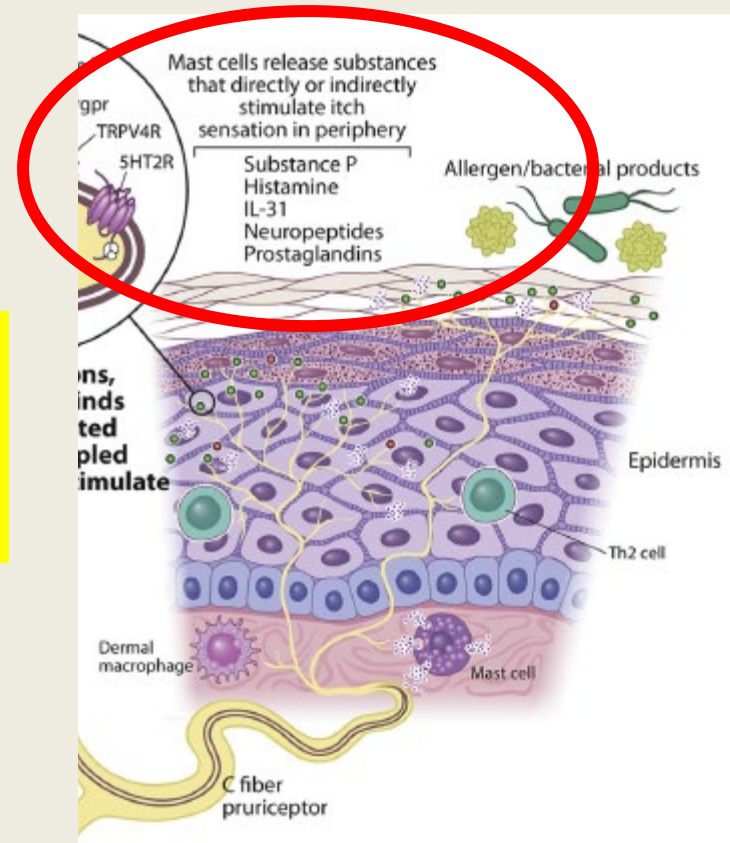


Pruritus in pediatric patients with atopic dermatitis: a multidisciplinary approach, summary

document from an Italian expert group

In press

The sensation of itching is mediated by cytokines, neuropeptides, and endogenous secreted factors.

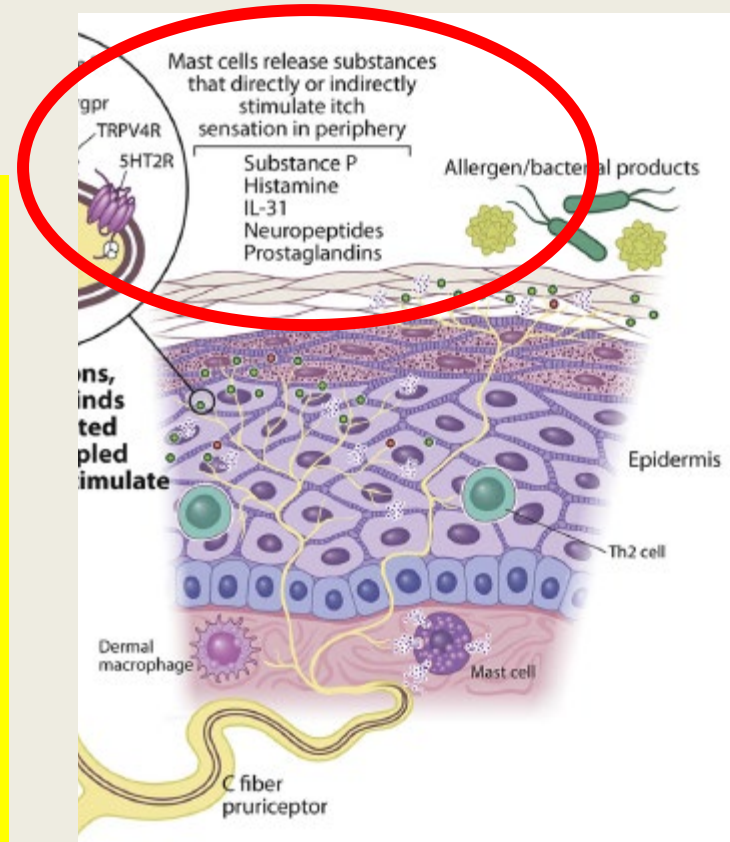


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In press

Histamine is one of the earliest identified pruritogens; among four receptors, H1R and H4R are potential mediators of pruritus. Others endogenous and exogenous factors produced from inflammation and xerosis result in the induction of non-histaminergic itch (i.e. protease, trypsin, dust mites, *Staphylococcus aureus*, or substance P, TSLP, Notch proteins).



A central neural circuit for itch sensation

Di Mu,^{1,2*} Juan Deng,^{1,2*} Ke-Fei Liu,^{1†} Zhen-Yu Wu,³ Yu-Feng Shi,¹ Wei-Min Guo,¹ Qun-Quan Mao,¹ Xing-Jun Liu,^{1†} Hui Li,³ Yan-Gang Sun^{1§}

Mu *et al.*, *Science* **357**, 695–699 (2017) 18 August 2017

Although itch sensation is an important protective mechanism for animals, chronic itch remains a challenging clinical problem.

Itch processing has been studied extensively at the spinal level.

However, how itch information is transmitted to the brain and what central circuits underlie the itch-induced scratching behavior remain largely unknown.



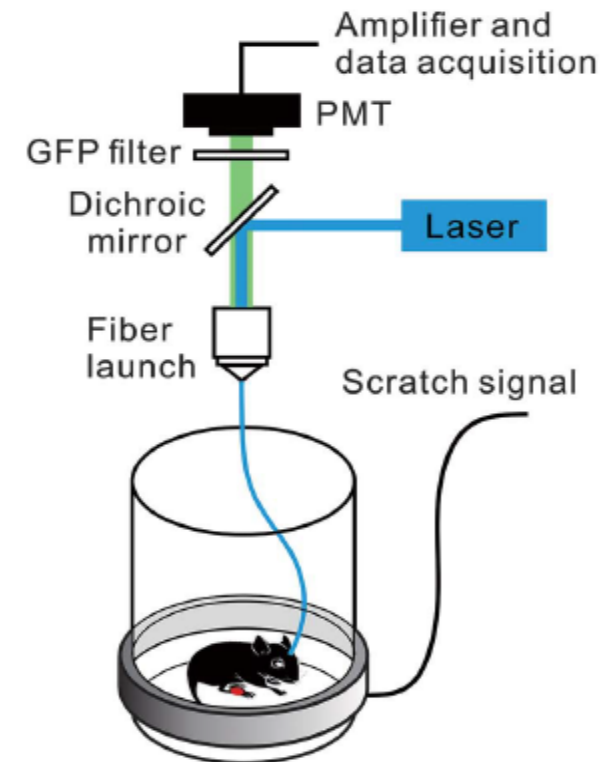
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Mu *et al.*, *Science* **357**, 695–699 (2017)

18 August 2017

We found that the spinoparabrachial pathway was activated during itch processing and that optogenetic suppression of this pathway impaired itch-induced scratching behaviors.

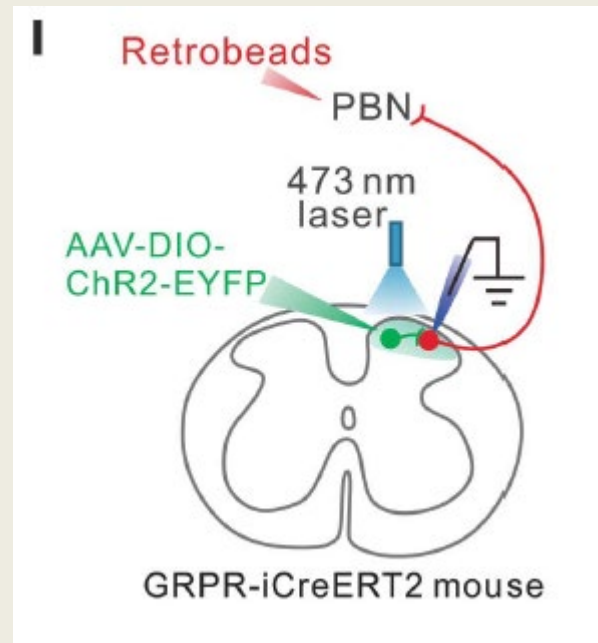


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Mu *et al.*, *Science* **357**, 695–699 (2017) 18 August 2017

Itch-mediating spinal neurons, which express the gastrin-releasing peptide receptor, are disynaptically connected to the parabrachial nucleus via glutamatergic spinal projection neurons.



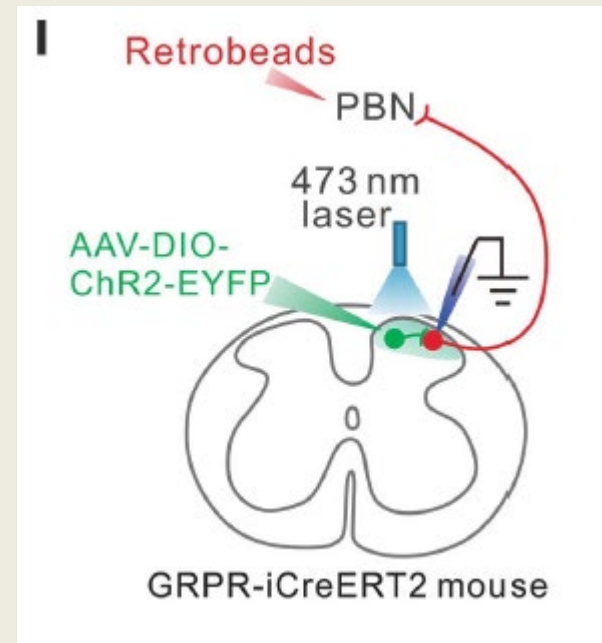
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Mu *et al.*, *Science* **357**, 695–699 (2017) 18 August 2017

Blockade of synaptic output of glutamatergic neurons in the parabrachial nucleus suppressed pruritogen-induced scratching behavior.

Thus, our studies reveal a central neural circuit that is critical for itch signal processing.



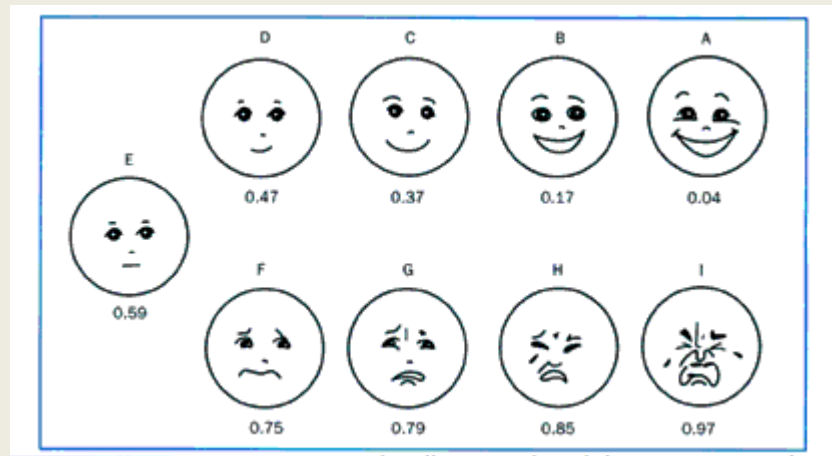
Pruritus in pediatric patients with atopic dermatitis: a multidisciplinary approach, summary document from an Italian expert group

Pruritus can occur in different clinical forms depending on the age of the child, chronicity of symptoms, trigger factors, and psychological attitude. In AD, itching is the main, constantly present symptom, and is of variable intensity, associated with pain and/or burning, and generally worsens at night causing sleep disturbance.



Pruritus in pediatric patients with atopic dermatitis: a multidisciplinary approach, summary document from an Italian expert group

In the literature, there are 62 separate severity scales and 28 quality of life tools (QOL) used in clinical research. The tools used for assessment of the intensity of itching are the Visual Analogue Scale (VAS), Numerical Scale, Verbal Scale, and Itching Severity Scale (ISS). However, there is no gold standard instrument for accurate assessment of the intensity and severity of pruritus and it is widely recommended that at least two should be used for reliable judgment.



Pruritus in pediatric patients with atopic dermatitis: a multidisciplinary approach, summary document from an Italian expert group



In patients with DA, constant pruritus can lead to chronicity with the appearance of nummular eczema, lichenification and/or nodular prurigo. Bacterial and viral superinfections are a frequent complication due to altered skin barrier and itching. In addition, scratching may induce autoinoculation, particularly in the presence of contagious molluscum and impetigo.



**Pruritus in pediatric patients with atopic dermatitis: a multidisciplinary approach, summary
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The persistence of pruritus, sleep disturbance, and worsening of skin conditions have a negative impact on psychological development of the child and on the emotional status of both the child and his/her parents, affecting daily activities, social relationships, and quality of life. In some cases, care to the AD patient may generate a conflict between the parents and the non-affected children, who may feel neglected.



Medical treatment

Antipruritic therapy is multidimensional aimed at minimizing symptoms and contributing factors such as dry skin, inflammation, and related scratch lesions. Therefore, several measures can be recommended.

Topical Therapy

Topical therapy is mandatory to repair skin barrier and reduce itching and skin susceptibility to irritants. Hydration is always essential, even during remission. Several topical products are available, and the selected formulation should be cosmetically acceptable to the patient, and possibly inexpensive, in order to encourage good compliance. The specific choice of treatment depends on both individual and clinical features



Anti-inflammatory Therapy

Corticosteroids: topical corticosteroids (TCS) are still considered the mainstay of pharmacological treatment and first choice agents for inflammation and itching

Calcineurin inhibitors: tacrolimus ointment (0.03% and 0.1%) and pimecrolimus cream (1%) are immunomodulators used for moderate/severe and mild forms, respectively.

It is important to take into account the age limit and possible contraindications (immunosuppression, exudative and infected lesions)



Antimicrobial Therapy

Antimicrobials and antiseptics are necessary to treat infected lesions.

Fusidic acid, retapamulin, and mupirocin are the most appropriate antibiotics



Upcoming topical therapies

Topical phosphodiesterase 4 inhibitor, crisaborole, is an effective treatment of mild-to-moderate AD in patients from 2 years of age and is still experimental in Italy.

Topical Janus kinase (JAK) inhibitors are being studied in clinical trials.

Paller AS et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol.* 2016 Sep;75(3):494-503.e6.

Wet dressing, or wet-wrap therapy

The application of a topical medication followed by bandaging or wet dressing (a double layer of gauze or tubular dressings, the first layer moistened and the second layer dry). It is indicated in **exudative, infected or lichenified lesions**, and protects against scratching and environmental irritants. It is also useful to promote absorption of topical products. Thus, it is important to take into account possible side effects, especially with concomitant corticosteroids



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PHOTOTHERAPY

UV therapy can be used in AD to relief pruritus.

Narrowband UV-B and UV-A has been demonstrated to be the most preferable artificial radiation



SYSTEMIC THERAPY

- Antihistamines.
- Systemic corticosteroids
- Systemic antimicrobial therapy
- Oral immunomodulatory therapies
- Target therapy:
 - a) **Dupilumab (anti IL-4 and 13)** is recommended as a disease-modifying drug for moderate-to-severe AD in Europe
 - b) Ustekinumab (anti IL-12 and IL-23)
 - c) Tralokinumab (anti IL-13)
 - d) Nemolizumab (anti-IL-31)

In some situations, targeted psychological intervention may be necessary.

Therapeutic patient education (TPE)

The WHO defines therapeutic patient education (TPE) as a continuous process to train and guide the patient and his/her family to acquire the competencies needed to manage his/her chronic disease.

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TPE is mandatory for adequate management of AD and itching for several reasons:

- AD is a multidisciplinary disease with discordant opinions between specialists
- clinical features are polymorphic in the same day in the same patient
- early age of disease onset
- lack of specific treatment against pruritus
- sleep disturbance involving the family
- scarce compliance due to chronicity, time and costs for dressing
- esthetic damage
- psychosocial impact



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TPE should be performed within the **multidisciplinary approach** required for AD.

The specifically trained team should be minimally composed of a pediatrician, dermatologist, and dedicated nurse. In some cases, a psychologist is also required.

All specialists should use the same language and provide the patient/family with a specific and tailored educational program. When required, other professional categories (e.g. allergologist) should be informed and take part in the TPE.



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Therapeutic patient education follow-up and psychological support

The educational approach should be preferably focused on families of children below 6 years of age because of the significant and high impact on disease and allow good management following disease onset.



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Therapeutic patient education follow-up and psychological support

Parents who play a key role in their children's treatment can considerably reduce the severity and impact of AD.

This suggests that in addition to pharmacological treatment, providing educational support to parents is an important factor in achieving a positive long-term outcome.

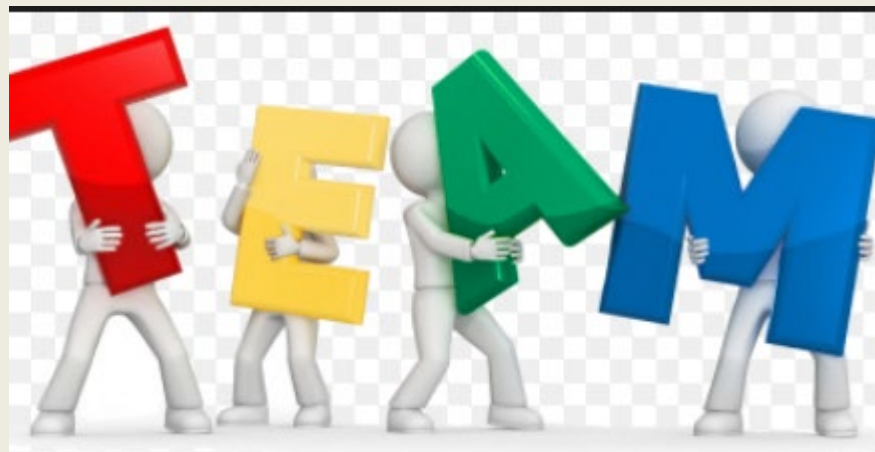


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Therapeutic patient education follow-up and psychological support

Attention to the emotional area allows:

- (i) promotion of a psychological elaboration that integrates information and emotions, facilitating memorization and consolidation of new information;
- (ii) creation of a relational context in a dedicated area for listening to the patient and his/her parents (knowing what he/she knows, how the patient lives with the illness, how much it influences them and their family);
- (iii) supporting the resources and skills of the patient and parents.



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Therapeutic patient education follow-up and psychological support

One of the most important interventions in the management of AD is spending time listening to patients' concerns, explaining its causes, and showing how to apply topical therapies on the basis of clinical features of the lesions and patient age.



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Adjuvant therapies: distraction techniques

In order to facilitate the management of pediatric patients during application of dressings and to provide tools to deal with frequent itching, the use of specific distraction techniques is crucial.



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Adjuvant therapies: distraction techniques

These techniques are based on two principles that allow one to use the remarkable imaginative skills of children:

- boundaries between fantasy and reality are much more fluid and permeable in children than in adults, amplifying their ability to use their fantasy**
- it is difficult, if not impossible, for a human being to focus attention on more than one or two sensory stimuli at once.**



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Adjuvant therapies: distraction techniques

These techniques imply the involvement of **parents** and, as soon as possible, as well as siblings, so that the dressing becomes a moment of sharing that stimulates family relationships.

They can be used during dressing or when the itching becomes unbearable, if the child is already familiar with dressing that they can applied more easily and automatically use the techniques when needed.





The focus of the present summary document was to increase awareness of pruritus in pediatric patients with AD. In addition, the authors tried to provide a useful tool for all specialists who managed patient with this disease and pruritus.



Emollients, as reported by the literature are considered the backbone in restoring the skin barrier, reducing itching and relapses.



The psychological support should be contemplated as one of the several therapeutic options available or on trial.



Finally, it is emphasized that a multidisciplinary approach is always necessary to guarantee an adequate management of patients with AD.



Moreover, educational interventions can greatly improve reducing symptoms, improving the adherence to treatment and the overall quality of life for both young sufferers and their parents.



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