All About ITCH

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Board Member, NEA

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Disclosures

Relationship	Manufacturer
Speaker	Regeneron/Sanofi Genzyme, Pfizer, Eli Lilly, LEO, Galderma, Incyte, L'Oreal
Advisory Board	Almirall, ASLAN Pharmaceuticals, Dermavant, Regeneron/Sanofi Genzyme, Pfizer, LEO Pharmaceuticals, AbbVie, Eli Lilly, Micreos, L'Oreal, Pierre-Fabre, Johnson & Johnson, Level Ex, KPAway, Unilever, Menlo Therapeutics, Theraplex, IntraDerm, Exeltis, AOBiome, Realm Therapeutics, Altus Labs, Galderma, Verrica, Arbonne, Amyris, Bodewell, YobeeCare, Burt's Bees, My-Or Diagnostics, Kimberly-Clark
Research	AOBiome, Regeneron/Sanofi Genzyme, and AbbVie
Patent Holder	Theraplex AIM (Patent Pending)
Stockholder	Micreos, YobeeCare, and Altus Labs, KPAway, LearnSkin

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Definitions: What Is Itch?

"[A] sensation resulting in an urge to scratch."

Yosipovitch G, Rosen JD, Hashimoto T. Itch: From mechanism to (novel) therapeutic approaches. *J Allergy Clin Immunol*. 2018;142(5):1375-1390. doi:10.1016/j.jaci.2018.09.005

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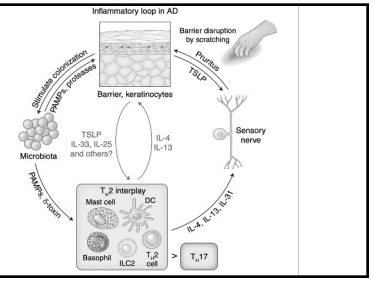
Inflammatory loop in AD



The epithelial immune microenvironment in atopic dermatitis and psoriasis. Ebrecht T, et al. Nat Immunol. 2018;19:1286–1298.

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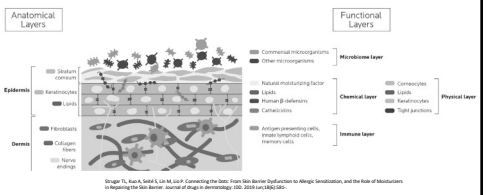
Barrier



Struge TL, Kuo A, Sehl S, Lin M, Lio P. Connecting the Dots: From Skin Barrier Dysfunction to Allergic Sensitization, and the Role of Moisturizers in Repairing the Skin Barrier. *Journal of drugs in dermatology: JDD*. 2019 Jun;18(6):585-.

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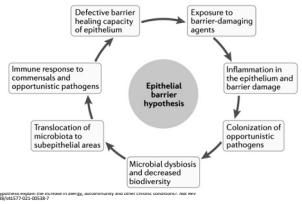
Barrier Hypothesis



Akdis, C.A. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions?. *Nat Rev Immunol* (2021). https://doi.org/10.1038/s41577-021-00538-7

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Selected Barrier Disruptors

Substance	Evidence
Polystyrene microplastic	Mouse models show effect of polystyrene microplastics on gut barrier
Ozone	Mouse models show respiratory barrier injury through ozone
Cigarette smoke	Mouse models show that cigarette smoke causes acute lung injury
Particulate matter	Ex vivo experiments with human and rat alveolar epithelial cells show that particulate matter affects the distribution of occludin and the alveolar barrier; PM2.5 causes defects in the nasal epithelial barrier in non-inflamed nasal biopsy samples of patients with sinusitis; PM10 stimulates myeloid dendritic cells to induce T_H17 cells with brain-homing property in vitro
Diesel exhaust particulates	Human and rat alveolar epithelial cells exposed to diesel exhaust particulates show low occludin expression and barrier leakiness
Nanoparticles	Human cell cultures show that nanoparticles disrupt intestinal barrier homeostasis
Anionic surfactants and commercial detergents	Human skin keratinocyte cultures show that anionic surfactants and commercial detergents decrease tight junction barrier integrity
Detergent residue	Human bronchial epithelial cell air-liquid interface cultures show that detergent residues disrupt tight junction barrier integrity in human bronchial epithelial cells even at low concentrations
Emulsifiers in processed food	Emulsifiers increased damage to the structure of hamster small intestine in vivo and the translocation of Escherichia coli across Mcells in vitro

PM2.5, particulate pollutant that is 2.5 μm or smaller in size; PM10, particulate pollutant that is 10 μm or smaller in size; T_H17, T helper 17.

Akdis, C.A. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat Rev Immunol* (2021). https://doi.org/10.1038/s41577-021-00538-7

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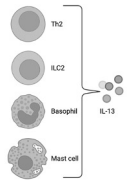
Th2 cells, ILC2 cells (type 2 innate lymphoid cells), Basophils, and Mast cells all release IL-13



- IL-13 promotes IL-31 expression→ "Master Itch" cytokine
- Decreases antimicrobial peptides
- Increases IgE production

Palomares, O., Akdis, M., Martín-Fontecha, M., & Akdis, C. A. (2017). Mechanisms of immune regulation in allergic diseases: the role of regulatory T and B cells. Immunological Reviews, 278(1), 219–236. doi:10.1111/imr.12555
Figure prepared by Peter Lio, MD using biorender.com

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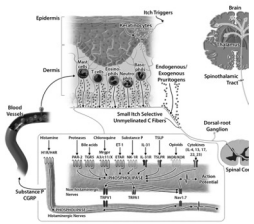
Pathways



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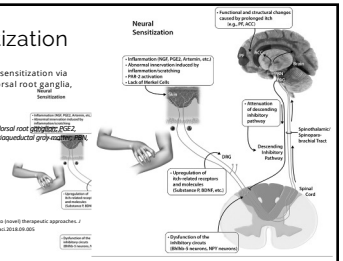
Neural Sensitization

- It is possible to induce neural sensitization via various triggers in the skin, dorsal root ganglia, spinal cord, and brain

BDNF, Brain-derived neurotrophic factor; DRG, dorsal root ganglion; PGE2, prostaglandin E2; NPY, neuropeptide Y; PAG, periaqueductal gray-matter; PBN, parabrachial nucleus.



Yosipovitch G, Rosen JD, Hashimoto T. Itch: From mechanism to (novel) therapeutic approaches. *J Allergy Clin Immunol.* 2018;142(5):1375-1390. doi:10.1016/j.jaci.2018.09.005

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Itch: Diagnosis

4 categories of Itch:

1. Dermatologic (e.g., AD or psoriasis)
2. Neuropathic (e.g., brachioradial pruritus, small-fiber polyneuropathy)
3. Psychogenic (e.g., delusions of parasitosis, anxiety)
4. Systemic (e.g., end stage renal disease)

Yosipovitch G, Rosen JD, Hashimoto T. Itch: from mechanism to (novel) therapeutic approaches. Journal of Allergy and Clinical Immunology. 2018 Nov 1;142(5):1375-90.

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What is Sensitive Skin?

- Theories include:
- Heightened neurosensory input
- Enhanced immune reaction
- Damaged skin barrier function
- Increased vascular reactivity

Cho HJ, Chung BY, Lee HB, Kim HO, Park CW, Lee CH. Quantitative study of stratum corneum ceramides contents in patients with sensitive skin. *J Dermatol.* (2012) 39:295–300. doi: 10.1111/j.1346-8138.2011.01406.x

Chen SY, Yin J, Wang XM, Liu YQ, Gao YR, Liu XF. A new discussion of the cutaneous vascular reactivity in sensitive skin: a sub-group of SS. *Skin Res Technol.* (2018);24:432–9. doi: 10.1111/srt.12446

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Sensitive Skin

- Ceramides appear to be reduced in the facial skin of sensitive skin patients versus controls in at least one study
- Suggests disruption in barrier function; but reproducible differences between sensitive skin and controls using transepidermal water loss (TEWL) have proven elusive

Cho HJ, Chung BY, Lee HB, Kim HO, Park CW, Lee CH. Quantitative study of stratum corneum ceramides contents in patients with sensitive skin. *J Dermatol*. (2012) 39:295–300. doi: 10.1111/j.1346-8138.2011.01406.x

Farage MA. The prevalence of sensitive skin. Frontiers in medicine. 2019 May 17;6:98.

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Subtypes?

- Type I: "Delicate skin":
  - Characterized by easily disrupted barrier function without inflammatory response
- Type II: "Reactive skin"
  - Characterized by a strong inflammatory response
- Type III: "Stingers"
  - Characterized by heightened neurosensory perception to minor cutaneous stimulation

Mulzzuddin N, Marenus KD, Maes DH. Factors defining sensitive skin and its treatment. American Journal of Contact Dermatitis. 1998 Sep 1;9(3):170-5.

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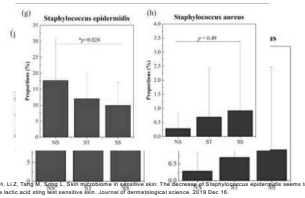
Decreased Staphylococcus epidermidis correlates with lactic acid sting test sensitive skin



Zheng Y, Liang H, Li Z, Tang M, Song L. Skin microbiome in sensitive skin: The decrease of Staphylococcus epidermidis seems to be related to female lactic acid sting test sensitive skin. Journal of dermatological science. 2019 Dec 16.

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Itch: Therapeutic Ladder

Basic Ladder:

1. Topicals
2. "Safe" Systemics
3. More Powerful Systemics
4. Alternatives

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Itch: Topicals

Class of medication	Medication	Potential antipruritic uses	Notable adverse effects
Corticosteroids	Mometasone, Betamethasone, Clobetasol, etc	AD Inflammatory skin disease itch	Skin atrophy Telangiectasia Striae Changes in pigmentation
Calcineurin inhibitors	Tacrolimus (0.03-0.10%) Pimecrolimus (1%)	Anogenital pruritus AD Cholestatic pruritus Lichen sclerosis Hand dermatitis Neuropathic pruritus Posterior blepharitis Prurigo nodularis Uremic pruritus	Temporary localized pain or burning FDA boxed warning for increased risk of malignancy
Anesthetics	Pramoxine (1%) Lidocaine (2.5% to 5%) Prilocaine (2.5%) Ketamine-amitriptyline-lidocaine	Neuropathic itch Uremic pruritus AD Pruritus pruritus Old-age immunosenescence itch Prurigo nodularis	Temporary localized decreased sensation
Ion channels blockers	Capsaicin cream (0.025% to 0.1%) Patch (8%)	AD Aquagenic pruritus Prurigo nodularis Psoriasis Uremic pruritus Neuropathic itch	Temporary localized pain or burning
	Menthol (1% to 3%)	Pruritus of various causes	Mild localized inflammation or burning
	Camphor Strontium chloride (4%)	Localized itch	To our knowledge, no known side effects have been reported thus far.
JAK inhibitors	Tofacitinib (2%)	AD Psoriasis	Skin irritation
Phosphodiesterase-4 inhibitors	Crisaborole (2%)	AD	Temporary localized pain or burning
Topical cannabinoids	N-palmitoylethanolamine	AD Dry skin Lichen sclerosis	Unknown

Yosipovitch G, Rosen JD, Hashimoto T. Itch: from mechanism to (novel) therapeutic approaches. Journal of Allergy and Clinical Immunology. 2018 Nov 1;142(5):1375-90.

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Topicals

- Topical steroids and TCIs
- Various "Anti-Itch" (3% Calamine, 1% Pramoxine HCl, 0.47% Camphor)
- ~~Topical Antihistamines~~
- Topical Hydrogels

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Itch: Systemics

Class of medication	Medication	Dosage	Antipruritic indications	Notable adverse effects
Antihistamine H1 blockers	First generation	Varies depending on medication	Nocturnal itch	Somnolence
	Second generation	Varies depending on medication	Reaction to insect bites Urticaria or chronic idiopathic urticaria Mastocytosis	Somnolence (less severe)
Anticonvulsants	Gabapentin	300-1200 mg thrice daily	Neuropathic itch Prurigo nodularis Postburn pruritus Uremic pruritus Paraneoplastic pruritus	Somnolence Weight gain Gastrointestinal symptoms Lower extremity swelling
	Pregabalin	25-225 mg twice daily		
Antidepressants	SSRIs Paroxetine Sertraline Fluvoxamine	 10-40 mg daily 75-100 mg daily 25-150 mg daily	 Paraneoplastic pruritus Cholestatic pruritus Pruritus coexisting with depression or anxiety	 Somnolence Insomnia Gastrointestinal symptoms Reduced sexual desire or ability to reach orgasm
	TCAs Doxepin Amitriptyline	 10-100 mg nightly 25-75 mg nightly	 Neuropathic itch Chronic idiopathic urticaria	 Anticholinergic side effects Hypotension and other cardiovascular effects
	Mirtazapine	7.5-15 mg nightly	Nocturnal itch Paraneoplastic pruritus AD Systemic itch	Somnolence Weight gain
Opioid κ agonists and μ antagonists	Butorphanol	1-4 mg/mL nightly	Generalized severe intractable pruritus	Somnolence Disorientation Bizarre dreams Gastrointestinal symptoms
	Nalfurafine	2.5-5 micrograms daily	Uremic pruritus	Insomnia
	Naltrexone	25-50 mg daily	Cholestatic pruritus AD Chronic idiopathic urticaria Uremic pruritus	Skin reaction Gastrointestinal symptoms
	Nalbuphine, extended release	120 mg	Uremic pruritus Prurigo nodularis	Gastrointestinal symptoms
	Asimadoline		AD	Phase II, clinical trials completed
	CR845		Uremic pruritus	Phase III, clinical trials ongoing
NK-1 inhibitors	Aprepitant	80 mg daily	Paraneoplastic pruritus Prurigo nodularis	Gastrointestinal symptoms
	Serlopitant Tradipitant		Chronic pruritus Prurigo nodularis AD	Mild somnolence, diarrhea Phase II-III, clinical trials ongoing
Immunosuppressants	Thalidomide	100-200 mg daily	Prurigo nodularis Uremic pruritus Actinic prurigo	Peripheral neuropathy Teratogenicity in female subjects Somnolence
	Dapsone	0.5-1 mg/kg daily	Dermatitis herpetiformis	Neuropathy Hemolytic anemia Methemoglobinemia

Yosipovitch G, Rosen JD, Hashimoto T. Itch: from mechanism to (novel) therapeutic approaches. Journal of Allergy and Clinical Immunology. 2018 Nov 1;142(5):1375-90.

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Itch: Systemics

			AD Prurigo nodularis Old-age immunosenescence itch	Decreased hematopoiesis Liver function abnormalities
	Cyclosporine	2.5-5 mg/kg daily	Generalized pruritus AD Psoriasis Prurigo nodularis Chronic idiopathic urticaria	Hypertension Renal toxicity Hirsutism
Class of medication	**Medication**	**Dosage**	**Antipruritic indications**	**Notable adverse effects**
	Mycophenolate Mofetil	2 g daily	AD Immunosenescence itch	Gastrointestinal symptoms Leukopenia
	Azathioprine	25-275 mg daily	Chronic pruritus AD	Transaminitis Gastrointestinal symptoms Hypersensitivity drug reaction Myelosuppression Skin cancer
Biologics and small-molecule inhibitors	Dupilumab (anti–IL-4Ra)	600 mg, followed by 300 mg biweekly	AD	Injection-site reaction Conjunctivitis
	Ixekizumab (anti–IL-17A)	160 mg, followed by 80 mg biweekly for the first 12 weeks, then monthly	Psoriasis	Injection-site reaction Upper respiratory tract infection Systemic infections Rare IBD
	Secukinumab (anti–IL-17A)	300 mg weekly for 5 weeks, then monthly	Psoriasis	Upper respiratory tract infections Rare IBD
	Nemolizumab (anti–IL-31Ra)		AD Prurigo nodularis	Phase II, clinical trials ongoing
	Omalizumab (anti-IgE)	150-375 mg, biweekly or monthly	Chronic idiopathic urticaria Aquagenic pruritus Bullous pemphigoid Solar urticaria	Anaphylaxis Injection-site reaction Viral infection Upper respiratory tract infection
	Apremilast (anti-PDE4)	Over 1-wk titrate up to 30 mg twice daily	Psoriasis AD	Gastrointestinal symptoms Weight loss Rare depression
JAK inhibitors	Tofacitinib	5-10 mg daily	Psoriasis	Upper respiratory tract infection Systemic bacterial and fungal infections FDA boxed warning for increased risk of malignancy
	Baricitinib	2 mg daily	AD	Nausea Upper respiratory tract infection Herpes simplex or zoster infection
	Oclacitinib		Allergic dermatitis in dogs AD in dogs	Used in veterinary medicine

Yosipovitch G, Rosen JD, Hashimoto T. Itch: from mechanism to (novel) therapeutic approaches. Journal of Allergy and Clinical Immunology. 2018 Nov 1;142(5):1375-90.

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Risks and Side Effects

- Mirtazapine (black box warning: suicidality)
- Doxepin (black box warning: suicidality)
  - Binds to histamine receptor with 800x the affinity of hydroxyzine
- Aprepitant (Neutropenia, bradycardia)
- Butorphanol (Respiratory depression, dependency)

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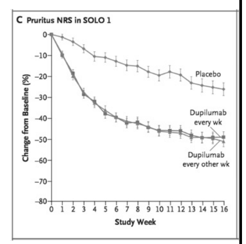
Dupilumab



Simpson EL, et al; SOLO 1 and SOLO 2 Investigators. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. N Engl J Med. 2016 Dec 15;375(24):2335-2348.

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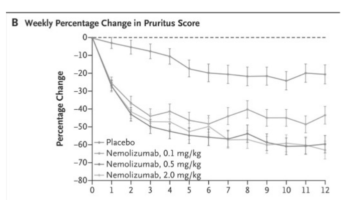
Nemolizumab



Anti-Interleukin-31 Receptor A Antibody for Atopic Dermatitis. Ruzicka T, Hanifin JM, Furue M, Pulka G, Mlynarczyk I, Wollenberg A, Galus R, Etoh T, Mihara R, Yoshida H, Stewart J, Kabashima K; XCIMA Study Group. N Engl J Med. 2017 Mar 2;376(9):826-835.

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Alternatives

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Quercetin

- A plant-derived flavonoid
- Anti-inflammatory and antioxidant properties
- Some discussion of cancer-fighting properties as well

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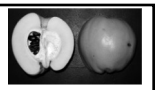
Quercetin



- Study of extract of Chaenomeles sinensis fruit (*Motkua*), long utilized as folk medicine for cough
- Active ingredients include quercetin

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Quercetin

- A pruritogenic agent was injected into mouse skin (mast cell degranulator)
- Extracts from the fruit were administered orally (dissolved in water)
- Significantly inhibited scratching behavior in mice: they controlled for sedation, direct histamine itch, and locomotive behavior

Oku H, Ueda Y, Ishiguro K. Antipruritic effects of the fruits of Chaenomeles sinensis. Biol Pharm Bull. 2003 Jul;26(7):1031-4.

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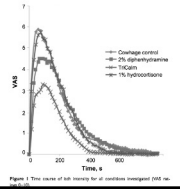
Clinical, Cosmetic and Investigational Dermatology

ORIGINAL RESEARCH

TriCalm® hydrogel is significantly superior to 2% diphenhydramine and 1% hydrocortisone in reducing the peak intensity, duration, and overall magnitude of cowhage-induced itch

"The exact antipruritic mechanism of TriCalm is not yet elucidated, but it can be attributed (at least in part) to the astringent action of its active ingredient, aluminum acetate."



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CBD

- Cannabinoids have anti-inflammatory, anti-itch, and pain-relieving properties
- Have potential to treat eczema topically
- Can be made to have no psychoactive components
- However: we have very little clinical data at this point

The Therapeutic Potential of Cannabinoids in Dermatology Marks DH, Friedman A. Skin Therapy Lett. 2018 Nov;23(6):1-5.

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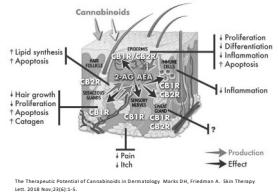
CBD



The Therapeutic Potential of Cannabinoids in Dermatology Marks DH, Friedman A. Skin Therapy Lett. 2018 Nov;23(6):1-5.

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PEA

- The endocannabinoid palmitoylethanolamide (**PEA**) has anti-pruritic properties when applied topically
- Several studies in both adults and children converge on demonstrating reduced pruritus and improved dryness, excoriation, lichenification, scaling, and erythema in ~70% of patients with AD
- Also shown to decrease weekly topical steroid use by 62%

The Therapeutic Potential of Cannabinoids in Dermatology. Marks DH, Friedman A. Skin Therapy Lett. 2018 Nov;23(6):1-5.

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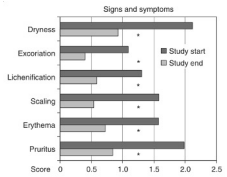
PEA on AD



Adjuvant treatment of atopic eczema: assessment of an emollient containing N-palmitoylethanolamine (ATOPA study). Eberlein B, Eicke C, Reinhardt HW, Ring J. J Eur Acad Dermatol Venereol. 2008 Jan;22(1):73-81.

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Conclusions: Itch

- Itch is pretty terrible
- Thus far, we are fairly limited in our treatments
- With new understanding and new developments in therapeutics, this may soon change!

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Thank you!

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EczemaExpo.org
NationalEczema.org

National Eczema Association

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