THURSDAY PROGRAM

Spotlight on Allergic Conditions of the Skin

November 6

Tangerine Ballroom
Salons 1 & 2
Orange County
Convention Center
and Livestreamed

American College of
Allergy, Asthma & Immunology

2025 ANNUAL SCIENTIFIC MEETING

Podium to Practice®

INSPIRING VISION

NOVEMBER 6-10

ORLANDO, FLORIDA

education.acaai.org/Thursday

American College of Allergy, Asthma & Immunology

Call for Session Proposals

American College of
Allergy, Asthma & Immunology

2026

Podium to Practice®

BUILDING BRIDGES FOR THE FUTURE

Annual Scientific Meeting

November 12-16

PHOENIX, AZ

The College is accepting proposals for Educational Sessions and Hands-On Workshops that echo the theme of the 2026 Annual Scientific Meeting, and:

- Reflect clinical innovation and cutting-edge research
- Convey best practices
- Present evidence-based medicine
- Stimulate discussion and challenge mindsets

Deadline for submission is: **January 10, 2026**

college.acaai.org/26proposals

ACAAI 2025 Thursday Program

November 6, 2025
ACAAI 2025 Annual Scientific Meeting
Orange County Convention Center
Orlando, FL

Spotlight on Allergic Conditions of the Skin
Syllabus

Thursday Program Morning and Afternoon Sessions
Supported by an independent medical education (IME) grant from Novartis Pharmaceuticals Corporation

Thursday Program Luncheon Symposium
Supported by an independent medical education (IME) grant from Incyte

Sponsored by the
American College of Allergy,
Asthma & Immunology

NOTE: The Thursday Program syllabus is available online to those registered for the Thursday Program at the following website:
https://education.acaai.org/Thursday

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ACAAI 2025 Annual Scientific Meeting
Thursday Program

Target Audience
Allergists, immunologists and other healthcare professionals

Learning Objectives
Upon completion of this session, participants should be able to:

1. Evaluate potential underlying causes of idiopathic angioedema, differentiate between truly idiopathic cases and those with identifiable (but lesser known) triggers, and develop evidence-based management strategies to optimize patient outcomes.
2. Analyze the role of genetic variants and associated biomarkers in the pathophysiology of angioedema and assess how these factors influence the selection of targeted therapeutic approaches.
3. Implement a stepwise approach to diagnosing and managing histaminergic and non-histaminergic angioedema, including selecting appropriate therapies based on underlying mechanisms and patient-specific factors.
4. Evaluate the importance of measuring quality of life in patients with CSU, select appropriate QoL assessment tools, and integrate them into personalized treatment plans to improve patient outcomes.
5. Apply evidence-based strategies for the diagnostic work-up of CSU, interpret the relevance of biomarkers in predicting disease outcomes, and incorporate these insights into the selection of current and emerging therapies.
6. Identify and evaluate emerging treatments for CSU, understand their mechanisms of action, and incorporate these advancements into clinical practice to enhance patient care.
7. Elucidate the pathophysiology of chronic itch, assess the utility of potential biomarkers in diagnosis and treatment planning, and integrate emerging therapies into patient management strategies to improve outcomes.
8. Evaluate the evidence of supportive and foundational therapies in the management of atopic dermatitis and apply these essential treatments effectively to improve patient care.
9. Assess the mechanisms of action, efficacy, and safety profiles of current and emerging biologic therapies for atopic dermatitis and apply this knowledge to optimize personalized treatment strategies for diverse patient populations.
10. Determine optimal timing and strategies for incorporating JAK inhibitors into treatment plans for atopic dermatitis, based on an understanding of their mechanism of action, indications, and patient-specific considerations.
11. Explain the procedures and interpretation of patch testing and apply this knowledge to identify and manage allergic contact dermatitis and other rashes.
12. Assess the utility of patch testing in managing various drug-induced rashes and integrate this knowledge into clinical practice.
13. Recognize delayed hypersensitivity reactions to metals and other implantable devices, interpret diagnostic testing results including patch tests, and develop effective management plans for affected patients.

Accreditation and Credit Statements

The American College of Allergy, Asthma & Immunology (ACAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The American College of Allergy, Asthma & Immunology (ACAAI) is a provider, approved by the California Board of Registered Nursing, Provider Number CEP17239.

The American College of Allergy, Asthma & Immunology (ACAAI) designates this live activity for a maximum of **28.75** *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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This continuing medical education activity has been reviewed by the American Academy of Pediatrics and is acceptable for a maximum of **28.75** AAP credits. These credits can be applied toward the AAP CME/CPD Award available to Fellows and Candidate Members of the American Academy of Pediatrics.

NOTE: Thursday Program ticket holders can claim up to **6.75** credits for their in-person participation in the Morning and Afternoon sessions, plus the Luncheon Presentation, as part of the **28.75** credits offered in the in-person annual meeting.

Credit for the Thursday Program may be claimed online at: annualmeeting.acaai.org. Use your last name and ACAAI ID number to complete the appropriate evaluations, claim your credit and obtain your certificate as soon as possible, either onsite or online.

Credit should be claimed by December 31, 2025.

DISCLOSURES

ACAAI 2025 Annual Scientific Meeting
Thursday Program
November 6, 2025
Orlando, FL

Disclosure Statement
As required by the Accreditation Council for Continuing Medical Education (ACCME) and in accordance with the American College of Allergy, Asthma and Immunology (ACAAI) policy, all individuals in a position to control or influence the content of an activity must disclose **all** financial relationships with any ineligible company that have occurred within the past **24 months**.

Ineligible companies are those whose primary business is producing, marketing, selling, re-selling, or distributing health care products used by or on patients. The ACCME does not consider providers of clinical service directly to patients to be ineligible companies. Examples of ineligible companies include:

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- Compounding pharmacies that manufacture proprietary compounds
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- Diagnostic labs that sell proprietary products
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Learners must also be informed when off-label, experimental/investigational uses of drugs or devices are discussed in an educational activity or included in related materials.

Disclosure in no way implies that the information presented is biased or of lesser quality. It is incumbent upon course participants to be aware of these factors in interpreting the program contents and evaluating recommendations. Moreover, expressed views do not necessarily reflect the opinions of the ACAAI.

All relevant financial relationships with ineligible companies have been mitigated.

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Mark Boguniewicz, MD, FACAAI
Advisor: *Lilly;* ***Advisor, Researcher:*** *Regeneron, Sanofi*

Martin Metz, MD, PhD
Advisor, Speaker: *Novartis*

The following have no relevant financial relationships with ineligible companies to disclose:

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Anil Nanda, MD, FACAAI
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Kristin C. Sokol, MD, MS, MPH, FACAAI
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ACAAI 2025 Annual Scientific Meeting
Thursday Program
SPOTLIGHT ON ALLERGIC CONDITIONS OF THE SKIN
Orange County Convention Center
Tangerine Ballroom Salons 1 & 2 and Livestream
Thursday, November 6, 2025

Supported by an independent medical education (IME) grant from Novartis Pharmaceuticals Corporation

Morning Session

Moderator: ***Kristin C. Sokol, MD, MS, MPH, FACAAI*** **Page**

ANGIOEDEMA

9:20 am **Questions & Discussion**

9:30 am **Refreshment Break**

CHRONIC SPONTANEOUS URTICARIA

11:20 am **Questions & Discussion**

11:30 am **Adjourn**

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Luncheon Presentation

Moderators: S. Shahzad Mustafa, MD, FACAAI; and Kristin C. Sokol, MD, MS, MPH, FACAAI

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CHRONIC ITCH

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Afternoon Session

ATOPIC DERMATITIS

CONTACT DERMATITIS AND DRUG ALLERGY

Idiopathic Angioedema – Is It Really Idiopathic?

Jonathan A. Bernstein, M.D.
Professor of Medicine
University of Cincinnati

department of Internal Medicine

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Conflict of Interests

- Investigator and consultant: ADARx, Ajou University, Allergy therapeutics, Amgen, Apogee, Areteia, ARS, Astra Zeneca, Astria, Biocyrst, Blueprint Medicine, Celldex, Cogent, CSL Behring, Eli Lilly, Escient, Evommune, Fresenius Kabi, Genentech, GSK, Incyte, Intellia, Ionis, Japan Tobacco Company, Jasper, Kalvista, Kenvue, Kymeria, Kyowa Kirin, Medscape, Merck, Novartis, Opella, Pharming, Pharvaris, Proctor and Gamble, Regeneron, Sanofi, Takeda/Shire, Telios, Teledoc, TEVA, Yuhan, WebMD news.
- Consultant: Enanta, Pfizer, RAPT
- Speaker: Pharming, Kalvista, CSL Pharming, Novartis
- AAAAI Foundation, HAEA MAB, UCARE, JTF Co-Chair Urticaria Guidelines

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Learning Objectives

- Define potential underlying causes of idiopathic angioedema
- Discuss how to differentiate between truly idiopathic cases of angioedema from those with identifiable (but lesser known) triggers
- Determine how to best develop evidence-based management strategies to optimize patient outcomes

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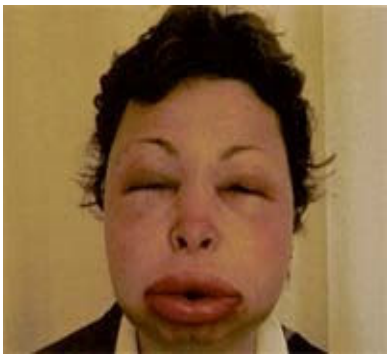
What is Angioedema?

- Angioedema (AE) is characterized by swelling of the mucosa or submucosa and/or the subcutaneous tissue of the skin[1]



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Kaplan AP, Greaves MW. *J Am Acad Dermatol.* 2005;53:373-388.

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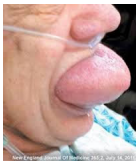
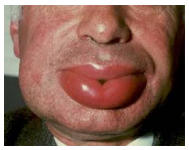
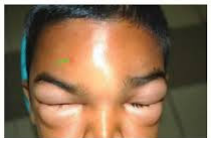
Different Presentations of Angioedema



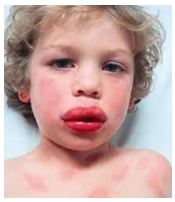
ACE induced



HAE or AAE

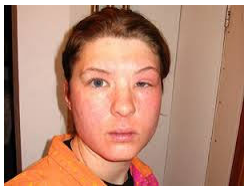


Food allergy



Infection

Severe Allergic Rhinitis



Drug reaction

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Physical Examination Doesn't Differentiate Types Of Angioedema

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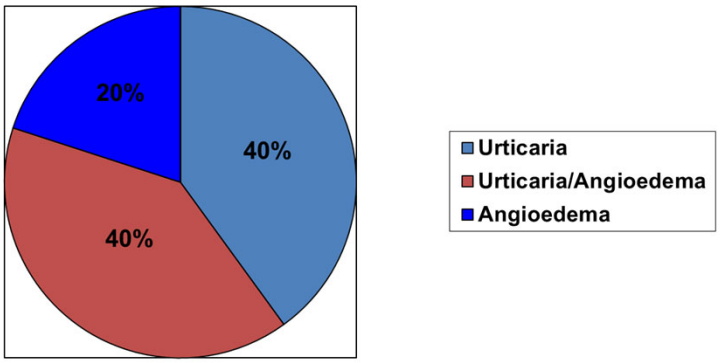
Prevalence of Angioedema With and Without Urticaria



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Angioedema without urticaria: a large clinical survey

Table 1: Classification of angioedema without urticaria according to clinical or etiopathogenetic characteristics, *n* = 776

	Patients		M:F ratio	Age at onset, yr	
	No.	%		Median	Range
Related to a specific factor*	124	16	0.51	39	13-76
Autoimmune disease/infection	55	7	0.62	49	3-78
ACE inhibitor-related	85	11	0.93	61	32-84
C1-inhibitor deficiency	197	25			
Hereditary	183		0.88	8	1-34
Acquired	14		1.8	56.5	42-76
Unknown (idiopathic) etiology	294	38			
Histaminergic	254		0.56	40	7-86
Nonhistaminergic	40		1.35	36	8-75
Peripheral/generalized edema	21	3	0.17	–	

Zingale LC et.al, CMAJ 2006. 24;175(9):1065-70.

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Clinical Characteristics of Angioedema Subtypes

Nonhistaminergic Angioedema (Bradykinin-Mediated)[1-3]	Histaminergic Angioedema (Histamine-Mediated)[1,3]
• Not mediated by immunoglobulin (Ig) E	• Mediated by IgE
• Not usually associated with urticaria	• Usually associated with urticaria
• Attacks may last up to 5 days	• Swelling normally subsides within 24–48 hours
• Generally unresponsive to antihistamines and/or corticosteroids	• Responsive to antihistamines and/or corticosteroids
• Onset in childhood or young adulthood, worsening at puberty	

1. Zuraw BL. *N Engl J Med*. 2008;359(10):1027-1036.
2. Nzeako UC, et al. *Arch Intern Med*. 2001;161(20):2417-2429.
3. Kaplan AP, Greaves MW. *J Am Acad Dermatol*. 2005;53(3):373-388.

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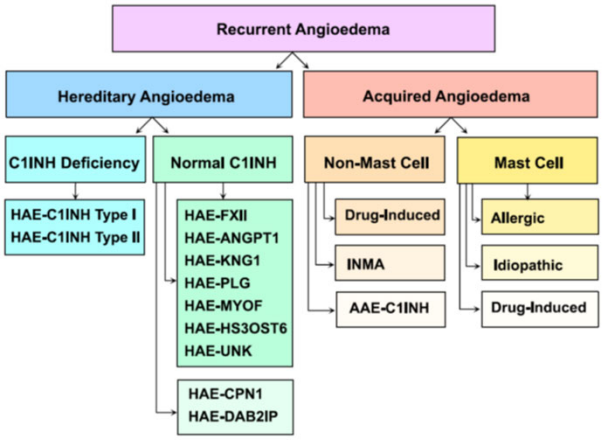
Types of Angioedema: Classification



INMA -idiopathic non-mast cell mediated angioedema; HAE – hereditary angioedema; AAE – Acquired angioedema; HAE-ANGPT1 (angiopoietin); *HAE-CPN1 (carboxypeptidase N)*; *HAE-DAB2IP (*a GTPase activating scaffold protein involved in a plethora of signaling pathways); *HAE-FXII*; *HAE-HS3OST6 (*heparan sulfate-glucosamine 3-sulfotransferase 6), *HAE-KNG1 (kininogenase)*; *HAE-MYOF (Myoferolin)*; *HAE-PLG (Plasminogen)*; *HAE-UNK* (unknown cause).

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Christiansen SC, et.al. Hereditary Angioedema With Normal C1 Inhibitor: A Quarter Century of Forward Progress and Persisting Obstacles. J Allergy Clin Immunol Pract. 2025 Jun;13(6):1300-1309.

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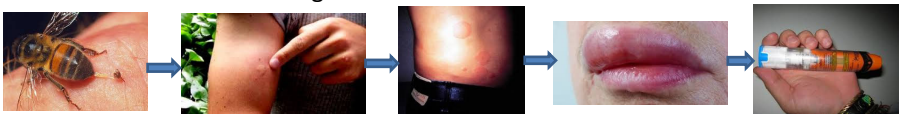
Case Presentation 1

- 30 year-old male gardening was stung by an honeybee
- Immediately started swelling as the site of sting; stinger removed
- Within 20 minutes developed diffuse hives, lip swelling, chest tightness, difficulty swallowing and dizziness
- 911 called; epinephrine administered along with diphenhydramine IM on way to ED; in ED IV corticosteroids also administered
- Symptoms resolved within 30 minutes but several hours later in the ED the patient had recurrence of hives and lip swelling; epinephrine IM re-administered
- Symptoms resolved; patient discharged home after 23 hour observation and referred to an Allergist for further evaluation



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Anaphylaxis in the USA

- Food (29.6%)
  - 86% of all cases in children
  - Peanut is #1 cause
- Insects (11.1%)
- Medications (22.2%)
  - adults
- Others (7.4%)
- Unknown (29.6%)

Fatal anaphylaxis in the UK

- Medication (44%)
- Foods (31%)
- Insect stings (23%)
- Other (4%)

Epinephrine was given for 62% of fatal reactions but to only 14% of pts. before arrest!

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Manivannan V, et al. Ann Allergy Asthma Immunol 2009; 103:395-400.
Pumphrey R. J. Clin. Pathol 2000; 53: 273-6.

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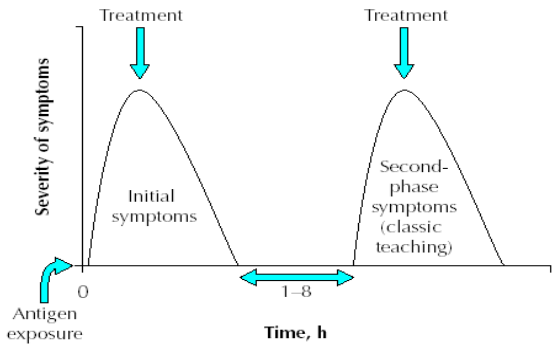
Biphasic anaphylactic reactions

1-23 % of anaphylactic episodes
Late phase: begin 1-10 hours post-allergen



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Acute Treatment of Allergic Angioedema

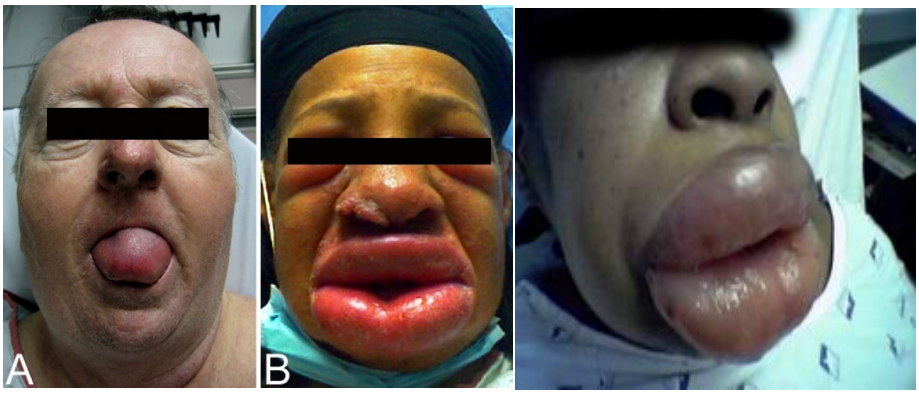
- Histamine-mediated
- Administer IM/SC epinephrine (1:1000) or intranasal epinephrine(2mg) for anaphylaxis, respiratory distress or laryngeal edema[1,2,3,4]
  - Adults: 0.2 to 0.5 mL (mg)/ Children: 0.01 mL (mg/kg); for intranasal epi 4 yrs and older (wt 15-29kg) 1mg with repeat dose after 5 minutes); greater 30kg same as adult dose
  - May need second dose for late phase reaction
- Antihistamines
  - Effective for most cases[1]
  - Diphenhydramine IM/IV for more severe reactions[5,6]
- Corticosteroids
  - Indicated for laryngeal edema and for poor antihistamine responders[1]
  - Does not always prevent late phase reactions

1. Winters M.. American Academy of Emergency Medicine Position Statement 2006. Available at: http://www.aaem.org/emtopics/urticaria_angioedema.pdf. Accessed on January 19, 2011.
2. Simons F, et al. *WAO Journal*.2011;4:13-47.
3. Lieberman P, et al. *J Allergy Clin Immunol*. 2005;115(suppl):S483-S523.
4. Lieberman P, et al. *J Allergy Clin Immunol*. 2010:126:477-80.
5. Frigas E, Park MA. *Am J Clin Dermatol*. 2009;10(4):239-50.
6. Kaplan AP, Greaves MW. *J Am Acad Dermatol*. 2005;53(3):373-88.

Case Study Presentation 2

- 46-year-old female presents to the ED with angioedema of the lips and tongue that had been present when she awoke
- She has had 2 other episodes in the past 3–4 weeks which were milder and resolved on their own after 2–3 hours without medication
- She has no associated urticaria and there were no known triggers for the onset of the swelling
- Hypertension, GERD, high cholesterol, with no history of allergies or asthma
- Medications: lisinopril 10 mg qd for the past 6 months, omeprazole, and simvastatin

ACE Inhibitor-Induced Angioedema (ACEI AE)



1. http://www.maricopaemergencymedicine.com/gallery/CaseImage/28/28_xlarge.jpg
2. http://www.pharmacy-and-drugs.com/illnessessimages/angioedema.jpg

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ACEI-induced Angioedema (ACEI AE)

- **Epidemiology**
  - ACEI AE rate (FDA AERS): 3.5% to 6.5%[1]
  - In ED, 30% to 46% of AE cases[2-4]
  - Risk highest in first 3 months of ACEIs, but can occur years later[5,6]
- **Presentation**
  - Swelling in face and oral cavity (57%), base of tongue and soft palate (26%), and oropharyngeal area (17%)[7]
  - GI symptoms uncommon but can develop
  - Normal C4
- **Morbidity and mortality**
  - Intubation or airway surgery ranges from 7% to 14%[3,7]
  - Mortality rate is 0.1%[8]

1. *Am J Manag Care*. 2005;11(13 Suppl):S392-4.
2. Bluestein HM, et al. *Ann Allergy Asthma Immunol*. 2009;103:502-7
3. Banerji A, et al. *Ann Allergy Asthma Immunol.* 2008;100:327-32.
4. Sondhi D, et al. *Chest*. 2004;126:400-4.
5. Grigoriadou S, Longhurst HJ. *Clin Exp Imunol*. 2009;155:367-77.
6. Weis M. *Postgrad Med. 2009*; 121: 113-120.
7. Chiu AG, et al. *Ann Otol Rhinol Laryngol . 2001*;110:834-40.
8. Bas M, et al. *Curr Opin Otolaryngol Head Neck Surg*. 2006;14:170-75.

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Is ACE-Induced Angioedema Bradykinin Mediated?

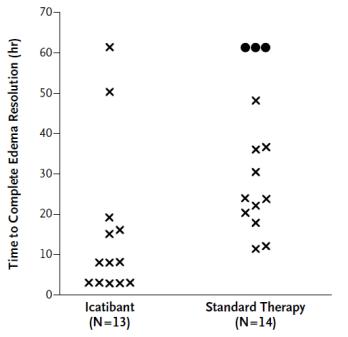
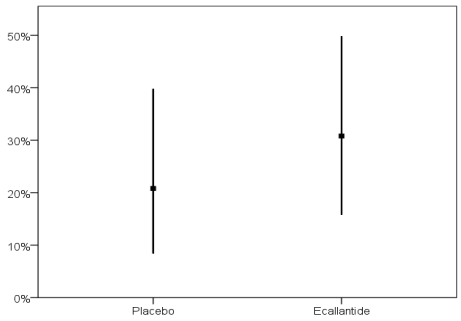


Figure 1. Time to Complete Resolution of Edema, According to Study Treatment.

Bas M, et al. *NEJM*. 2015;372:418.



Proportions Of Patients Meeting Objective Discharge Criteria In Four Hours Or Less With 95% Confidence Intervals For The Placebo And Ecallantide Groups

Bernstein JA, et.al. Ann Allergy Asthma Immunol 2015;114:245-9.

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10/27/2022

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Subsequent Studies

- Ecallantide - Bernstein JA, Moellman JJ, Collins SP, et.al. Effectiveness of ecallantide in treating angiotensin-converting enzyme inhibitor-induced angioedema in the emergency department. Ann Allergy Asthma Immunol. 2015 Mar;114(3):245-9.
- Icatibant - Sinert R, Levy P, Bernstein JA, et.al.. Randomized Trial of Icatibant for Angiotensin-Converting Enzyme Inhibitor-Induced Upper Airway Angioedema. J Allergy Clin Immunol Pract. 2017 Sep-Oct;5(5):1402-1409.
- Tranexamic Acid - Hasara S, Wilson K, Amatea J, Anderson J. Tranexamic Acid for the Emergency Treatment of Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema. Cureus. 2021 Sep 20;13(9):e18116.

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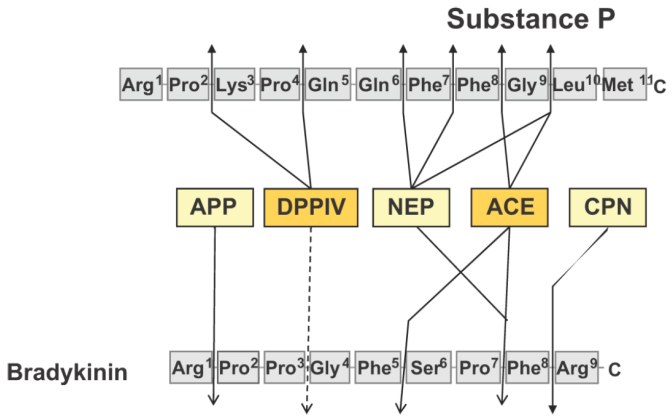
Role Of ACE And Dipeptidyl Peptidase-iv In Degradation Of Bradykinin And Substance P



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Brown NJ, et.al. Dipeptidyl peptidase-IV inhibitor use associated with increased risk of ACE inhibitor-associated angioedema. Hypertension. 2009 Sep;54(3):516-23.

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Acute Treatment of ACEI AE

- Discontinue ACEI[1,5]; even after discontinuation recurrent angioedema can occur for several weeks or months
- Administer epinephrine for respiratory distress[2]; not effective for angioedema[5]
- Antihistamines and corticosteroids not effective[1,3]
- Fresh frozen plasma reported to be effective
- C1-INH has shown efficacy in case reports[4,5,6]
  - Tongue and facial edema, dyspnea, and dysphagia resolve within 20 minutes[6]
- Icatibant (bradykinin receptor antagonist)[1] and Ecallantide (kallikrein inhibitor)[1]
  - Approved as on-demand therapy for HAE
  - Recent single site study demonstrating efficacy for Icatibant[1]; multicenter studies for icatibant and ecallantide not effective

1. Bas M, et al. *NEJM*. 2015;372:418.
2. Nielsen EW, Gramstad S. *Acta Anaesthesiol Scand*. 2006;50:120-2.
3. Steinbach O, et al. *Anaesthesiol Reanim*. 2001;26:133-7.
4. Gelée B, et al. *Rev Med Interne*. 2008;29:516-9.
5. Moellman JJ, Bernstein JA, Lindsell C, et. al. Acad Emerg Med. 2014; 21: 469-84.
6. Bernstein JA, et.al. Ann Allergy Asthma Immunol 2015;114:245-9.

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Case Presentation 3

- 30 year-old female presents with a history of recurrent swelling of the face, neck, hands and feet, abdomen with occasion throat swelling sensation
- Notices symptoms worse with menses, stress or after trauma; associated with a rash preceding the swelling episodes
- Mother, aunt and two sisters with similar symptoms
- At age 19 had an emergency appendectomy for an acute abdomen

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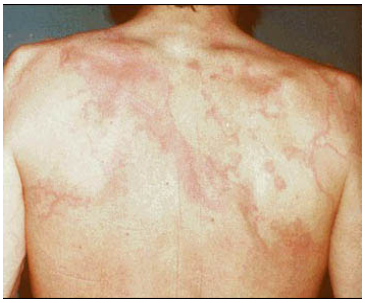
Before and After Angioedema Episode

Erythema Marginatum



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Clinical Features of HAE

- Severe angioedema without hives
- Age of onset varies between studies; 5- 11 years of age
- Face including mouth, tongue, airway, arms, legs, stomach, genitourinary tract
  - May be mistaken for rupture of appendix or other causes that lead to unnecessary surgery
  - May have prodromal symptoms; triggers variable
- Attacks last several days
  - Usually gets worse over 24 hours, and improves in 2–4 days without treatment
  - No improvement with antihistamines, corticosteroids, or epinephrine

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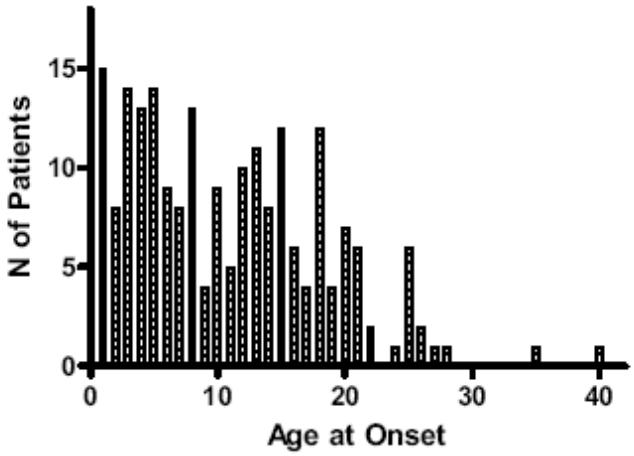
Age at Onset of HAE



Bork K, et.al. Am J Medicine 2006;119,267-274.

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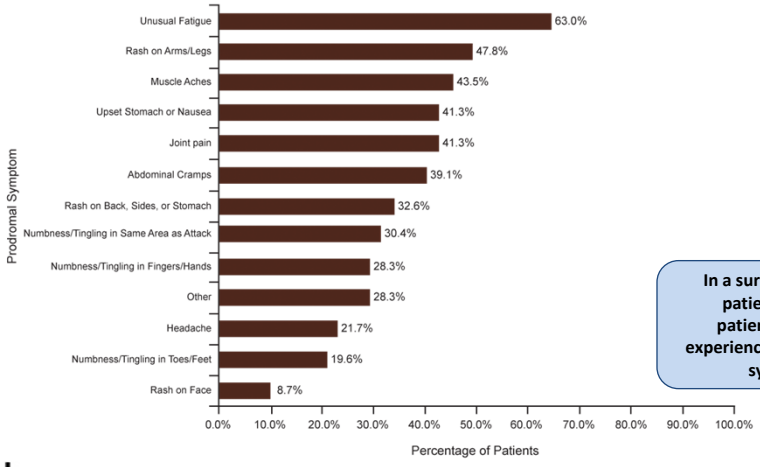
Most HAE Patients Report Prodromal Symptoms

Prodromal Symptoms Reported by Patients Before Their Last Acute HAE Attack



In a survey of 46 HAE patients, 87% of patients reported experiencing a prodromal symptom

Prematta MJ, et al. *Allergy Asthma Proc*. 2009;30(5):506-511.

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HAE triggers

- Attacks not always predictable and may not be in the same place/intensity
  - Disease may vary in family members
  - Stress, physical trauma, infection, medical/dental procedures, menstruation
- Medications that may worsen HAE
  - Oral contraceptives with estrogen
  - Hormone replacement therapy
  - ACE-inhibitors
- 60% of attacks unidentifiable triggers

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Sites of Edema[1,2]

- Head and Neck
  - Face
  - Tongue
  - Pharynx
  - Larynx
  - Subglottis
  - Lips
- Extremities
- Gastrointestinal tract
- Genital region

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1. Megerian CA, et al. *Laryngoscope*. 1992;102(3):256-260.
2. Bas M, et al. *Allergy*. 2007;62(8):842-856.

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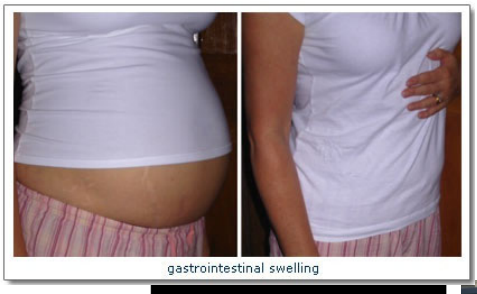
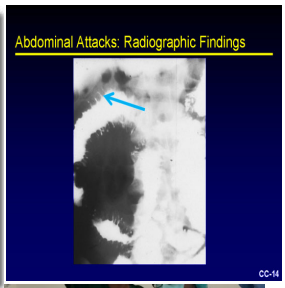
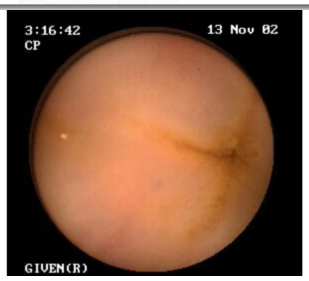
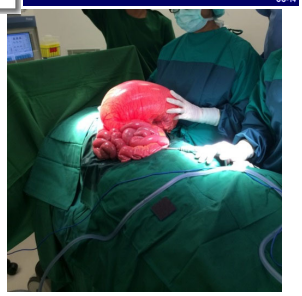
Abdominal Swelling


gastrointestinal swelling







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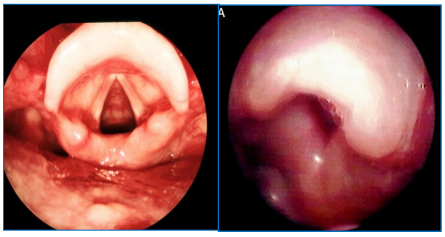
Upper Airway Edema

- Inspection by indirect Laryngoscopy or flexible nasal endoscopy



- 94% of patients experience swelling of head and neck
  - 50% of patients will have a laryngeal attack at some time in their life
  - About 18% require intubation[1]
- First attack can be laryngeal
- Most common cause of death due to asphyxiation

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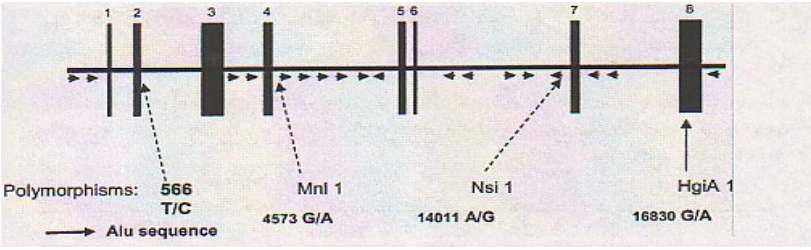
C1INH Gene and Mutation Sites



- Located on chromosome 11, consists of 8 exons and 7 introns and is approximately 1.7 x 10^4 base pairs in length
- 25% of cases are spontaneous mutations without a family history

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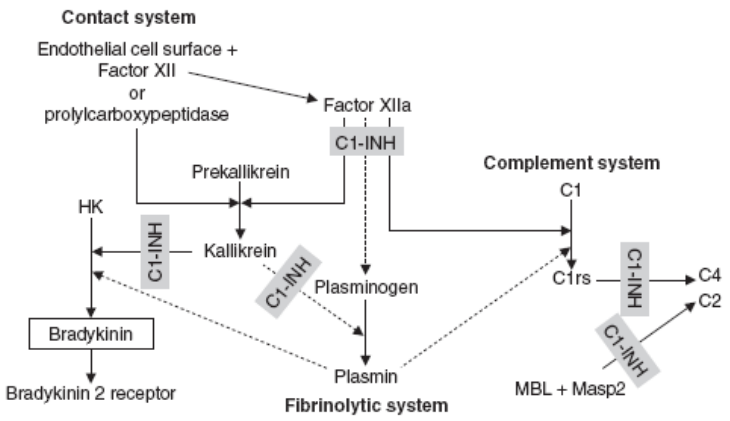
Biologic Role of C1-Inhibitor



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Diagnosis: C1INH and Complement Levels in Angioedema

	C1INH antigen	C1INH function	C4	C2	C1q	Auto-antibody
HAE Type I *85% of cases	↓	↓	↓	↓	NI	Absent
HAE Type II *15% of cases	NI or ↑	↓	↓	↓	NI	Absent
HAE with NI complement (akaType III)	NI	NI	NI	NI	NI	Absent
Acquired Angioedema	NI or ↓	↓	↓	↓	↓	Present
ACE Induced Angioedema	NI	NI	NI	NI	NI	Absent
Idiopathic	NI	NI	NI	NI	NI	Absent

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Genetic Testing

- SERPING1 gene
  - only definitive way to differentiate HAE patients without family history and genetic mutation from Acquired Angioedema
- Factor XII enzyme mutation and other mutations in HAE with normal complement
  - Rarely found in the US thus far; middle European ancestry
- Expensive and not always approved by insurance

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Criteria for HAE C1INH-nl

1) Age at onset - Often teenage to young adult.
2) Hives as part of disorder - No
3) Family history of angioedema - Usually yes
4) C1INH function - Normal
5) Identified pathogenic variant – Yes
6) Response to mast cell directed treatment - No

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Genes With Pathogenic Variants Linked To HAE C1INH Normal

Disorder	Gene	OMIM No.	Protein	Complementary DNA	Protein	Reference
HAE-C1INH	*SerpinG1*	106100	C1INH	many	many	8
HAE-FXII	*F12*	610618	Coagulation FXII	c.983C>A	p.Thr328Lys	14
HAE-FXII	*F12*	610618	Coagulation FXII	c.983C>G	p.Thr328Arg	14
HAE-FXII	*F12*	610618	Coagulation FXII	c.971_1018+24 del72	del	15
HAE-FXII	*F12*	610618	Coagulation FXII	c.892_909dup	p.Pro298_Pro303dup	16
HAE-PLG	*PLG*	619360	Plasminogen	c.988A>G	p.Lys330Glu	17
HAE-KNG1	*KNG1*	619363	Kininogen	c.1136T>2	p.Met379Lys	18
HAE-ANGPT1	*ANGPT1*	619361	Angiopoietin 1	c.807G>T	p.Ala119Ser	19
HAE-MYOF	*MYOF*	619366	Myoferlin	c.651G>T	p.Arg217Ser	20
HAE-HS3OST6	*HS3OST6*	619367	3-OST-6	c.430A>T	p.Thr144Ser	21
HAE-CPN1	*CPN1*	Not available	Carboxypeptidase N	c.533G>A	p.Gly178Asp	22
HAE-CPN1	*CPN1*	Not available	Carboxypeptidase N	c.582A>G	p.Glu194= (splice)	22
HAE-CPN1	*CPN1*	Not available	Carboxypeptidase N	c.734C>T	p.Thr245Met	22
HAE-DAB2IP	*DAB2IP*	Not available	Disabled homology 2 interacting protein	c.715G>A	p.Asp239Asn	23
FACAS	*F12*	Not available	Coagulation FXII	c.859T>A	p.Trp268Arg	24

Christiansen SC, et.al. Hereditary Angioedema With Normal C1 Inhibitor: A Quarter Century of Forward Progress and Persisting Obstacles. J Allergy Clin Immunol Pract. 2025 Jun;13(6):1300-1309.

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Proposed Biomarker Assays

C1INH level	Relatively easy to perform; critical for diagnosis of HAE-C1INH and AC1D	Antigenic level may give deceiving result; can show false positive or negative; can be influenced by treatment
C4 level	Important for diagnosis of HAE-C1INH and ACID	Substantial variability in the general population; can be influenced by treatment
Protease–inhibitor complexes	Relatively easy to measure as biomarker of contact system activation; may be useful as novel assay for C1INH function	Complexes are short-lived in vivo; subject to ex vivo artifact; may be artificially low in C1INH deficiency
Cleaved protease	Directly reflects contact system activation	Difficult to measure, requires immunoblotting or antibody to neoepitope; subject to ex vivo artifact
Kallikrein activity	Relatively simple and straightforward assay; able to be standardized	Spontaneous activity subject to ex vivo artifact; activity not completely specific
Cleaved HMWK	Relatively stable biomarker of contact system activation; moderately sensitive	Difficult to measure, requires immunoblotting or antibody to neoepitope; subject to ex vivo artifact
Bradykinin level	Theoretically the best biomarker of contact system activation	Very difficult to measure; extremely short half-life of peptide; subject to ex vivo artifact
Fibrinolysis	Easy to measure; may reflect primary or secondary events in contact system activation	Very nonspecific and subject to variability
TSKA, cold activation, sgp120	Biomarkers to confirm the diagnosis of HAE-nl-C1INH and other forms of non-mast cell-mediated angioedema	Not commercially available. Unlikely to detect variants such as HAE-PLG which is thought to bypass the contact system cascade

Christiansen SC, Zuraw BL. Contact System Activation and Bradykinin Generation in Angioedema: Laboratory Assessment and Biomarker Utilization. Immunol Allergy Clin North Am. 2024 Aug;44(3):543-560.

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Goals of Management and Treatment

- Reduce HAE morbidity and mortality by making an early and accurate diagnosis
- Treatment should be individualized to the patient's needs
  - On demand vs. prophylactic
- HAE patients should be followed by a specialist familiar with HAE involved in their care
- Optimal care should attempt to restore a normal quality of life to the patient

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Cicardi M, et.al. Allergy 2012;67(2):147-57.

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Categories of Treatment

- **Acute "on-demand" treatment**

  To ameliorate symptoms of angioedema

- **Short-term prophylaxis**

  To protect against a likely attack

- **Long-term prophylaxis**

  To minimize the frequency/severity of attacks

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On Demand Treatment

- C1 – Inhibitor replacement therapy
  - Plasma derived
  - Recombinant
- B2K antagonist – icatibant (branded and now 8 biosimilars)
- Kallkrein inhibitor – Ecallantide
- Oral kallikrein inhibitor – sebetralstat (Ekterly™)
- Oral BK2 receptor inhibitor - deucribtibant

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Short-Term Prophylaxis: A Clinical Decision

- Short-term prophylaxis should be based on an individualized assessment of harm/burden compared with benefit, cost considerations, and patient values and preferences.
- When trauma is expected to be minimal and on-demand therapy is readily available, deferring pre-procedural treatment in favor of observation for first signs of an attack with rapid treatment can be an alternative management strategy.
- For emergent procedures and in pregnant patients, administration of plasma derived C1 inhibitor is preferred.
- On-demand acute treatment drug (plasma derived C1 inhibitor, ecallantide or icatibant) should always be readily available in case it is needed especially for dental procedures or surgical procedures requiring intubation.

Zuraw B, Bernstein JA, Lang D, et.al. J Allergy Clin Immunol. 2013 Jun;131(6):1491-3.
Nanda MK, et.al. Ann Allergy Asthma Immunol 2014 Aug;113(2):198-203.

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Long Term Prophylaxis

- C1 Inhibitor subq – Haegarda
- Kallikrein inhibitor – Lanadelumab (Takhyzro)
- Oral kallikrein inhibitor – Berotralstat (Oledayo)
- Prekallikrein anti-sense directed oligonucleotide inhibitor – Donidalorsen (Dawnzera)
- Factor 12a inhibitor – Garadacimab (Andembry)
- Intellia –(NTLA-2002), uses CRISPR technology to inactivate the kallikrein B1 (KLKB1) gene, which encodes for prekallikrein
- Long acting kallikrein inhibitors (Astria)
- Small interfering RNA that targest mRNA for prekallikdrein (ADARx)

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Case Presentation 4

- 69 year old female presents with recurrent lip and tongue edema initially once very 3 months but now occurring on a weekly basis
  - No hives
  - No known triggers
  - No prodrome
  - No family history
  - No ACE inhibitors

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Evaluation and Diagnosis

- C4 - 8 (low)
- C1INH functional - <40 (low)
- C1INH protein - 9 (low)
- C1q - 6 (low)

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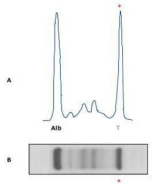
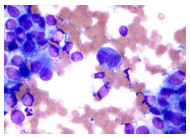
Further Evaluation

- SPEP – M spike



- Bone marrow biopsy consistent MGUS



- C1INH antibody 245 (normal 0-36)
- Dx: Acquired Angioedema

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Acquired Angioedema

- Onset > 40 years old

Table 1 Differences between acquired and hereditary angioedema due to C1-INH deficiency

	Onset < 20 y.o. % pts.	Onset >40 y.o. % pts.	Abdominal % pts.	C1q < 50% %pts
Acquired angioedema	0	94	48	70
Hereditary angioedema	12	3	87	< 5

Data are based on a personal case list of 43 patients with acquired and 448 with hereditary angioedema.

- Incidence: 1:100,000 to 1:500,000
- No family history
- Associated with MGUS, lymphoproliferative disease (type 1) and/or autoantibody to C1INH (type 2)
- No genetic mutation in SERPING1 gene

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Cicardi M, et.al. Allergy Asthma Clin Immunol.2010 Jul 28;6(1):14.

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Laboratory testing

- C4, C1INH function and antigen levels below 50% of normal

(Agostoni J allergy Clin Immunol 2004; Zingale Immunol Allergy Clin N Am 2006; Cicardi and Zanichelli Allergy Asthma Clin Immunol 2010)

  - Temporary normalization of one of these parameters has been reported

(Spath Arch Intern Med 1989)

- Low C1q
  - 70% of patients **(Cicardi Allergy Asthma Clin Immunol 2010)**
  - Review of the 168 cases of AAE shows that the C1q value is normal in 10 cases and diminished in 94 cases **(Breitbart Allergy Asth Proc 2010)**
- Presence of anti-C1INH antibodies in 71 out of 136 pts

(Zingale Immunol Allergy Clin N Am 2006)

  - tested only in few specialized research labs!

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Is C1q a reliable marker for AAE?

TABLE 1. Genetic and clinical data of our 13 unrelated Japanese patients with HAE

Family	Traditional genomic numbering	cDNA numbering	Effect on protein	Location	Clinical type	C4 level	C1q level	References
1	638G>T	c.51 + 1G>T	Splicing defect	Intron 2	Type 1	Low	[a]	25
2	2281_2350del70	c.137_206del70	Frameshift	Exon 3	[a]	Low	[a]	This study
3	2611C>A	c.467C>A	A134D	Exon 3	[a]	Low	Normal	25
4	8728T>G	c.895T>G	W277G	Exon 6	Type 1	Low	Low	This study
5	8831C>A	c.996C>A	A311D	Exon 6	[a]	Low	[a]	This study
6	14030G>C	c.1030-1G>C	Splicing defect	Intron 6	[a]	Low	Normal	35
7	14058insT	c.1057insT	Frameshift	Exon 7	[a]	Low	[a]	26
8	14158delT	c.1157delT	Frameshift	Exon 7	Type 1	Low	[a]	This study
9	16661T>G	c.1269T>G	Y401stop	Exon 8	[a]	Low	[a]	This study
10	16788C>T	c.1396C>T	R444C	Exon 8	Type 2	Low	Normal	36
11	16789G>T	c.1397G>T	R444L	Exon 8	[a]	Low	Normal	37
12	16885C>A	c.1493C>A	P476H	Exon 8	Type 1	Low	Low	This study
13	Large deletion (at least 1 kb-length deletion including exon 4)				Type 1	Low	Low	This study

[a] Undetermined.
cDNA, complementary DNA.

Yamamoto T et.al. Am J Med Sci 2012;343(3):210–214.

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Is current terminology of type 1 and type 2 correct?

n	Sex	Present age (years)	Age at diagnosis (years)	Age at onset (years)	Length of follow up (years)	Disease at onset	Disease at follow-up	Anti C1-INH	Monoclonal component
1	M	86	72	72	10	No associate disease	No associate disease	Ig G k	none
2	M	78	60	57	16	No associate disease	No associate disease	Ig G k	none
3	M	62	58	58	4	No associate disease	No associate disease	Ig G k	none
4	F	58	47	40	11	No associate disease	No associate disease	IgA	none
5	F	65	56	56	1	No associate disease	No associate disease	IgM	none
6	F	57	53	54	2	No associate disease	No associate disease	IgG	none
7	F	57	56	49	1	No associate disease	No associate disease	none	none
8	F	75	74	74	1	No associate disease	No associate disease	none	none
9	M	84	70	67	14	No associate disease	MGUS	IgMκλ	Ig M k
10	F	69	57	56	12	MGUS	MGUS	IgG λ	IgG λ
11	M	83	72	62	11	MGUS	MGUS	IgG λ	IgG λ
12	F	84	79	74	8	No associate disease	MGUS	IgM λ	IgG λ
13	M	50	42	39	8	MGUS	MGUS	IgM/IgGλ	IgG λ
14	M	53	44	44	9	MGUS	MGUS	Ig A λ	IgG λ
15	F	dead	48	40	24	Hydatidosis	MGUS	Ig G k	Ig G k
16	M	61	51	51	4	MGUS	MGUS	Ig M k	Ig M k
17	F	82	73	71	9	MGUS	MGUS	none	IgG K
18	F	60	55	50	5	No associate disease	MGUS	none	IgG λ
19	F	52	48	43	4	MGUS	MGUS	none	IgG λ
20	F	60	59	53	1	MGUS	MGUS	none	IgM k
21	M	69	55	53	14	No associate disease	MGUS	IgA λ	Ig A λ
22	F	69	58	57	11	No associate disease	Large B cell Lymphoma	IgM	none
23	M	dead	53	52	12	No associate disease	Lymphoplasmotic lymphoma	Ig G k	Ig M k
24	M	dead	63	63	15	Mantle cell lymphoma	Large B cell Lymphoma	none	
25	F	81	76	75	5	Lymphocytic lymphoma	Lymphocytic lymphoma	none	none
26	M	dead	55	55	24	No associate disease	Lymphoplasmotic lymphoma	IgM λ	mg M λ
27	F	67	65	60	2	Splenic marginal zone lymphoma	Splenic marginal zone lymphoma	IgM	IgM k
28	F	81	78	66	3	lymphoplasmacytoid lymphoma Waldestrôm's disease	lymphoplasmacytoid lymphoma/ Waldestrôm's disease	Ig M	IgM k
29	F	48	45	45	3	Nodal marginal zone lymphoma	Nodal marginal zone lymphoma	IgM	none
30	F	76	72	71	4	Follicular lymphoma	Follicular lymphoma	none	
31	F	82	81	76	1	No associate disease	Urinary bladder cancer	IgM k	none
32	F	dead	65	63	12	No associate disease	Breast cancer	IgA λ	none

MGUS: monoclonal gammopathy unknown significance; anti C1-INH: autoantibodies anti C1-inhibitor.

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Castelli R, et.al. Haematologica May 2007 92: 716-718.

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Treatment

- Treat underlying lymphoproliferative disorder
  - Doesn't always prevent reoccurrence of angioedema
- Plasmapheresis of anti-C1INH followed by CTX or rituximab
- On demand therapy (icatibant, ecallantide)
- Tranexamic acid more effective than androgens
- C1INH not as effective

Zuraw B, Bernstein JA, Lang D, et.al. J Allergy Clin Immunol. 2013 Jun;131(6):1491-3.
Cicardi M, et.al. Allergy Asthma Clin Immunol.2010 Jul 28;6(1):14.

Summary

- Angioedema can be histamine-mediated or bradykinin mediated
  - Other mechanistic pathways may be involved
- All patients with isolated angioedema should have a C4 level to exclude bradykinin mediated AE (HAE and AAE)
- Previously diagnosed idiopathic angioedema in many cases may have been HAE nl complement angioedema
- Treatment of BK mediated angioedema has dramatically advanced over the past 15 years providing better outcomes for HAE patients
- Whether these treatments will also be beneficial for other non-histaminergic forms of angioedema requires further investigation

Genetic Variants in Angioedema and Associated Biomarkers: Does This Drive Therapeutic Choices?

Marc Riedl MD MS
Professor of Medicine
Division of Allergy & Immunology
University of California, San Diego

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Objectives

- Review subtypes of angioedema based on underlying pathophysiology
- Discuss recent advances in genetics of angioedema
- Summarize emerging diagnostic biomarkers in angioedema
- Discuss impact of diagnostic tests on clinical management of angioedema

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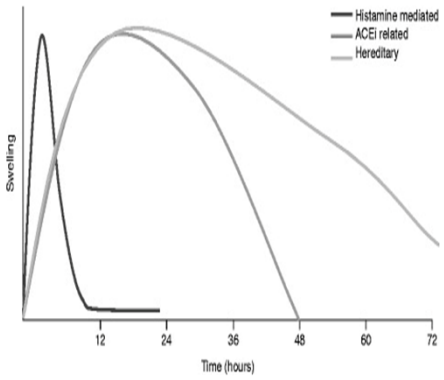
Major Types of Angioedema

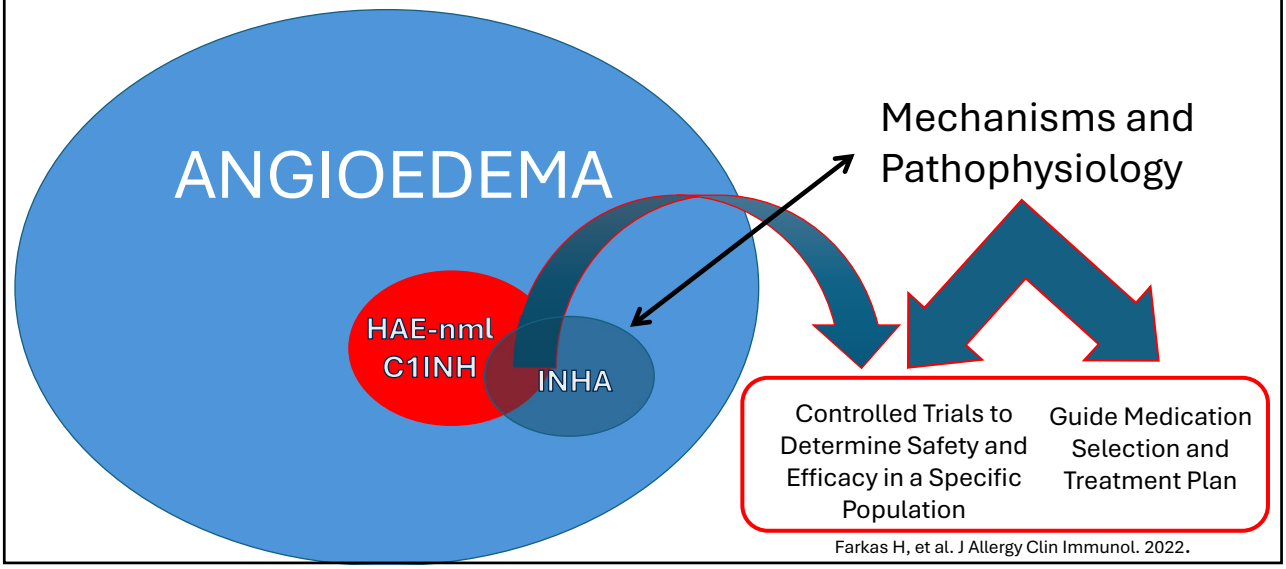
	Histaminergic/ Mast-cell Mediated	Non-histaminergic/Kinin-mediated
Onset/Duration ("Trajectory")	Minutes to hours	Hours
Urticaria	+	-
Pruritis	+	-
Pain/burning	-	May be present
Response to antihistamine	+	-
Response to steroids	+	-



Maurer M, et al. Clin Rev Allergy Immunol. 2021 Aug;61(1):40-4
Bernstein JA, et al. Int J Emerg Med. 2017;10(1):15.

3

The Clinical Challenge in Angioedema: HAE Normal C1INH and Idiopathic Non-histaminergic Angioedema (INHA)

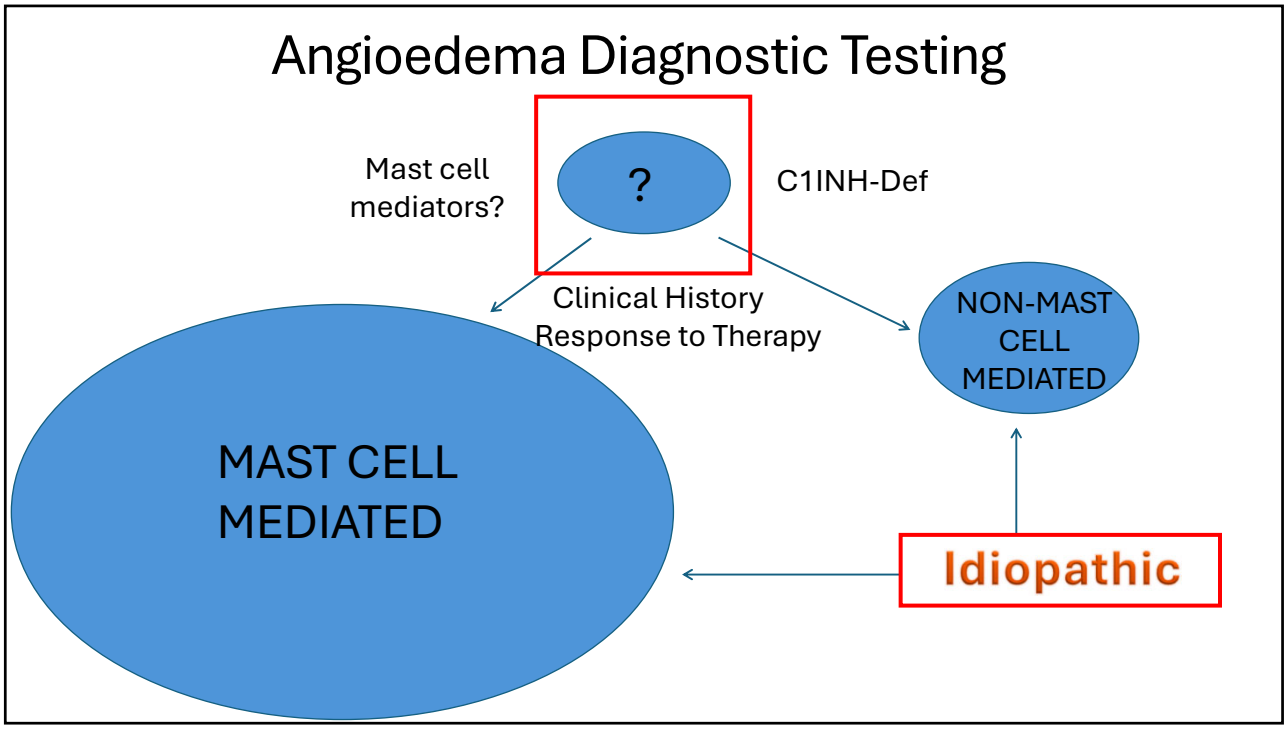


Farkas H, et al. J Allergy Clin Immunol. 2022.

4

RETURN TO AGENDA

Angioedema Diagnostic Testing



5

Causes of Isolated Angioedema

Table 1 *Types of recurrent angioedema diagnosed in 1058 patients examined between 1993 and 2012*

	Patients, *n* (%)	Male, *n* (%)	Female, *n* (%)	Male : female ratio
Hereditary angioedema	377 (36)			
~~C1-INH-HAE~~	~~353 (94)~~		202 (57)	0.75
FXII-HAE	6 (1)	1 (17)	5 (83)	0.2
U-HAE	18 (5)	12 (67)	6 (33)	2
AAE	681 (64)			
~~C1-INH-AAE~~	~~49 (7)~~		31 (63)	0.58
~~ACEI-AAE~~	~~183 (27)~~		76 (42)	1.4
IH-AAE	379 (56)	155 (41)	224 (59)	0.69
InH-AAE	70 (10)	36 (51)	34 (49)	1.06
Total		480 (45)	578 (55)	0.83

5%
95%
84%
16%
20%

C1-INH-HAE, hereditary angioedema (HAE) with C1-inhibitor deficiency; FXII-HAE, HAE with factor XII mutation; U-HAE, HAE of unknown origin; ACEI-AAE, acquired angioedema (AAE) related to angiotensin-converting enzyme inhibitor therapy; IH-AAE, idiopathic histaminergic AAE; InH-AAE, idiopathic nonhistaminergic AAE.

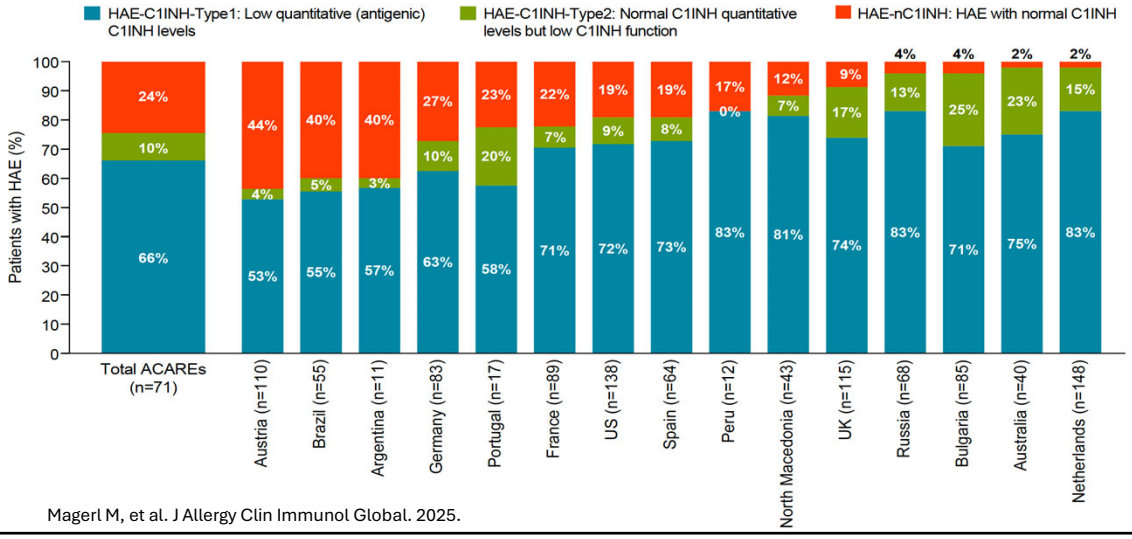
Mansi M, J Intern Med. 2014

6

RETURN TO AGENDA

HAE-Normal C1INH: Prevalence

- International Survey of 30 Angioedema Centers

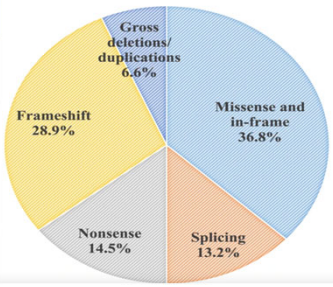


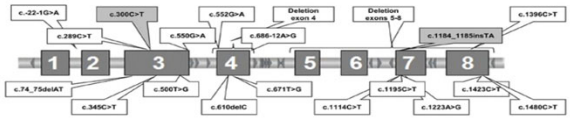
Magerl M, et al. J Allergy Clin Immunol Global. 2025.

7

Categories of HAE

	Type 1	Type 2
Percent of all HAE	~85%	~15%
C4 Level	Low	Low
C1-INH antigenic level	Low	Normal
C1-INH antigenic function	Low	Low





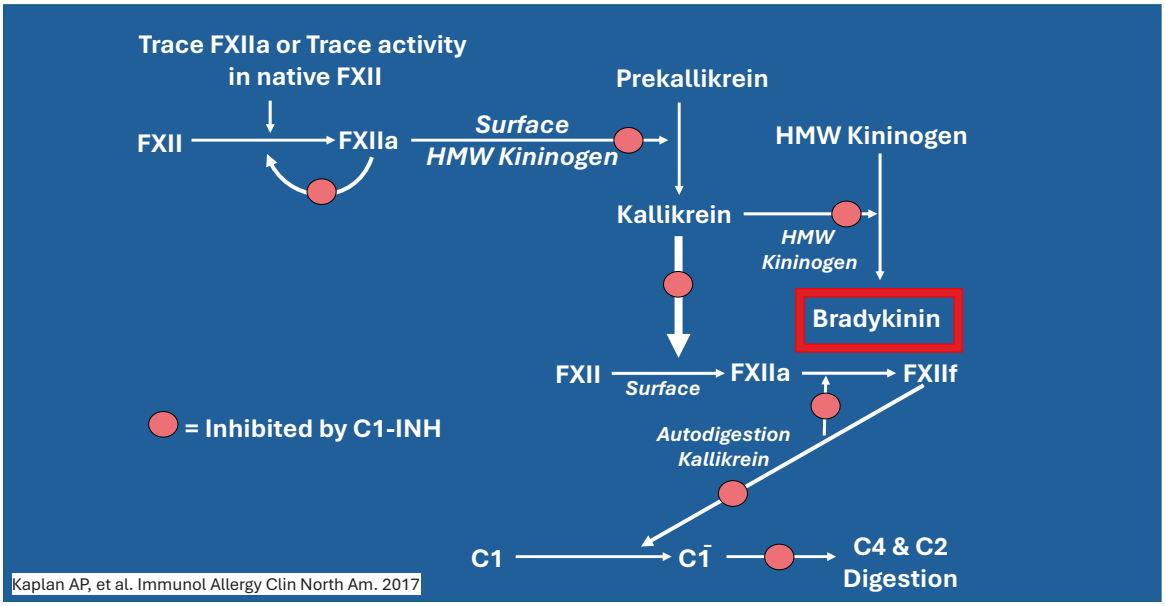
>800 described SERPING1 mutations

Andrejević S, et al. PLoS One. 2015.
Wang, X. et al. Hereditas 2022

8

RETURN TO AGENDA

Hereditary Angioedema Pathophysiology



Kaplan AP, et al. Immunol Allergy Clin North Am. 2017

9

Categories of HAE

	Type 1	Type 2	HAE-Normal C1INH
Percent of all HAE	~85%	~15%	Rare
C4 Level	Low	Low	Normal
C1-INH antigenic level	Low	Normal	Normal
C1-INH antigenic function	Low	Low	Normal

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RETURN TO AGENDA

Advances in Diagnostic Testing for Angioedema

- Genetic Markers
  - C1INH deficiency (SERPING1)
  - HAE-normal C1INH
    - Factor XII
    - Plasminogen
    - Angiopoetin-1
    - Kininogen-1
    - Myoferlin
    - HS3ST6
    - CPN1
    - DAB2IP
- Biochemical Markers
  - C1INH function
    - C1
    - Factor XIIa
    - Kallikrein
  - Threshold Kallikrein Activation
  - Cleaved Kininogen Levels
  - SGP120 Levels
  - Kinin Levels

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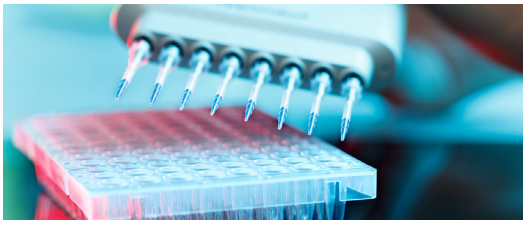
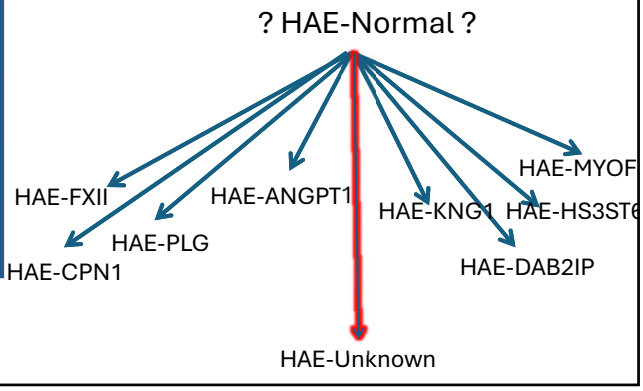
Identification of Genetic Markers

	HAE-Normal C1INH
Percent of all HAE	Rare
C4 Level	Normal
C1-INH antigenic level	Normal
C1-INH antigenic function	Normal





Bork K, et al. J Allergy Clin Immunol Pract. 2023

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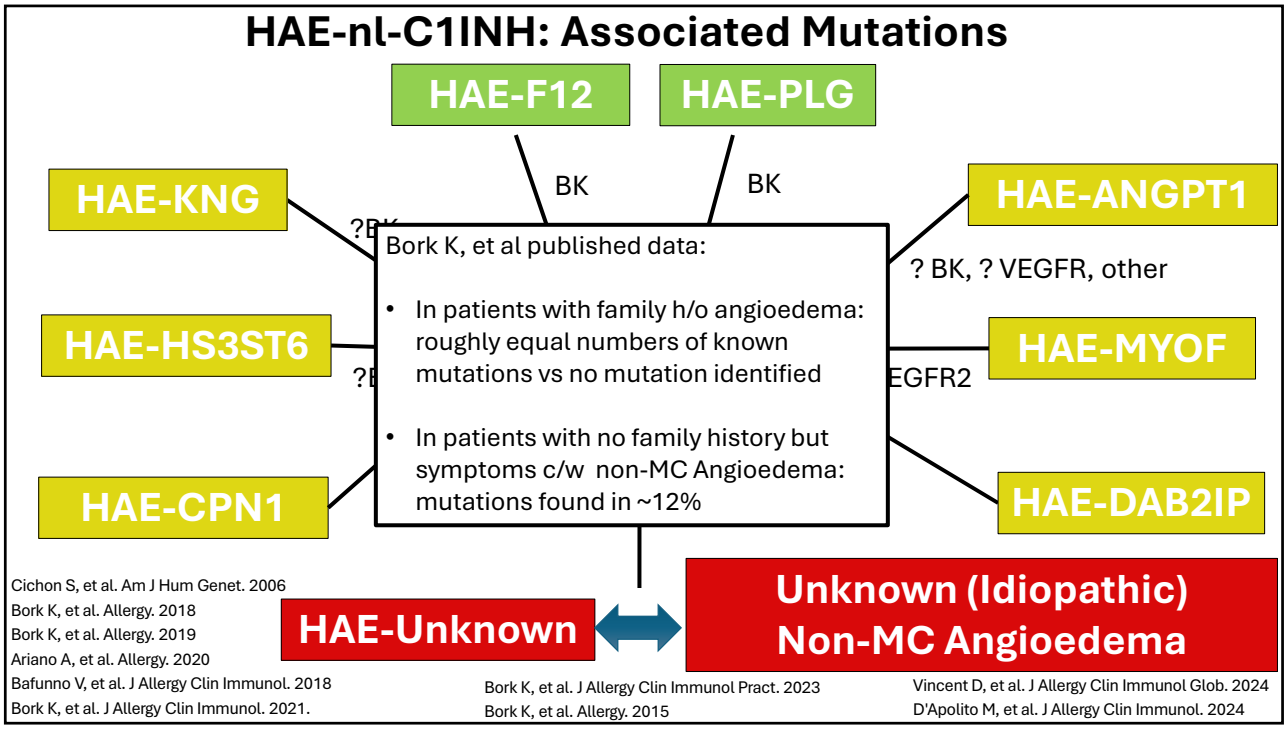
RETURN TO AGENDA



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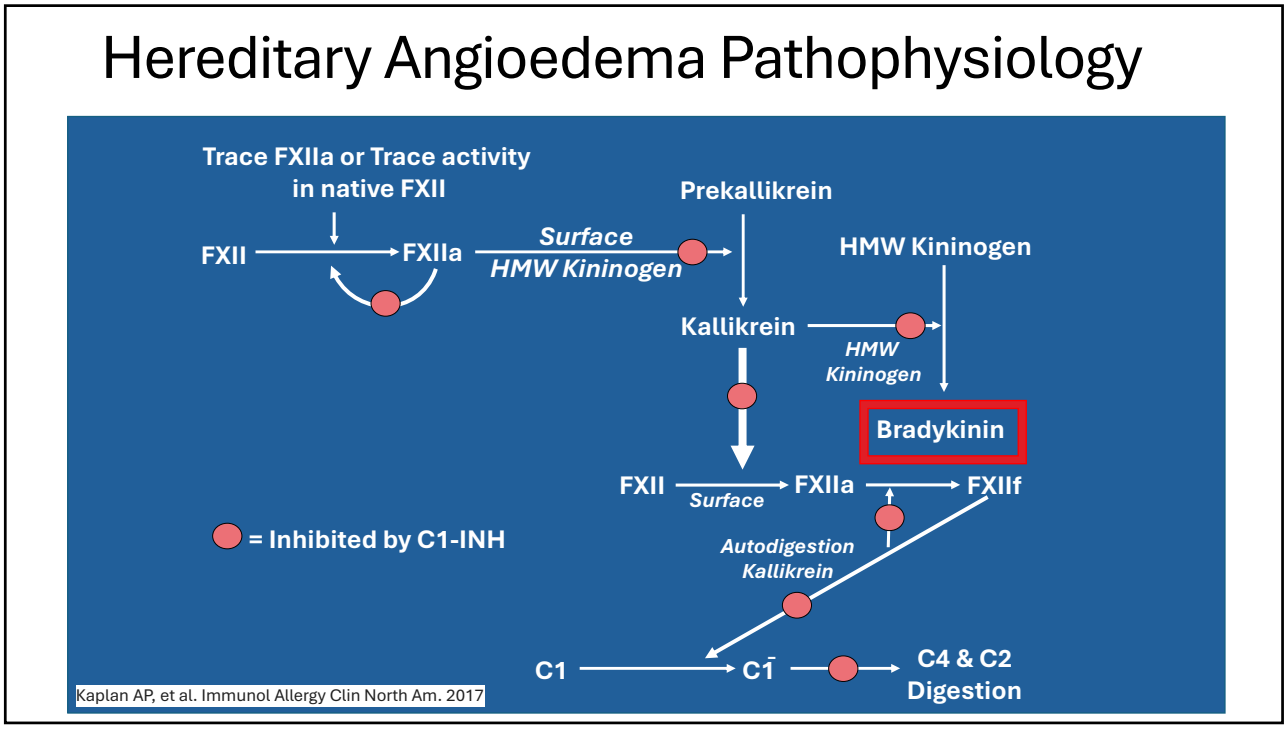

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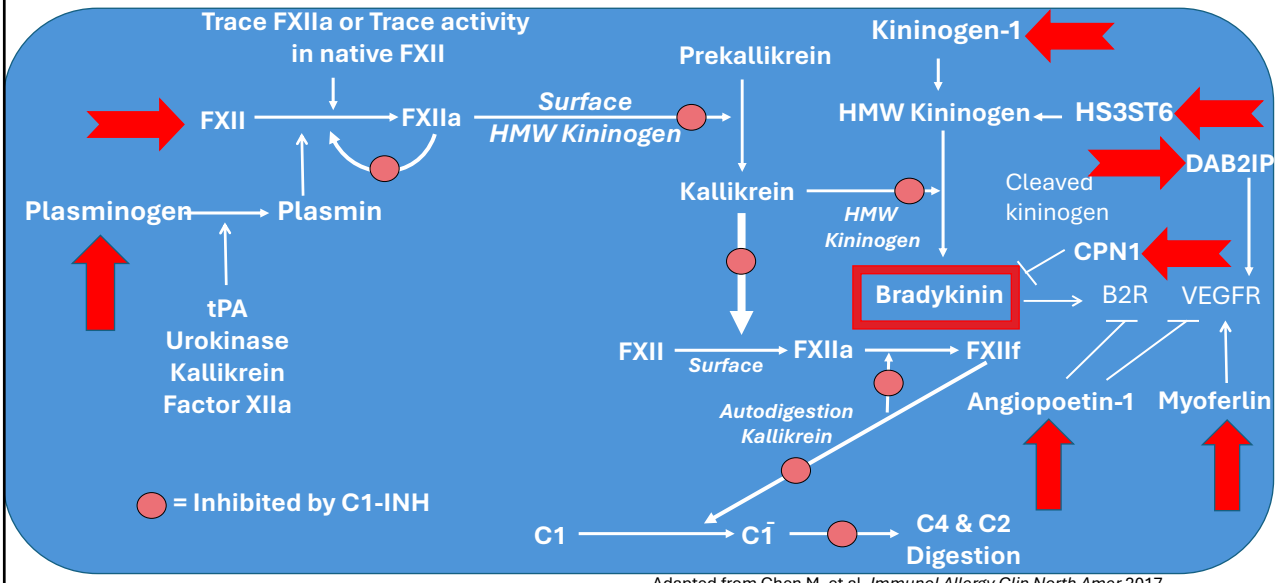
RETURN TO AGENDA

Non-Mast Cell Mediated Angioedema: Contact System and Other Mechanisms



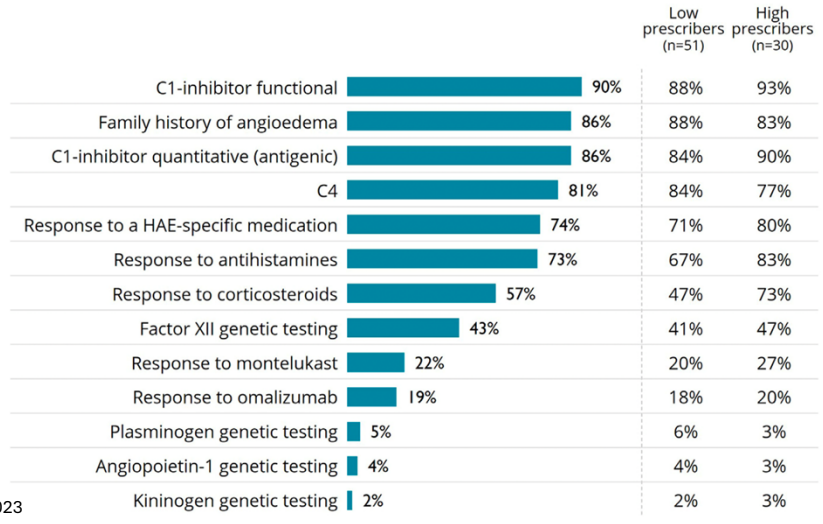
Adapted from Chen M, et al. *Immunol Allergy Clin North Amer* 2017

15

US Physician Survey: HAE-nl C1INH Diagnosis

- 81 Physicians: 100% A/I
- 72% Private Practice
- 28% Academics
- 63% Low-prescribers of HAE medications
- 37% High-prescribers of HAE medications

What assessments are used to inform a diagnosis of HAE-nlC1INH?



Riedl M, et al. J Allergy Clin Immunol Pract. 2023

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RETURN TO AGENDA

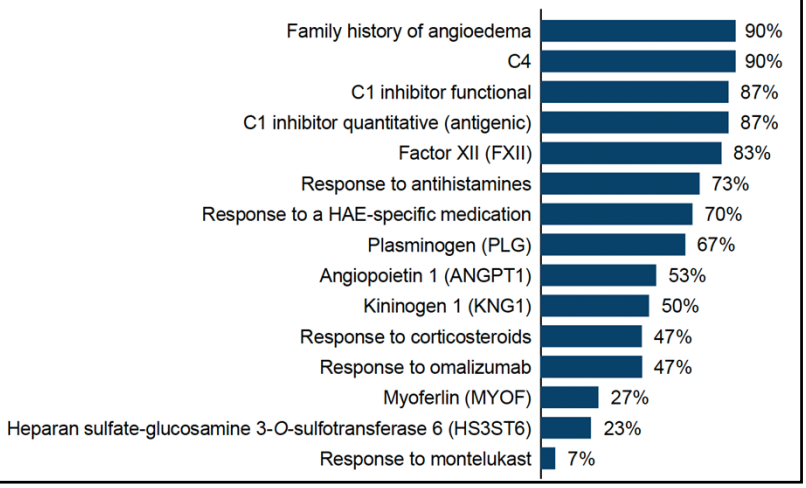
Global Survey on Diagnosis of HAE-nlC1INH

30 Angioedema Referral Centers in 15 countries

Characteristic
Country
Brazil
Germany
France
United States
Argentina
Portugal
Spain
Australia
Austria
Bulgaria
Netherlands
North Macedonia
Peru
Russia
United Kingdom
Specialty
Allergy and/or immunology
Dermatology
Internal medicine
Otolaryngology
Years in practice, mean (range)

Magerl M, et al. J Allergy Clin Immunol Global. 2025.

Diagnostic criteria utilized (n=30)



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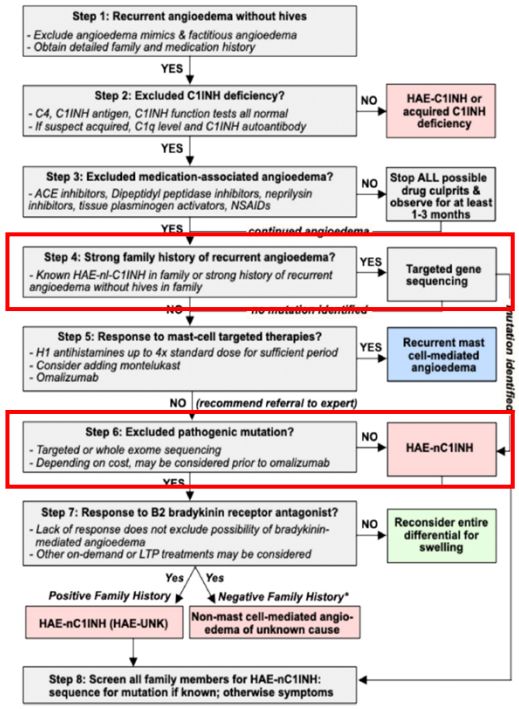
Clinical Reviews in Allergy & Immunology (2025) 68:24
https://doi.org/10.1007/s12016-025-09027-4

REVIEW

Hereditary Angioedema with Normal C1 Inhibitor: an Updated International Consensus Paper on Diagnosis, Pathophysiology, and Treatment

Bruce L. Zuraw[1,2] · Konrad Bork[3] · Laurence Bouillet[4,5] · Sandra C. Christiansen[1] · Henriette Farkas[6] · Anastasios E. Germenis[7] · Anete S. Grumach[8] · Allen Kaplan[9] · Alberto López-Lera[10] · Markus Magerl[11,12] · Marc A. Riedl[1] · Adil Adatia[13] · Aleena Banerji[14] · Stephen Betschel[15] · Isabelle Boccon-Gibod[4] · Maria Bova[16] · Henrik Balle Boysen[17,18] · Teresa Caballero[10,19] · Mauro Cancian[20] · Anthony J. Castaldo[17,18] · Danny M. Cohn[21] · Deborah Corcoran[17,18] · Christian Drouet[22] · Atsushi Fukunaga[23] · Michihiro Hide[24,25] · Constance H. Katelaris[26] · Philip H. Li[27] · Hilary Longhurst[28] · Jonny Peter[29,30] · Fotis Psarros[31] · Avner Reshef[32] · Bruce Ritchie[33] · Christine N. Selva[18] · Andrea Zanichelli[34,35] · Marcus Maurer[11,12]

Fig. 1 Algorithm for diagnosis of recurrent angioedema with normal C1 inhibitor. *Family history may be an unreliable marker of HAE as detailed in the text



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RETURN TO AGENDA

Genetic Markers

HAE-FXII

HAE-PLG

HAE-KNG1

HAE-ANGPT1

HAE-MYOF

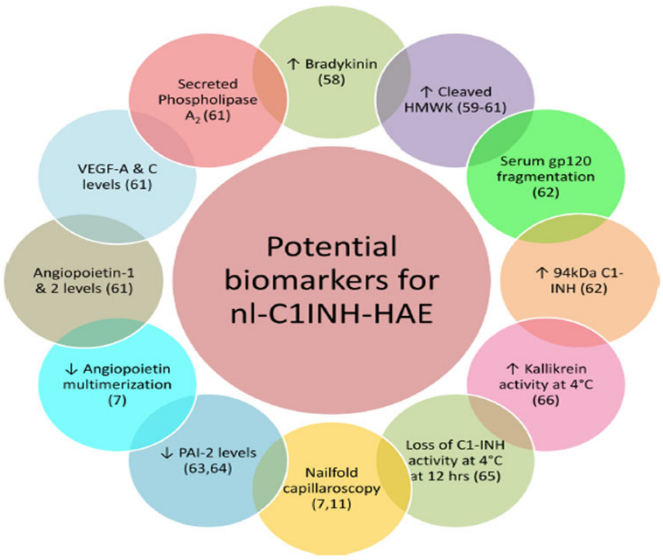
HAE-HS3ST6

HAE-CPN1

HAE-DAB2IP

HAE-Unknown

Biomarkers



Sharma J, et al. Clin Rev Allergy Immuno 2021
Porebski G, et al. Clin Rev Allergy Immuno 2021

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Biomarker Assays Assessing Contact System Activity

A novel assay to diagnose hereditary angioedema utilizing inhibition of bradykinin-forming enzymes

Joseph K. *Allergy*. 2015 Jan;70(1):115-119.

J Allergy Clin Immunol. 2017 Aug 3. pii: S0091-6749(17)31268-X. doi: 10.1016/j.jaci.2017.07.012. [Epub ahead of print]

Cleaved kininogen as a biomarker for bradykinin release in hereditary angioedema.

Hofman ZLM. *J Allergy Clin Immunol*. 2017 Aug 4. pii: S0091-6749.

Threshold-stimulated kallikrein activity distinguishes bradykinin- from histamine-mediated angioedema

Lara-Marquez M. *Clin Exp Allergy* 2018. Jun 29.

Mol Immunol. 2020 Jan 16;119:27-34. doi: 10.1016/j.molimm.2020.01.003. [Epub ahead of print]

sgp120 and the contact system in hereditary angioedema: A diagnostic tool in HAE with normal C1 inhibitor.

Larrauri B[1], Hester CG[2], Jiang H[2], Miletic VD[2], Malbran A[2], Bork K[3], Kaplan A[4], Frank M[2].

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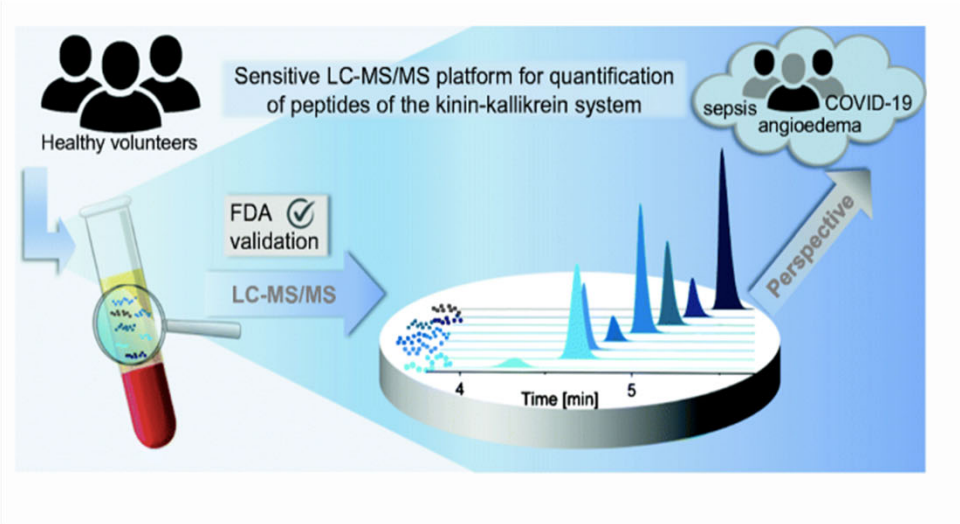
RETURN TO AGENDA

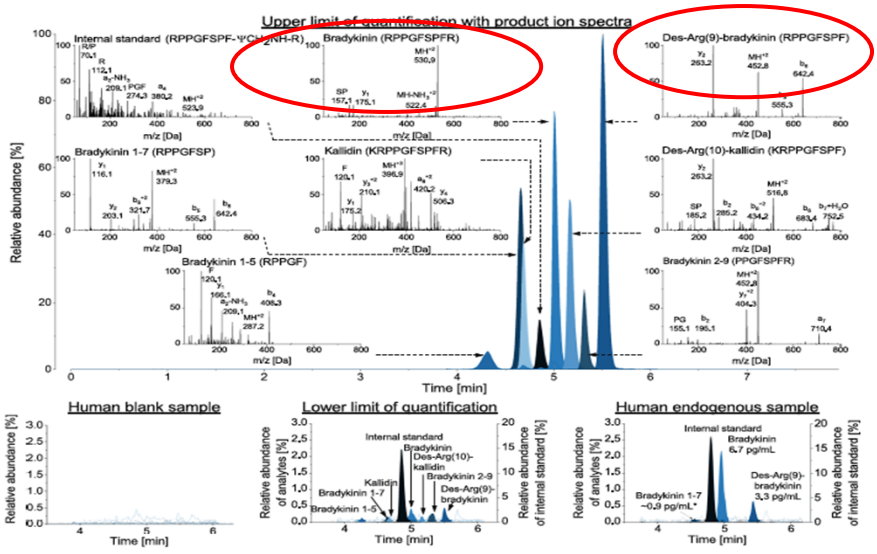
COVID and Renewed Interest in Kinins



Gangnus T, et al. An Bioanal Chem. 2021 May;413(11):2971-2984.

21

Liquid Chromatography with Tandem Mass Spectrometry (LC-MS/MS)



Gangnus T, et al. An Bioanal Chem. 2021 May;413(11):2971-2984.

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Pre-analytical Challenges in Measuring Bradykinin

Advised procedure	
A mixture of 3 mg/mL hexadimethrine bromide, 19.8 µM nafamostat, 83 mM EDTA, 20 mM citrate, 1% formic acid, 1 µM omapatrilat, and 1 mM chloroquine was found to be effective.[22]	
Butterfly-winged needles with a needle size of 21G are advisable.	
Polypropylene tubes with size from 1.2 up to 9 mL possible.	
Use the aspiration technique applying a constant move, rapidly perform sampling of blood and avoid any time delays after venipuncture.	
Centrifuge within 30 min after blood collection.	
Apply 2,000 *g* for 10 min at 21°C.	
Plasma storage	• 1.5 h on the benchtop at 21°C • At least 4 weeks at −80°C • 2 freeze-thaw cycles (−80°C–21°C) confirmed using the developed protease inhibitor.[21]

Gangnus T, et al. Res Pract Thromb Haemost. 2022 Jan 12;6(1).

23

Bradykinin-related Peptides in Plasma of Individuals with HAE-C1INHdef

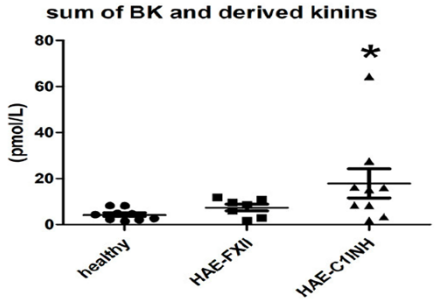

TABLE 1 | Summary of the pilot study (all HAE patients seen in remission).

Group	Age ± S.E.M.	Number of subjects	Number of female subjects	Sum of BK and fragments ± S.E.M. (pmol/L) *
Healthy volunteers	53.8 ± 4.7	9	7	4.3 ± 0.8
HAE-FXII	37.6 ± 4.7	7	6	7.4 ± 1.5
HAE-C1INH	50.1 ± 6.4	9	7	18.0 ± 6.3

Marceau F, et al. Front. Allergy 2022.

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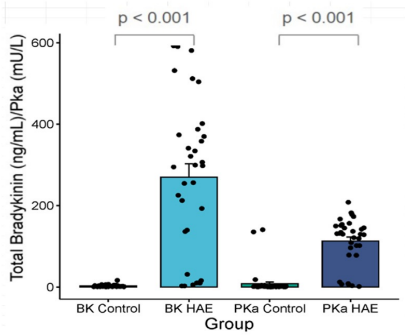
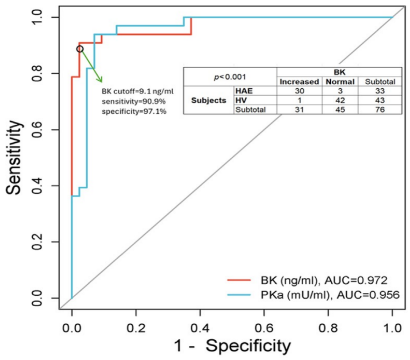
Bradykinin Measurement in C1INH Deficiency

A



D



B

Control p<0.001		BK		
		Increased	Normal	Subtotal
PKa	Increased	1	2	3
	Normal	0	40	40
	Subtotal	1	42	43

C

HAE Patients p=0.03		BK		
		Increased	Normal	Subtotal
PKa	Increased	28	2	30
	Normal	2	1	3
	Subtotal	30	3	33

Chen J, et al. J Allergy Clin Immunol Glob. 2025 Jun

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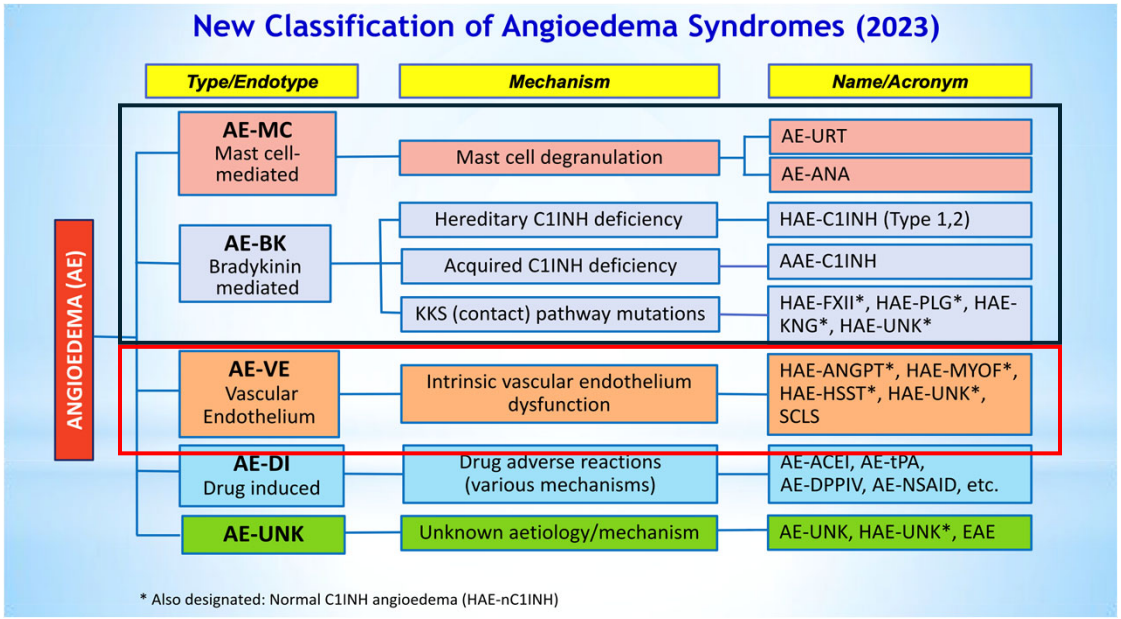

Reshef A, et al. J Allergy Clin Immunol 2024

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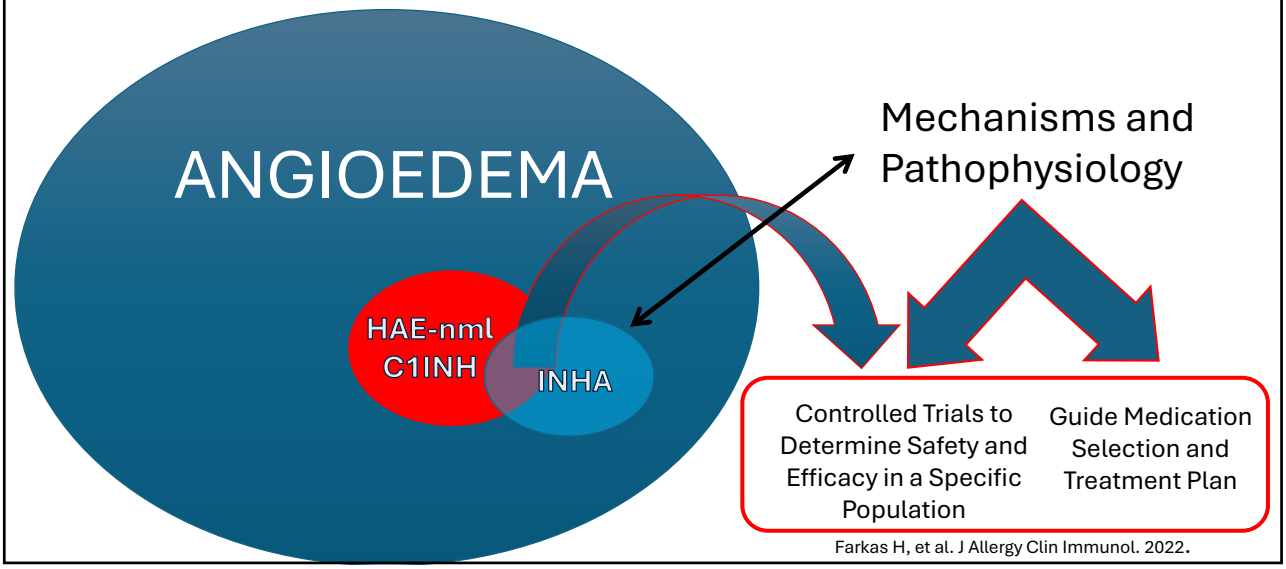
Right Treatment for the Right Patient



Farkas H, et al. J Allergy Clin Immunol. 2022.

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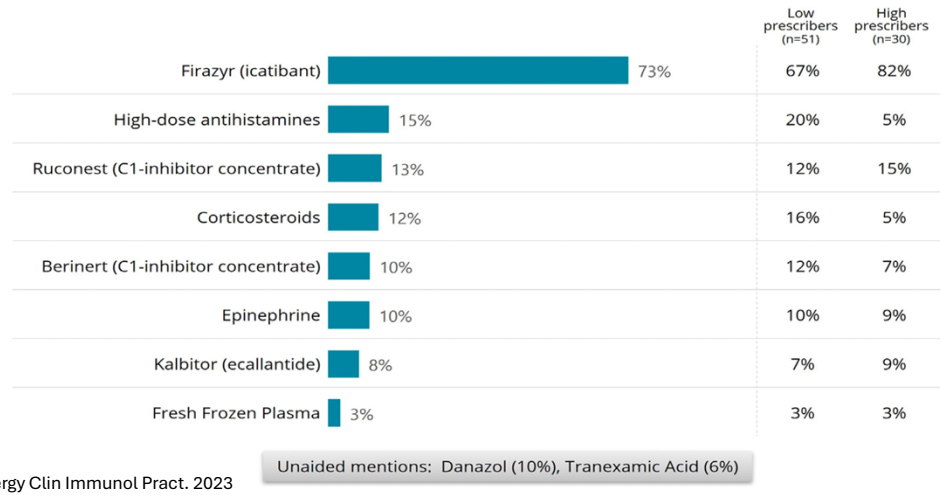
US Physician Survey: HAE-nl C1INH Management

Medications used for acute treatment in patients with HAE-nlC1INH



Riedl M, et al. J Allergy Clin Immunol Pract. 2023

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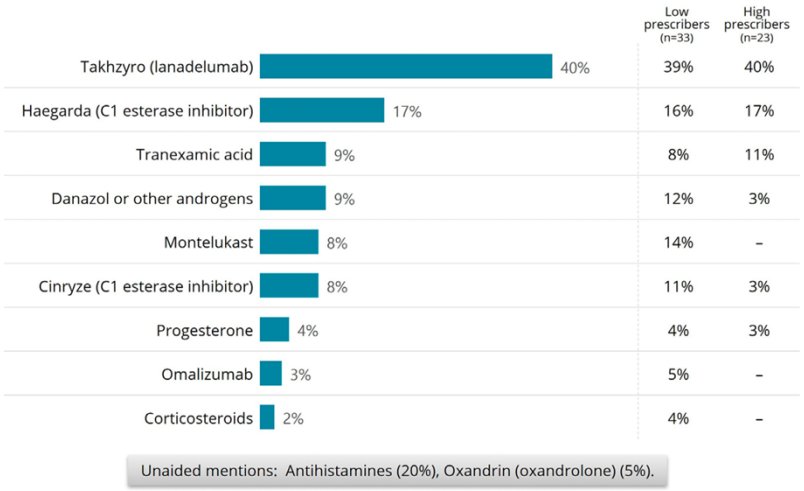
US Physician Survey: HAE-nl C1INH Management

Medications used for preventative treatment in patients with HAE-nlC1INH



Riedl M, et al. J Allergy Clin Immunol Pract. 2023

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RETURN TO AGENDA

Acute Treatment of HAE-nC1INH

- HAE-FXII, HAE-PLG, HAE-AGPT1, HAE-UNK: icatibant and pdC1INH effective in most reported cases
- HAE-CPN1, HAE-DAB2IP: icatibant effective
- HAE-MYO, HAE-KNG1: no data

Marcos et al Ann Allergy Asthma Immunol. 2012
Piñero-Saavedra et al. Ann Allergy Asthma Immunol. 2016
Bork et al. Allergy. 2017
Bouillet et al. Immun Inflamm Dis. 2017
Veronez, et al. J Allergy Clin Immunol Pract. 2018
McKibbin et al. Allergy Asthma Clin Immunol. 2019
Grumach et al. Arerugi. 2020
Maurer et al. Clin Exp Allergy. 2022
Bova et al Allergy. 2019
Bork et al Orphanet J Rare Dis. 2020
Dias de Castro et al. Ann Allergy Asthma Immunol. 2024
Vincent et al. J Allergy Clin Immunol Glob. 2024
D'Apolito et al. J Allergy Clin Immunol. 2024

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Optimal Prophylactic Management Likely Depends on Underlying Mechanism

- HAE-FXII: Tranexamic acid, lanadelumab, progestin
- HAE-PLG, HAE-AGPT1, HAE-KNG1, HAE-CPN1, HAE-DAB2IP: Tranexamic acid
- HAE-MYO, HAE-HS3ST6: minimal data
- HAE-UNK, INHA: mixed results with contact system targeted treatments likely due to heterogenous pathophysiology

Bouillet L, et al. Ann Allergy Asthma Immunol. 2021
Lochbaum R, et al. J Dermatolog Treat. 2024
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Yakushiji H, et al. Intern Med. 2023
Bafunno V, et al. J Allergy Clin Immunol. 2018
Adatia A, et al. J Allergy Clin Immunol Glob. 2023
Cobb G, et al. Cureus. 2023
Vincent et al. J Allergy Clin Immunol Glob. 2024
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Veronez, et al. J Allergy Clin Immunol Pract. 2018
Saule C, et al. Clin Exp Allergy. 2013
Jones DH, et al. World Allergy Organ J. 2022
Kanarek HJ, et al. J Asthma Allergy. 2024
Taha OS, et al. J Allergy Clin Immunol Glob. 2022

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RETURN TO AGENDA

HAE-XII LTP

Medication	Good	Partial	Low/None	References
Landadelumab	10	2	1	Bouillet, AAAI_21_378; Lochbaum, JDT_24_2290362; Christiansen, Munich_Symposium
Tranexamic acid	48	1	12	Bork, Allergy_17; Bova, Allergy_19 _1394; Dias de Castro, AAAI_24_730; Firinu, CI_15_239; Veronez, FM_19_80; Christiansen, Munich_Symposium
Garadacimab	2	0	1	Abstract only
Progestin	24	21	1	Bork, Allergy_17; Dias de Castro, AAAI_24_730; Christiansen, Munich_Symposium
IV pdC1INH	0	2	0	Christiansen, Munich Symposium
Anabolic androgen	0	3	0	Bork, Allergy_17_Bork; Dias de Castro, AAAI_24_730; Christiansen, Munich Symposium

Special case: Pregnancy

Medication	Good	Partial	Low/None	References
IV pdC1INH	3	2	0	Bova, Allergy_19 _1394; Garcia, JACIP_18_1406; Gibbons, AAAI_17_558
Tranexamic acid	0	1	0	Marcos, 109 AAAI_12_195

Zuraw BL, et al. Clin Rev Allergy Immunol. 2025 Mar

33

HAE-PLG LTP

Medication	Good	Partial	Low/None	References
Tranexamic acid	20	0	0	Belbezier, Allergy_18_2237; Bork, OJRD_20_52; Nakayama, MRCR_23_491; Yakushiji, IM_23_2005; Christiansen, Munich_Symposium
Anabolic androgen	3	0	0	Bork, OJRD_20_52
SC pdC1INH	0	1	0	Christiansen, Munich_Symposium
Progestin	2	1	3	Bork, OJRD_20_52
Lanadelumab	1	3	4	Lochbaum, JDT_24_2290362; Christiansen, Munich Symposium

HAE-ANGPT1 LTP

Medication	Good	Partial	Low/None	References
Tranexamic acid	2	0	1	Bafunno, JACI_18_1009; ; Christiansen, Munich_Symposium
Progestin	0	0	1	Christiansen, Munich_Symposium

Zuraw BL, et al. Clin Rev Allergy Immunol. 2025 Mar

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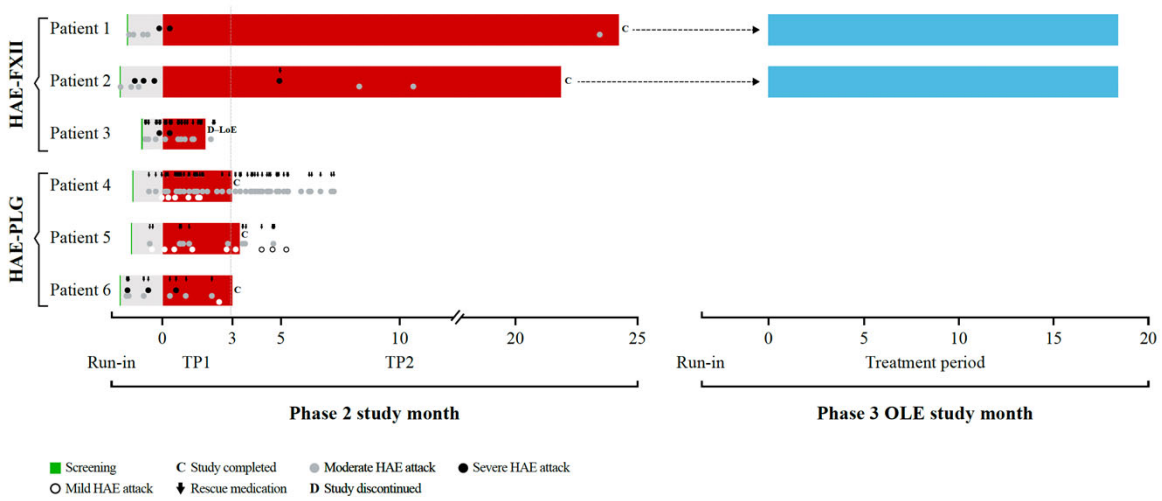
Garadacimab Treatment of HAE-FXII and HAE-PLG



Cohn DM, et al. J Allergy Clin Immunol. 2025 Aug

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Take Home Points

- Angioedema with normal lab results remains a challenging condition
- The majority of "idiopathic" angioedema is mast-cell mediated
- A subset of patients have non mast-cell mediated angioedema
- C1INH testing and targeted genetic testing (particularly if family history present) recommended as this may determine therapeutic approach
- Treatment plan often guided by clinical features and history: aggressive mast cell targeted therapy is recommended starting point

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Stepwise Approach to the Treatment of Histaminergic and Non-histaminergic Angioedema

ACAAI 2025

Aleena Banerji, MD
Professor, Harvard Medical School
Clinical Director, Allergy and Immunology Unite
Division of Rheumatology, Allergy & Immunology
Massachusetts General Hospital

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1

Ms. Ann

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Case: Ms. Ann

26-year-old female presents to you for recurrent symptoms of swelling and abdominal pain. She notes symptoms for the past 8 years. She has tried cetirizine 10 mg intermittently without much benefit and presents to your office asking about possible food allergy and MCAS.

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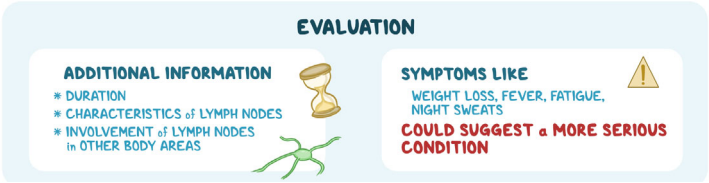
History, History, History…

Age of onset?
Itching?
Urticaria?
Length of symptoms?
Treatments?



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RETURN TO AGENDA

Case Ms. Ann

26-year-old female presents to you for recurrent symptoms of swelling and abdominal pain. She notes symptoms for the past 8 years. She has tried cetirizine 10 mg intermittently without much benefit and presents to your office asking about possible food allergy and MCAS.

On further history, she notes occasional hives. She has no family history of angioedema. She denies any specific food triggers.

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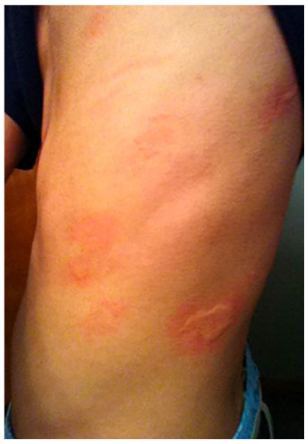
Chronic Spontaneous Urticaria and Angioedema: *Clinical Presentation*

- Well-circumscribed, raised, erythematous plaques, often with central pallor
- **Vary in size** <1 cm to several cm
- **Intensely itchy** which can disrupt work, school, or sleep
- Individual lesions are transient, usually appearing and enlarging over minutes to hours and then **resolving within 24 hours**
- Not normally painful and resolve **without leaving residual bruising** on the skin, unless there is trauma from scratching



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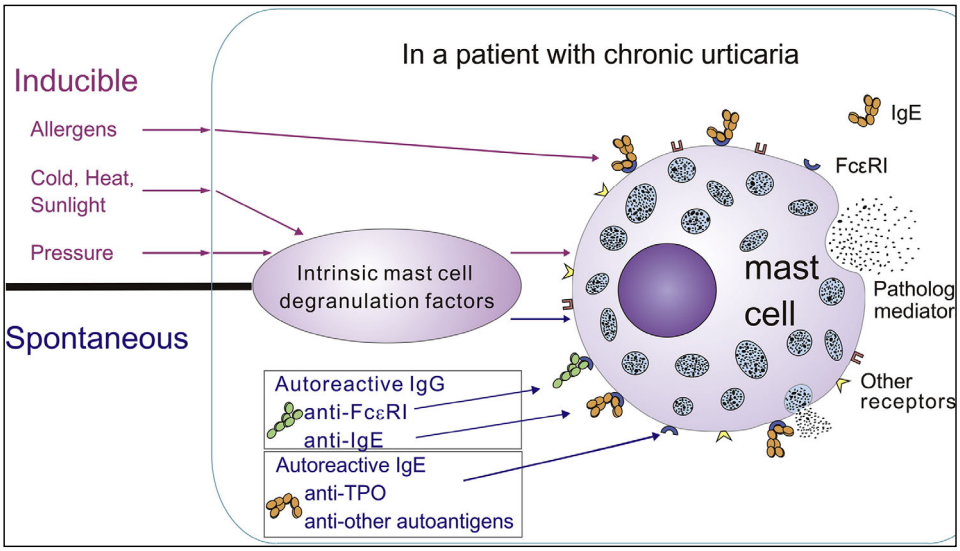
Mast Cell Mediated Angioedema ⟷ Chronic Spontaneous Urticaria and Angioedema



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Epidemiology: CSU

- Chronic urticaria (with or without angioedema) affects about **0.5–1% of the population**
- Angioedema alone (without urticaria) is less common, but up to **40% of patients with chronic urticaria** experience angioedema episodes
- **Drug-induced histaminergic angioedema** accounts for **10–20% of emergency department presentations** for angioedema, with ACEI, antibiotics, NSAIDs, and contrast agents being leading causes

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Recommended Diagnostic Tests: EAACI Guidelines

Routine

- Differential blood count and ESR or CRP
- Omission of suspected drugs (e.g. NSAID)

If Clinically Indicated

- Infectious diseases (H pylori)
- Type I allergy (latex)
- Functional autoantibodies, anti-FcεR
- Thyroid hormones or autoantibodies
- Physical urticaria tests
- Pseudoallergen-free diet for 3 weeks
- Autologous serum skin test
- Lesional skin biopsy

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First Line Treatments are Oral Antihistamines

- H1-antihistamines efficacious in numerous published RCTs
- 1st generation agents associated with risk for sedation and anti-cholinergic effects
- 2nd generation agents efficacious and better tolerated in most patients

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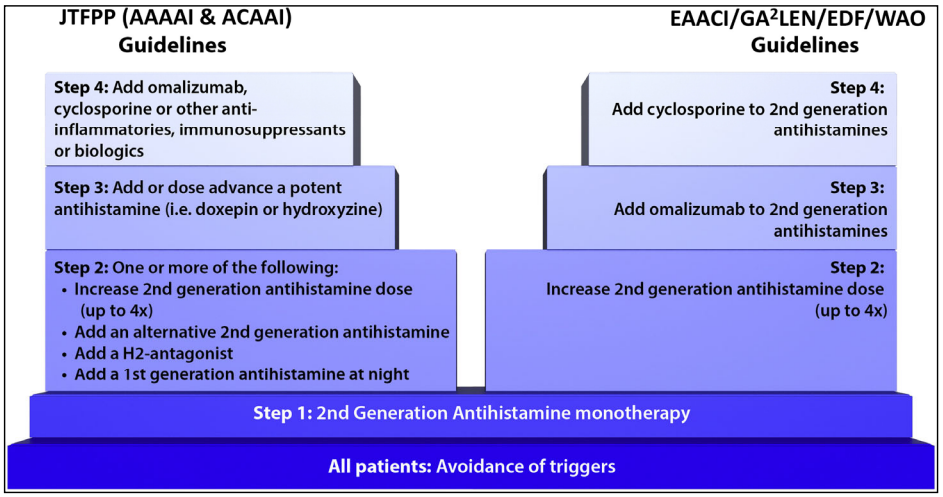
Management of CSU/Mast Cell Mediated Angioedema



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Johal et al, Annals of Allergy, Asthma & Immunology 2020

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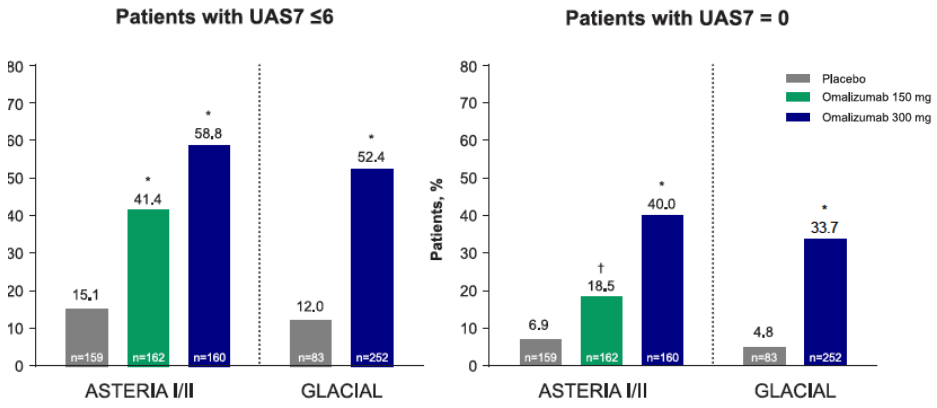
Omalizumab for Chronic Spontaneous Urticaria and Angioedema



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Kaplan et al. GLACIAL ; Casale et al. J Allergy Clin Immunol Pract 2015

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Case: Ms. Ann

26-year-old female presents to you for recurrent symptoms of swelling and abdominal pain. She notes symptoms for the past 8 years. She has tried cetirizine 10 mg intermittently without much benefit and presents to your office asking about possible food allergy and MCAS.

No response to high dose antihistamines, denies any urticaria, reports her father died in his 40s suddenly and used to have similar symptoms of swelling, notes starting OCPs 8 years ago

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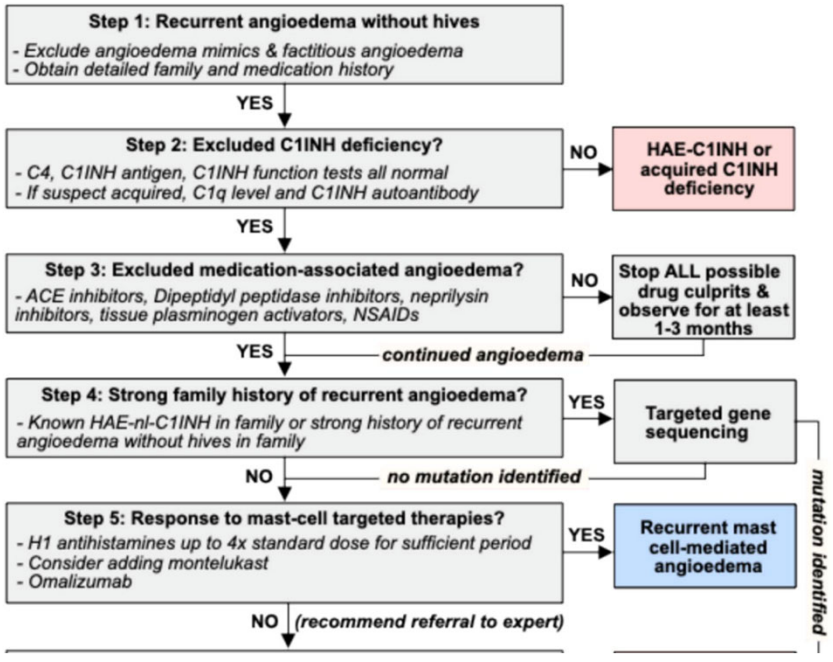

Zuraw et al. HAE with Normal C1 Inhibitor: an Updated International Consensus Paper. Clin Rev Allergy Immunol. 2025 Mar

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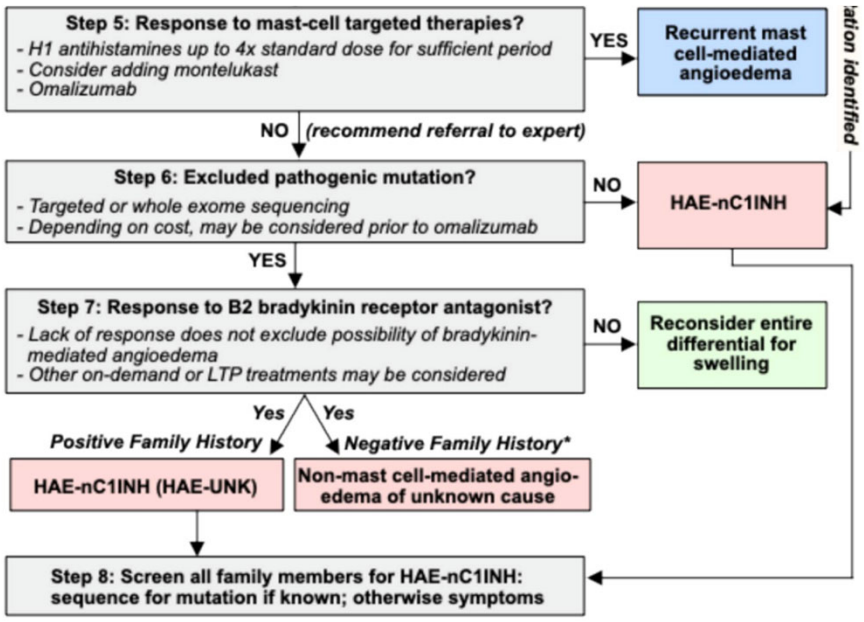

Zuraw et al. HAE with Normal C1 Inhibitor: an Updated International Consensus Paper. Clin Rev Allergy Immunol. 2025 Mar

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Laboratory Evaluation in Recurrent Angioedema

	C1-INH Level	C1-INH Function	C4 Level	C3 Level	C1q Level
HAE type I	<30%	<30%	Low	Normal	Normal
HAE type II	Normal	<30%	Low	Normal	Normal
HAE with normal labs	Normal	Normal	Normal	Normal	Normal
Acquired C1-INH I/II	Low	Low	<30%	Normal/Low	Low
ACE inhibitor	Normal	Normal	Normal	Normal	Normal
Idiopathic angioedema	Normal	Normal	Normal	Normal	Normal

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Recurrent Angioedema without Urticaria: Key Mediator?

Parameter	Bradykinin-mediated angioedema	Mast cell–mediated angioedema
Severity of swelling	Often severe and disfiguring; may be incapacitating	Mild to moderate swelling in most cases
Frequency of swelling (untreated)	Variable, averaging 2/mo	Variable but may occur daily
Duration of untreated swelling	Typically, 3-5 d	Typically, 1-2 d
Location of swelling	Extremities = abdominal > face > genital	Face > extremities >> abdominal
Frequency of abdominal attacks	High, typically 50% of attacks	Rare
Risk of asphyxiation from laryngeal attack	High	Low (unless anaphylaxis)
Response to antihistamines, corticosteroids, or epinephrine	Poor	Good

Christiansen SC., et al. JACI In Pract. 2025 Jun

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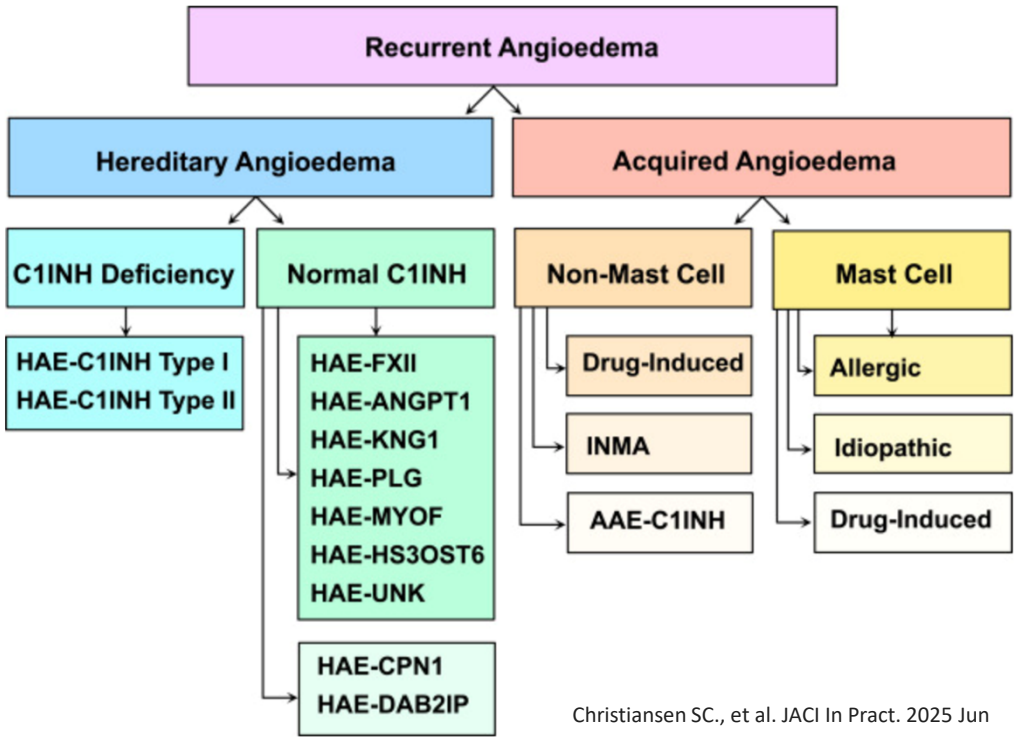

Christiansen SC., et al. JACI In Pract. 2025 Jun

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Recurrent Angioedema without Urticaria: *Clinical Survey*

- Tertiary level center where patients are referred mostly by specialists
- Reviewed all patients with angioedema without urticaria between January 1993 and December 2003
- Identified 929 patients and 776 patients completed the full work up

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Zingale CMAJ 2006

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Evaluation

- Clinical history and physical examination
- CBC, SPEP, CRP, ESR, LFTs, TSH, ANA
- C4, C1 inhibitor level and function, C1Q
- Stool studies
- Urinalysis
- Sinus and dental x-rays

If evaluation was negative, antihistamine treatment for one month was initiated

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Zingale CMAJ 2006

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Recurrent Angioedema without Urticaria: *Differential Diagnosis*

Table 1: Classification of angioedema without urticaria according to clinical or etiopathogenetic characteristics, *n* = 776

	Patients		M:F ratio	Age at onset, yr	
	No.	%		Median	Range
Related to a specific factor*	124	16	0.51	39	13-76
Autoimmune disease/infection	55	7	0.62	49	3-78
ACE inhibitor-related	85	11	0.93	61	32-84
C1-inhibitor deficiency	197	25			
Hereditary	183		0.88	8	1-34
Acquired	14		1.8	56.5	42-76
Unknown (idiopathic) etiology	294	38			
Histaminergic	254		0.56	40	7-86
Nonhistaminergic	40		1.35	36	8-75
Peripheral/generalized edema	21	3	0.17	—	

Note: M = male, F = female, ACE = angiotensin-converting enzyme.
*A food, drug, insect bite, environmental allergen or other physical stimulus.

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Zingale CMAJ 2006

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Algorithmic Evaluation of Patients Presenting with Recurrent Angioedema

Recurrent Angioedema without Urticaria

↓ No response to high dose antihistamines

Non-Mast Cell Mediated Angioedema without Urticaria

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Treatment: Mast Cell Mediated Angioedema *Idiopathic*

Similar to refractory cases of chronic Spontaneous urticaria and angioedema

- High dose antihistamines (4x standard doses)
- Leukotriene receptor antagonists
- Omalizumab
- Immunosuppressants
- *Corticosteroids*

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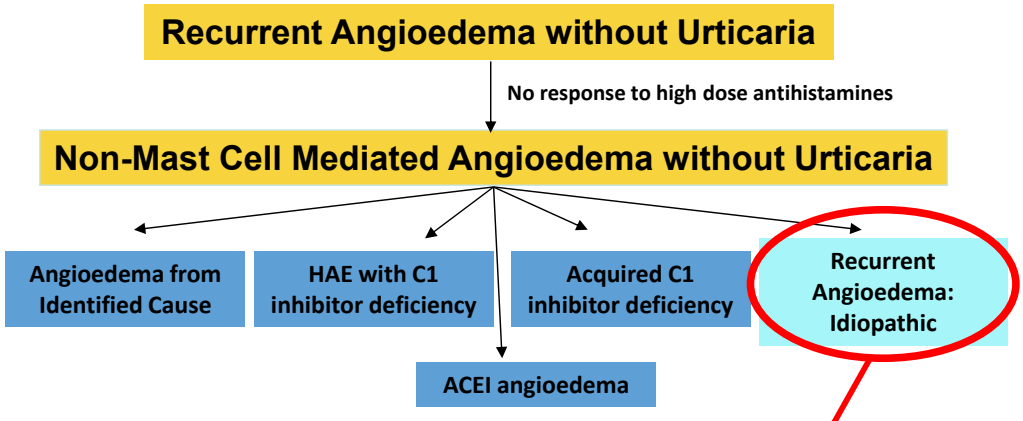
Algorithmic Evaluation of Patients Presenting with Recurrent Angioedema



How do we manage these patients?

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Differential Diagnosis and Clinical Criteria

Parameter	HAE-nl-C1INH	HAE-UNK	HAE-C1INH	INMA	Mast cell–mediated
Age at onset	Often teenage to young adult	Often teenage to young adult	Usually child to teenage	Variable	Variable
Hives as part of disorder	No	No	No	No	Usually yes
Family history of angioedema	Usually yes	Yes	Usually yes	No	No
C1INH function	Normal	Normal	Low	Normal	Normal
Identified pathogenic variant	Yes	No	n.a.	No	No
Response to mast cell–directed treatment	No	No	No	No	Yes

Christiansen SC., et al. JACI In Pract. 2025 Jun

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Non-Mast Cell Mediated Angioedema

Idiopathic Nonhistaminergic Angioedema

Marco Cicardi, MD, Luigi Bergamaschini, MD, Lorenza C. Zingale, MD, Daniela Gioffré, MD, Angelo Agostoni, MD

- 25 patients not responsive to antihistamines
- Excluded all known causes of angioedema

Table 2. Effects of Treatment with Tranexamic Acid in Patients with Idiopathic Nonhistaminergic Angioedema

Patient	Attacks/Year without Treatment	Attacks/Year with Tranexamic Acid	Minimal Effective Dose of Tranexamic Acid (g/day)	Length of Treatment with Tranexamic Acid (months)
1	>12	<1	2.5	29
2	6–11	<1	0.5	22
3	6–11	none	1.5	24
4	>12	3	2.0	12
5	>12	2–3	1.0	43
6	>12	3	3.0	12
7	>12	none	2.0	10
8	>12	none	2.0	53
9	>12	<1	1.0	72
10	>12	none	0.5	46
11	12	3	1.0	15
12	>12	none	1.0	21
13	>12	none	1.5	282
14	>12	none	1.5	256
15	>12	none	1.0	56

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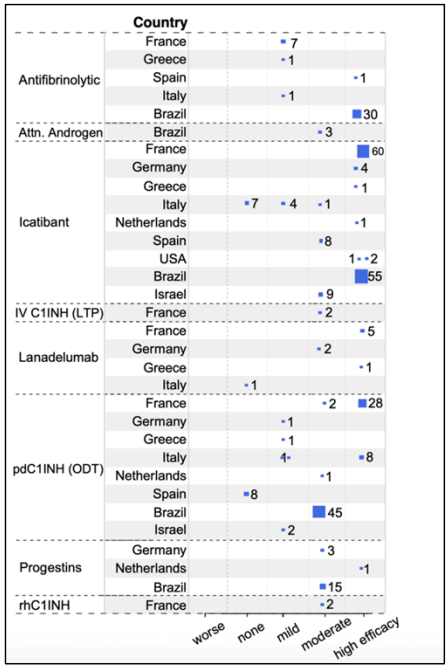
Treatment efficacy for HAE-FXII

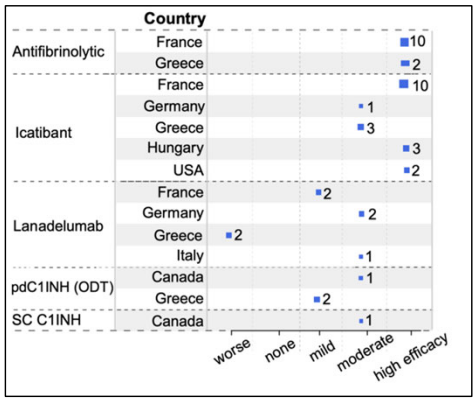


Hereditary Angioedema with Normal C1 Inhibitor: an Updated International Consensus Paper on Diagnosis, Pathophysiology, and Treatment

Bruce L. Zuraw[1,2] · Konrad Bork[3] · Laurence Bouillet[4,5] · Sandra C. Christiansen[1] · Henriette Farkas[6] · Anastasios E. Germenis[7] · Anete S. Grumach[8] · Allen Kaplan[9] · Alberto López-Lera[10] · Markus Magerl[11,12] · Marc A. Riedl[1] · Adil Adatia[13] · Aleena Banerji[14] · Stephen Betschel[15] · Isabelle Boccon-Gibod[4] · Maria Bova[16] · Henrik Balle Boysen[17,18] · Teresa Caballero[10,19] · Mauro Cancian[20] · Anthony J. Castaldo[17,18] · Danny M. Cohn[21] · Deborah Corcoran[17,18] · Christian Drouet[22] · Atsushi Fukunaga[23] · Michihiro Hide[24,25] · Constance H. Katelaris[26] · Philip H. Li[27] · Hilary Longhurst[28] · Jonny Peter[29,30] · Fotis Psarros[31] · Avner Reshef[32] · Bruce Ritchie[33] · Christine N. Selva[18] · Andrea Zanichelli[34,35] · Marcus Maurer[11,12]

Clinical Reviews in Allergy & Immunology

Treatment efficacy for HAE-PLG



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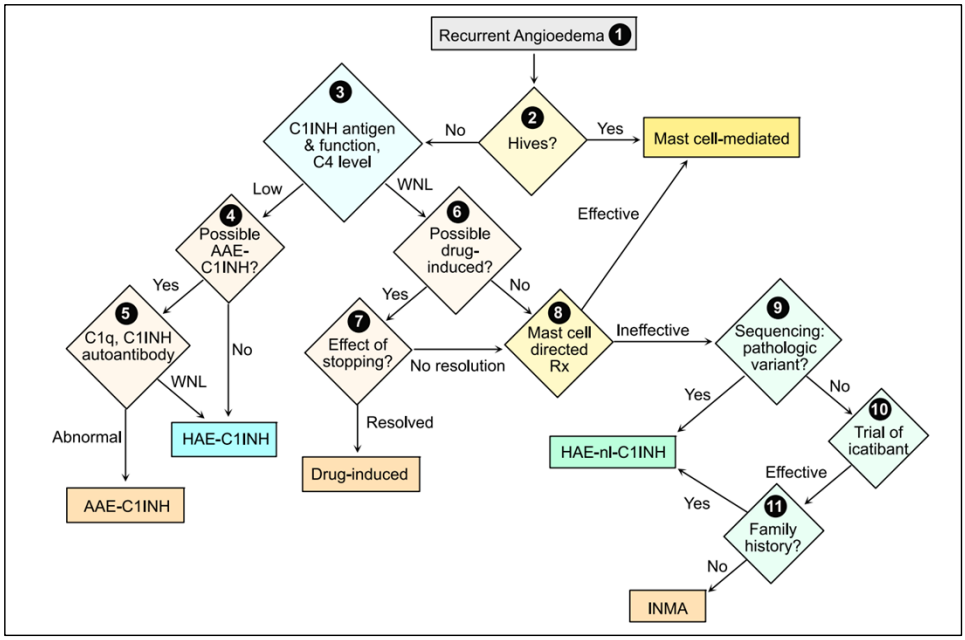
Algorithmic Approach to Recurrent Angioedema



Christiansen SC., et al. JACI In Pract. 2025 Jun

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RETURN TO AGENDA

Case Ms. Ann

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No response to high dose antihistamines, denies any urticaria, reports her father died in his 40s suddenly and used to have similar symptoms of swelling, notes starting OCPs 8 years ago

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Laboratory Evaluation in Hereditary Angioedema with C1 inhibitor deficiency

	C1-INH Level	C1-INH Function	C4 Level	C3 Level	C1q Level
HAE type I	<30%	<30%	Low	Normal	Normal
HAE type II	Normal	<30%	Low	Normal	Normal
HAE with normal labs	Normal	Normal	Normal	Normal	Normal
Acquired C1-INH I/II	Low	Low	<30%	Normal/Low	Low
ACE inhibitor	Normal	Normal	Normal	Normal	Normal
Idiopathic angioedema	Normal	Normal	Normal	Normal	Normal

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Clinical Presentation

Angioedema

- Repeated bouts of swelling of the face, extremities, genitals, intestines and larynx

No Urticaria

- Edema is *not* warm, usually nonpruritic and nonpitting
- Erythema marginatum present but **no urticaria**

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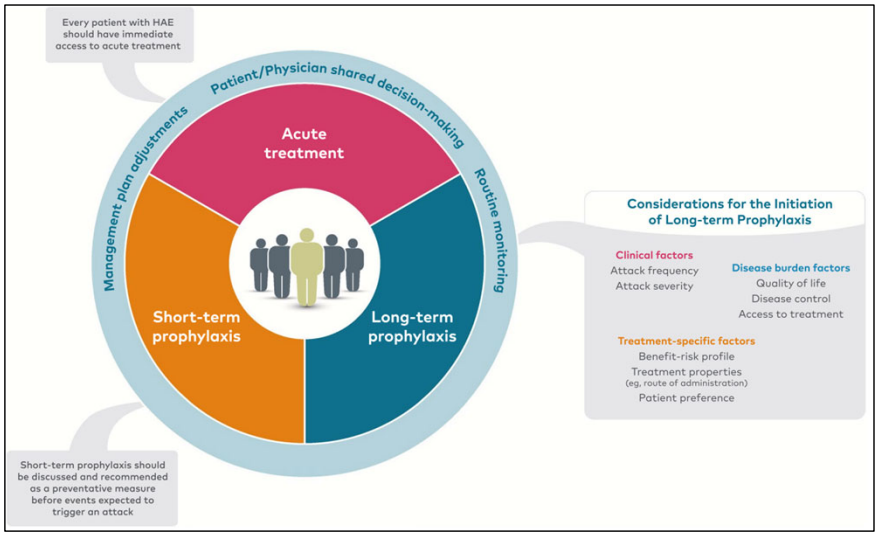
Treatment Approach in HAE



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Bork et al. Allergy Asthma Clin Immunol 2021

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ACE inhibitor-Induced Angioedema

- ACE is an enzyme that degrades bradykinin
- Occurs in about **0.1–0.7% of patients** taking ACEI
- **Risk Factors**
  - Race: African American patients have a 4–5 times higher risk than White patients.
  - Sex: Women are at modestly increased risk compared to men
  - Age: Older adults (>65) show higher susceptibility.
  - Other factors: Smoking, seasonal allergies, and a history of drug rashes or angioedema from other causes also raise risk
- Discontinuing ACEI is essential, rare angioedema after

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Take Home Points

- Recurrent angioedema without urticaria has a broad differential diagnosis
- Clinical history plays an important role in the evaluation of these individuals
  - Most patients are likely mast-cell mediated
  - Failure of high dose antihistamines is not enough to diagnose a patient with non-mast cell mediated angioedema
- Important to follow algorithmic approach if suspect non-mast cell mediated
- Hereditary angioedema with C1 inhibitor deficiency easy to diagnose and treatment options have expanded

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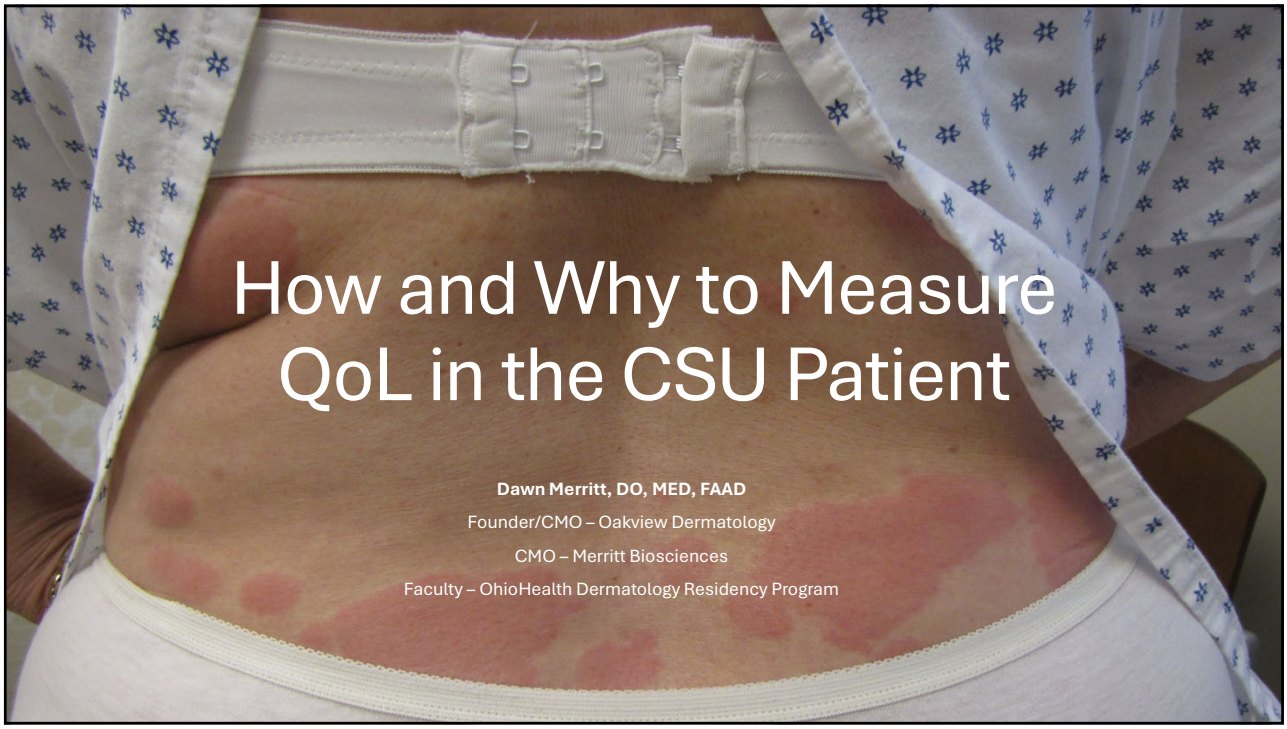

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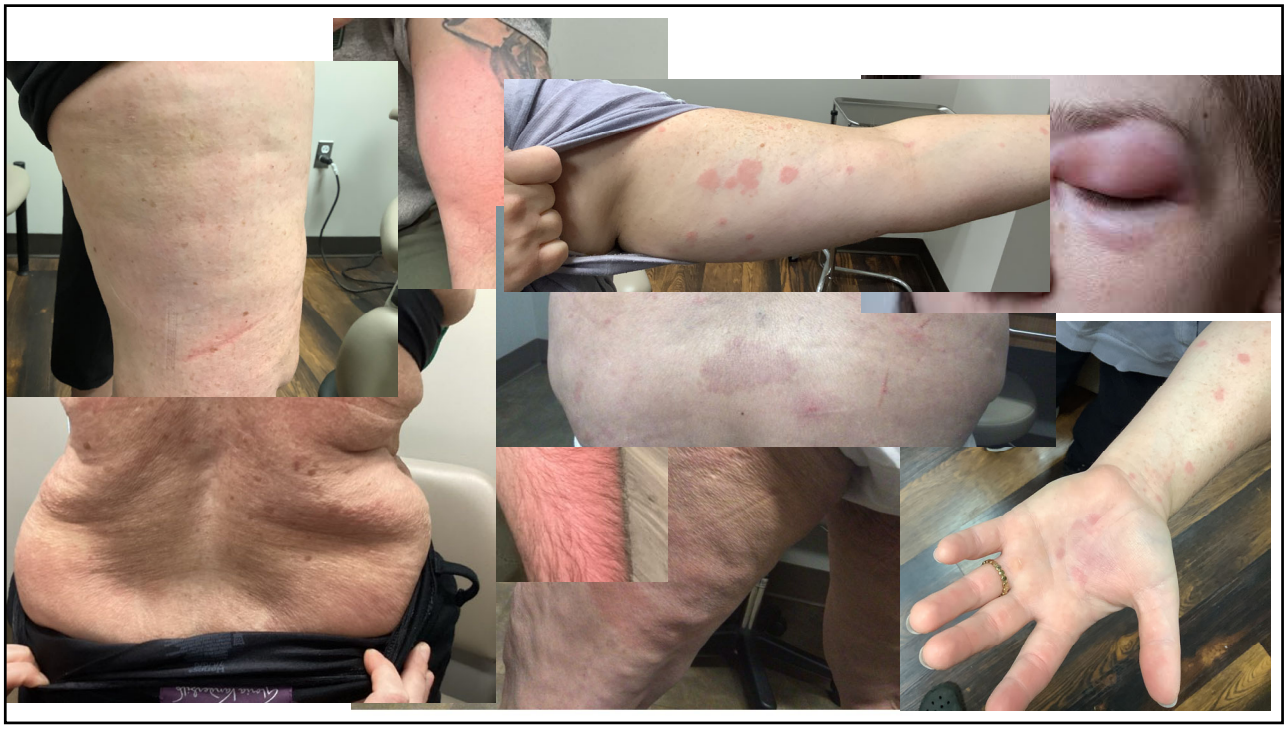

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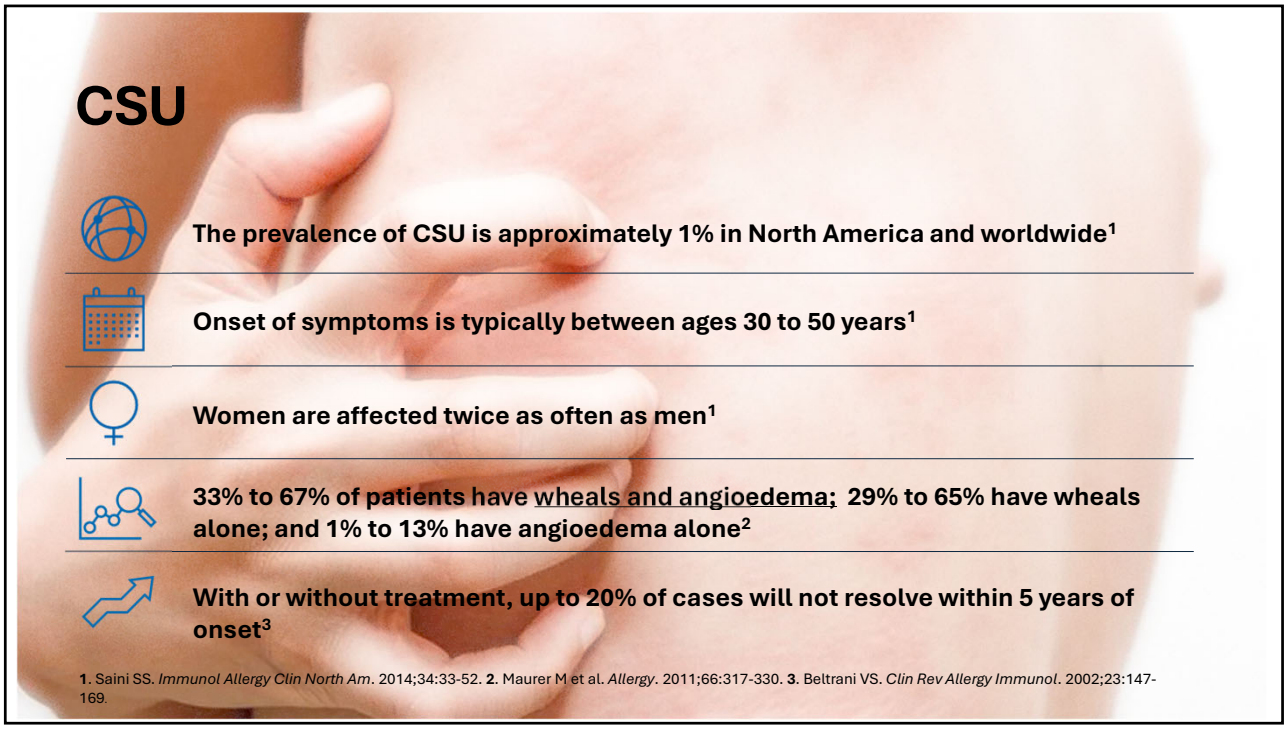

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Why Determine QoL and Disease Severity?

- Identifying candidates for specialist care
- Important for assessing our patient's experience
- Treatment approval
- Monitoring response to treatment

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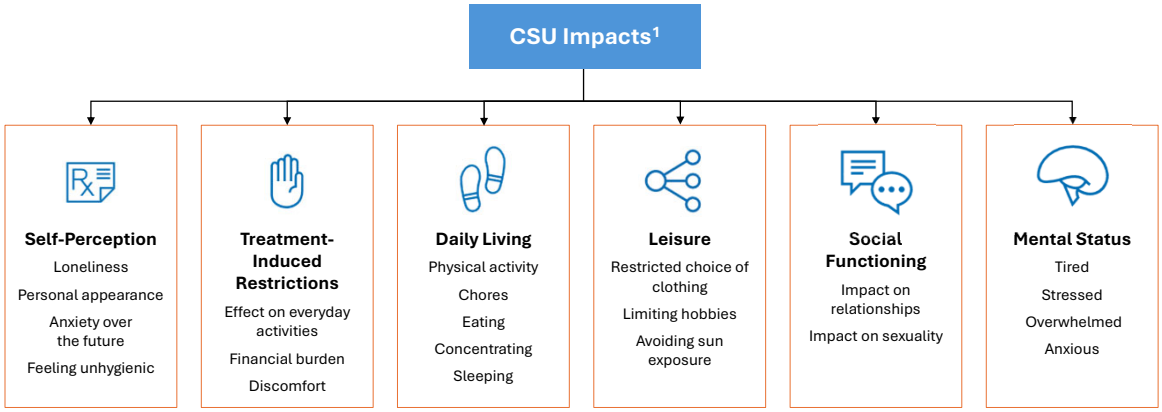
QoL in Patients With CSU



- Many aspects of QoL are negatively impacted by a diagnosis of CSU[1]
- The presence of angioedema further impairs QoL scores[2]

1). Balp, MM., Vietri, J., Tian, H. *et al.* The Impact of Chronic Urticaria from the Patient's Perspective: A Survey in Five European Countries. *Patient* **8,** 551–558 (2015). 2) Maurer M et all. The burden of chronic spontaneous urticaria is substantial: Real-world evidence from ASSURE-CSU. Allergy. 2017 Dec;72(12):2005-2016.

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The CSU Patient Experience

- Many aspects of QOL are negatively impacted by a diagnosis of CSU[1]
- Presence of angioedema shown to further impair QOL scores
- More than 20% of CSU patients report 1 hour or more of missed work each week[2]
- Productivity impairment has been shown to be as high as 27%[2]
- 1/3 of patients report considerable impairments in daily non-work activities

1). Balp, MM., Vietri, J., Tian, H. *et al.* The Impact of Chronic Urticaria from the Patient's Perspective: A Survey in Five European Countries. *Patient* **8,** 551–558 (2015).
2) Maurer M et all. The burden of chronic spontaneous urticaria is substantial: Real-world evidence from ASSURE-CSU. Allergy. 2017 Dec;72(12):2005-2016.

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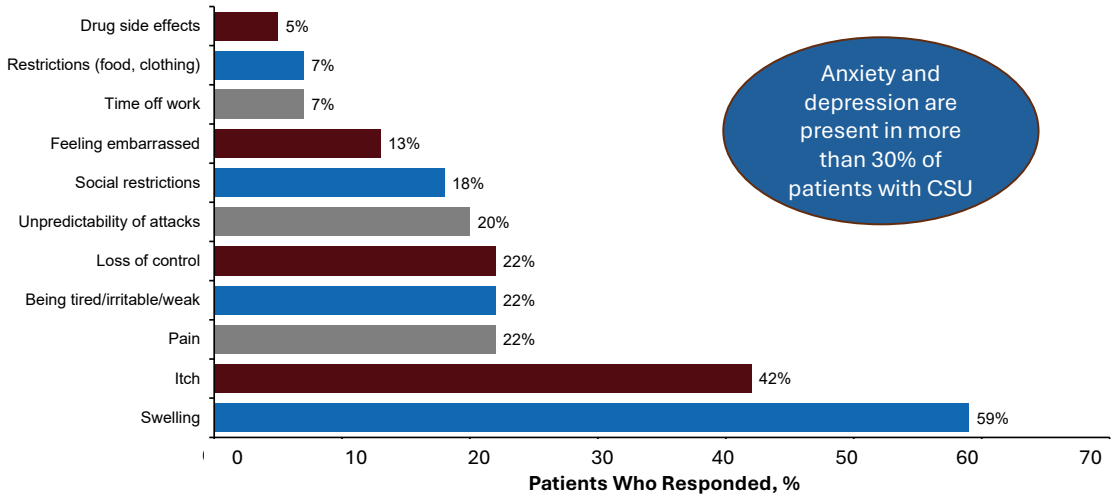
CSU Impact on Patient Quality of Life

How Patients Answered, "What Is the Worst Aspect of Your Urticaria[a]?"



Anxiety and depression are present in more than 30% of patients with CSU

1. O'Donnell BF. *Immunol Allergy Clin North Am.* 2014;34:89-104; 2. Sánchez-Borges M, et al. World Allergy Organ J. 2021;14(6):100533.

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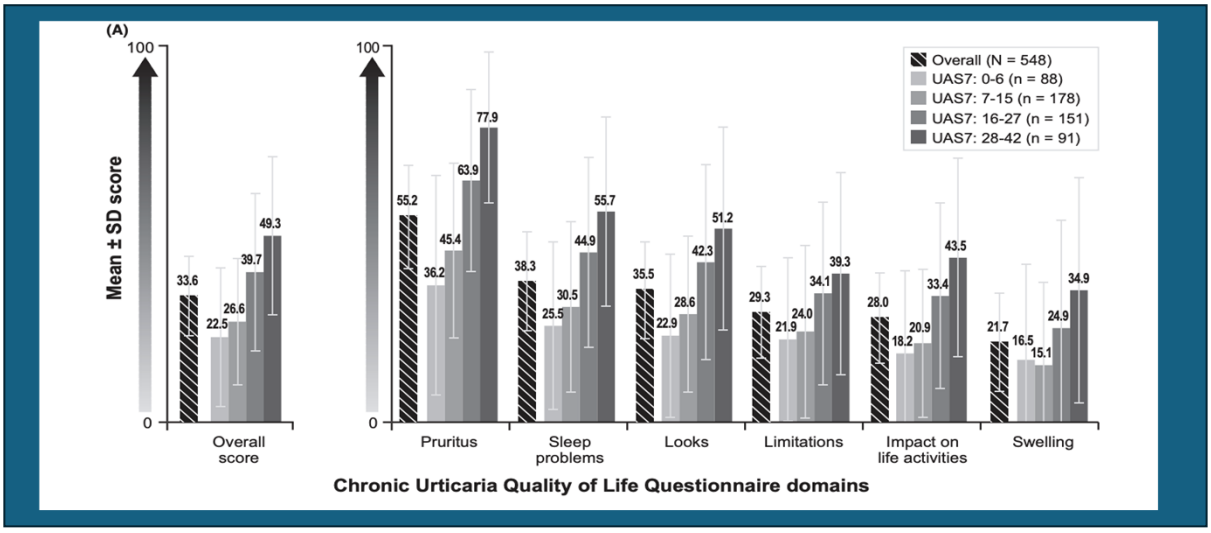
The CSU Impact on Patient QoL



Maurer M et all. The burden of chronic spontaneous urticaria is substantial: Real-world evidence from ASSURE-CSU. Allergy. 2017 Dec;72(12):2005-2016.

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CSU Impact on Sleep

Patients with higher pruritus scores were less satisfied with their sleep pattern

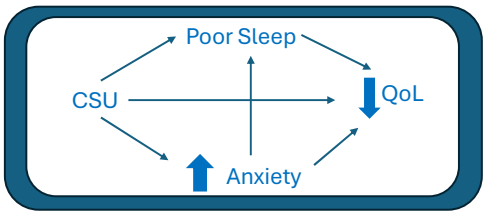
- Questionnaire-based cohort study
- Associations of insomnia with disease activity

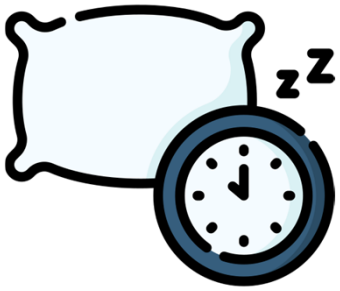
"Problems falling asleep"
"Problems maintaining sleep"
"Problems with waking up too early"

"Dissatisfied with sleep pattern"

"Interference with daily functioning"

"Worried about sleep"

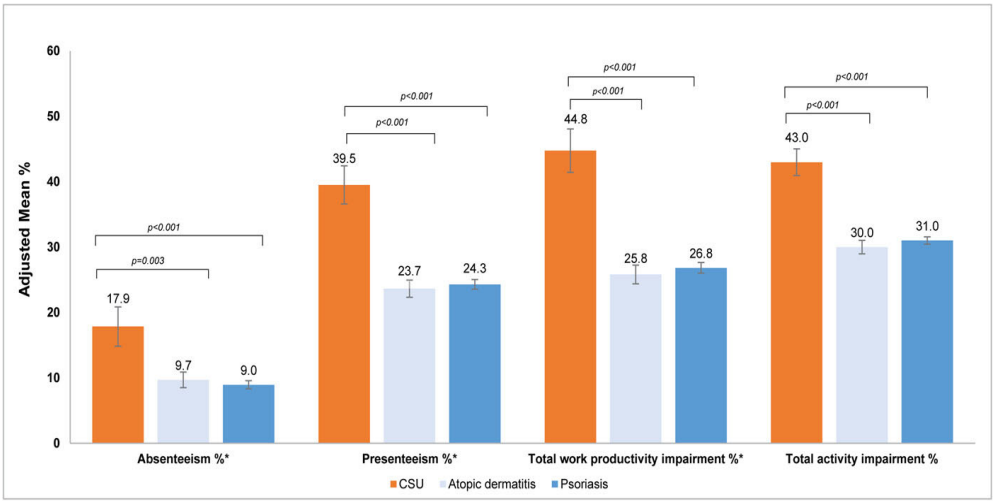




1. Mann C et al. *Acta Derm Venereol.* 2020;100:adv00073.

9

The comparative burden of chronic spontaneous urticaria, atopic dermatitis and psoriasis in five European countries



JEADV Clinical Practice, Volume: 3, Issue: 2, Pages: 508-520, First published: 25 January 2024, DOI: (10.1002/jvc2.324)

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RETURN TO AGENDA

CSU Is Associated with a Wide Range of Comorbidities

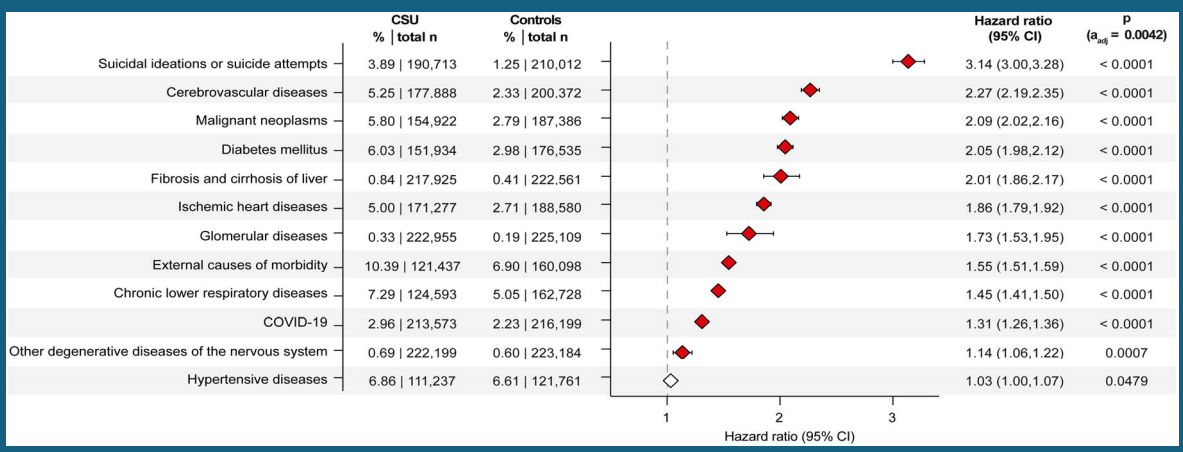
*A longer duration of CSU is associated with a higher frequency of comorbidities

- Thyroid disease
- Psychiatric disorders
- Atopic diseases
- Rheumatic diseases
- Inflammatory diseases
- Osteoporosis
- Cancer

Sanchez-Borges M et al. *World Allergy Organ J.* 2021;14:100533; Agondi RC et al. *An Bras Dermatol.* 2023;98:93-96.

11

Mortality in adult patients with chronic spontaneous urticaria



Kolkhir P, Bieber K, Hawro T, Kridin K, Ludwig MA, Olbrich H, Metz M, Vorobyev A, Ludwig RJ, Maurer M. Mortality in adult patients with chronic spontaneous urticaria: A real-world cohort study. J Allergy Clin Immunol. 2025 Apr;155(4):1290-1298.

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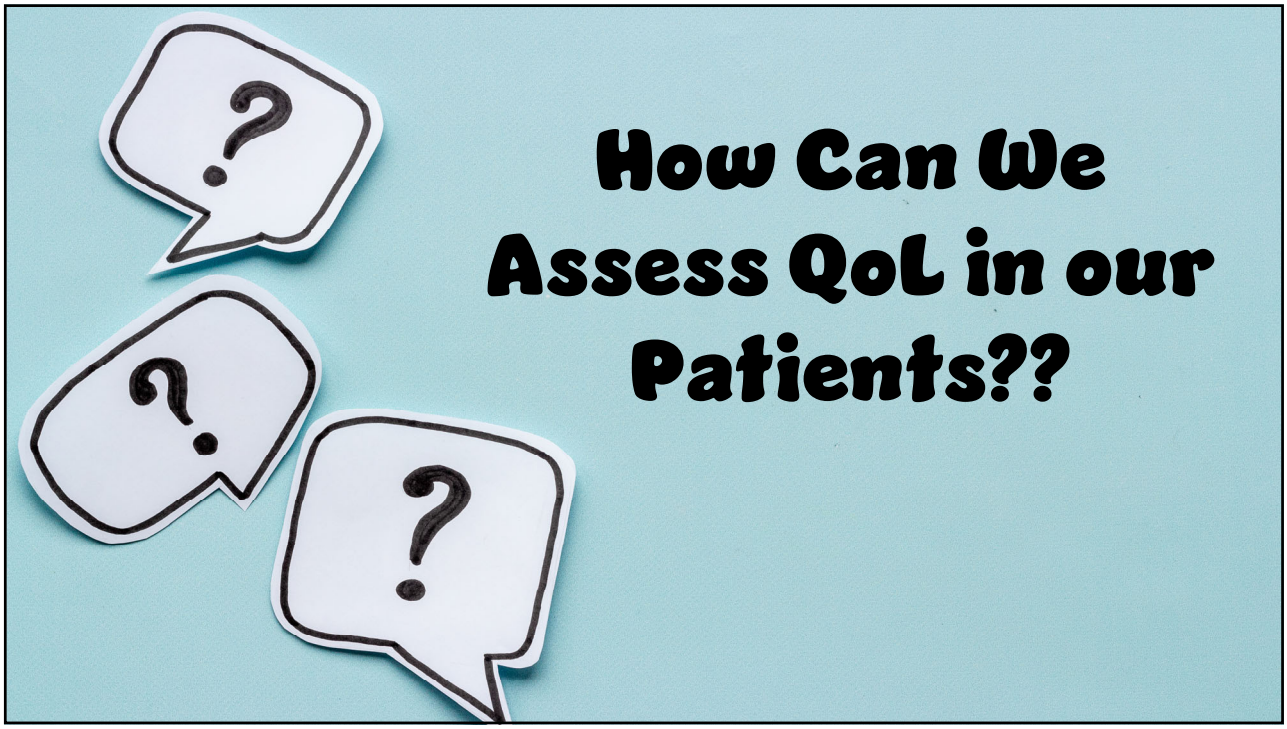

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RETURN TO AGENDA

7-Day Urticaria Activity Score (UAS7)

Score	Wheals	Itch
0 None	None	None
1 Mild	<20 wheals/24 h	Mild (present, but not annoying or troublesome)
2 Moderate	20–50 wheals/24 h	Moderate (troublesome, but does not interfere with normal daily activity or sleep)
3 Intense	>50 wheals/24 h or large confluent areas of wheals	Intense (severe itching, which is sufficiently troublesome to interfere with normal daily activity or sleep)

Itch (severity)
0 = none
1 = mild
2 = moderate
3 = severe
Once daily

+

Wheals (number)
0 = none
1 = 0–20 wheals
2 = 20–50 wheals
3 ≥ 50 wheals
Once daily

=

Sum for 7 Days

Daily UAS (0–6) → Weekly UAS7 (0–42)

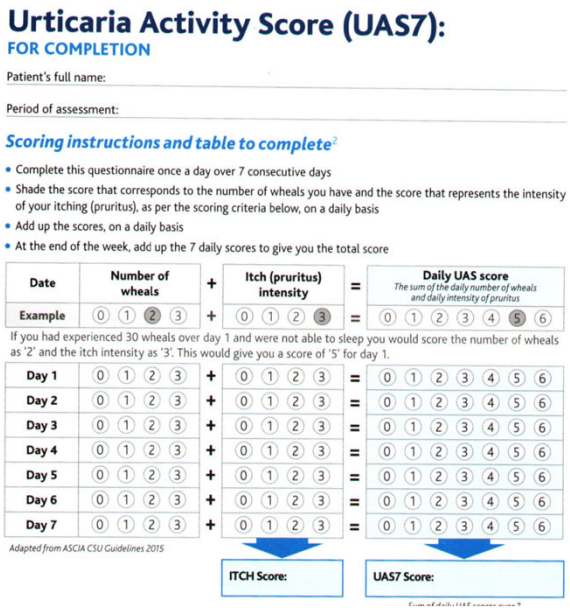
- **Gold standard**
- **Not always feasible - compliance**

Score	Severity
0	Complete Control
1-6	Well-controlled CSU
7-15	Mild
16-27	Moderate
28-42	Severe

Chung, Wen-Hung & Chu, Chia-Yu & Huang, Yu-Huei & Wang, Wei-Ming & Yang, Chih-Hsun & Tsai, Tsen-Fang. (2015). Taiwanese Dermatological Association consensus for the definition, classification, diagnosis, and management of urticaria. Journal of the Formosan Medical Association. 115.

15

7-Day Urticaria Activity Score (UAS7)



Urticaria Activity Score (UAS7):
FOR COMPLETION

Patient's full name:

Period of assessment:

Scoring instructions and table to complete[2]

- Complete this questionnaire once a day over 7 consecutive days
- Shade the score that corresponds to the number of wheals you have and the score that represents the intensity of your itching (pruritus), as per the scoring criteria below, on a daily basis
- Add up the scores, on a daily basis
- At the end of the week, add up the 7 daily scores to give you the total score

Date	Number of wheals	+	Itch (pruritus) intensity	=	Daily UAS score (The sum of the daily number of wheals and daily intensity of pruritus)
Example	0 1 **2** 3	+	0 1 2 **3**	=	0 1 2 3 4 **5** 6

If you had experienced 30 wheals over day 1 and were not able to sleep you would score the number of wheals as '2' and the itch intensity as '3'. This would give you a score of '5' for day 1.

Day 1	0 1 2 3	+	0 1 2 3	=	0 1 2 3 4 5 6
Day 2	0 1 2 3	+	0 1 2 3	=	0 1 2 3 4 5 6
Day 3	0 1 2 3	+	0 1 2 3	=	0 1 2 3 4 5 6
Day 4	0 1 2 3	+	0 1 2 3	=	0 1 2 3 4 5 6
Day 5	0 1 2 3	+	0 1 2 3	=	0 1 2 3 4 5 6
Day 6	0 1 2 3	+	0 1 2 3	=	0 1 2 3 4 5 6
Day 7	0 1 2 3	+	0 1 2 3	=	0 1 2 3 4 5 6

Adapted from ASCIA CSU Guidelines 2015

ITCH Score:

UAS7 Score:

- Patient self assessment
- Evaluates number of wheals and the itch intensity (ISS7 & HSS7)
- 4-Point Scale
- Allows for a quantitative measurement of patient outcomes
- Can be used to monitor patient response to Tx

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RETURN TO AGENDA

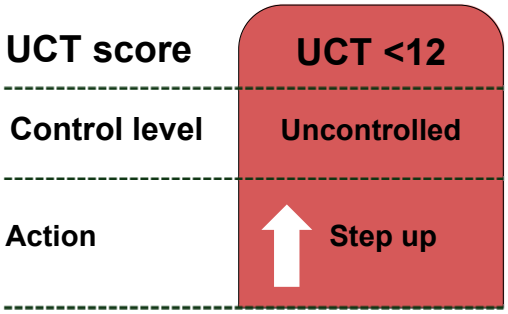
Urticaria Control Test (UCT)

1.How much have you suffered from the **physical symptoms of the urticaria (itch, hives [welts], and or swelling)** in the last four weeks?					
☐ Very much 0	☐ Much 1	☐ Somewhat 2	☐ A little 3	☐ Not at all 4	
2. How much was your **quality of life** affected by the urticaria in the last four weeks?					
☐ Very much 0	☐ Much 1	☐ Somewhat 2	☐ A little 3	☐ Not at all 4	
3. How often was the **treatment** for your urticaria in the last four weeks **not enough** to control your urticaria symptoms?					
☐ Very often 0	☐ Often 1	☐ Sometimes 2	☐ Seldom 3	☐ Not at all 4	
4.**Overall,** how well have you had your urticaria **under control** in the last four weeks?					
☐ Not at all 0	☐ A little 1	☐ Somewhat 2	☐ Well 3	☐ Very well 4	
TOTAL SCORE:					

Reproduced from Weller K, Groffik A, Church MK, et al. Development and validation of the Urticaria Control Test: A patient reported outcome instrument for assessing chronic urticaria. J Allergy Clin Immunol 2014; 133:1365

17

Treatment and Management of Urticaria



UCT = urticaria control test.
Zuberbier T, et al. *Allergy* 2022;7:734-766.

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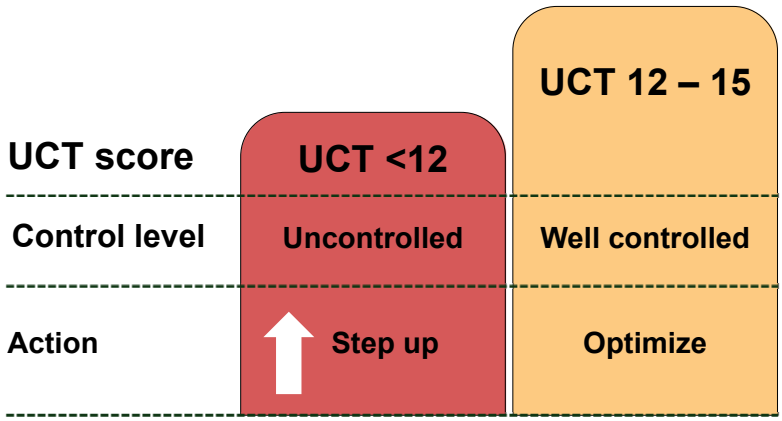
Treatment and Management of Urticaria



UCT = urticaria control test.
Zuberbier T, et al. *Allergy* 2022;7:734-766.

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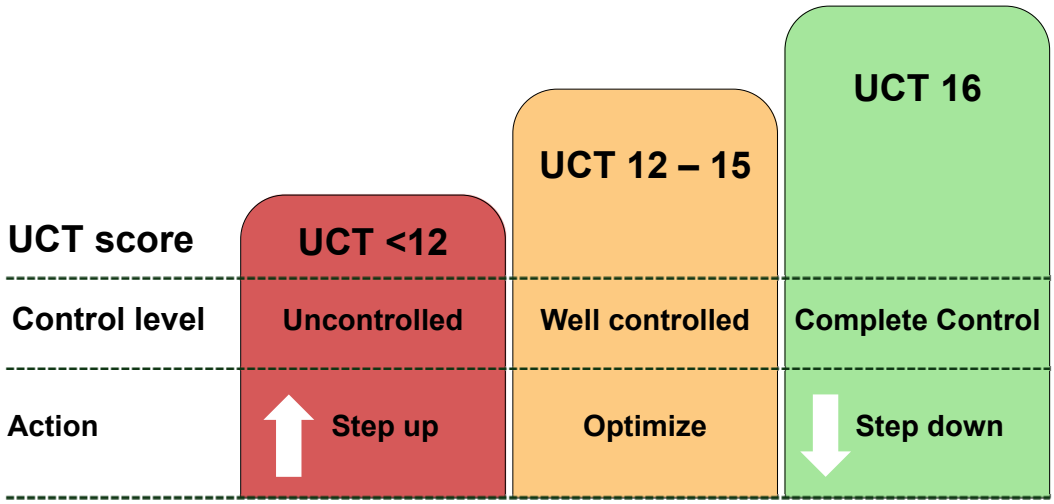
Treatment and Management of Urticaria



UCT = urticaria control test.
Zuberbier T, et al. *Allergy* 2022;7:734-766.

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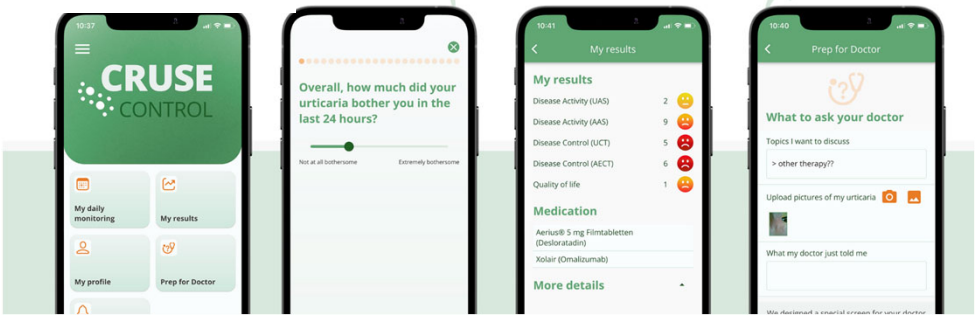
UCARE
Urticaria Centers of Reference and Excellence
A GA²LEN NETWORK

CRUSE®
Chronic Urticaria Self Evaluation

PROM Scores
Current Medication

Prep for Doctor
+ Send Report function



Neisinger S, et al. *Clin Transl Allergy*. 2024 Jan;14(1):e12328.

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CRUSE – *Chronic Urticaria Self-Evaluation App*

The CRUSE advantage for patients and physicians

- CRUSE enables patients to fill out their Patient Reported Outcome Measure (PROMs) daily on their smart device
- CRUSE reminds patients to monitor their quality of life through push notifications
- CRUSE allows patients to send a report of their PROM scores to their treating physician via e-mail, WhatsApp or other communication paths
- CRUSE promotes continued monitoring and documentation of CSU disease activity, impact, and control that is needed for patients to receive optimal treatment

CRUSE app contributes to the understanding of Urticaria through data collection (all anonymized)

- Giving us a true understanding on how patients live
- Seeing the patients' experience on how different medication affects their quality of life
- Allowing insight on how treatment can be improved

CRUSE app

CRUSE CONTROL

www.cruse-control.com

Neisinger S, et al. *Clin Transl Allergy*. 2024 Jan;14(1):e12328.

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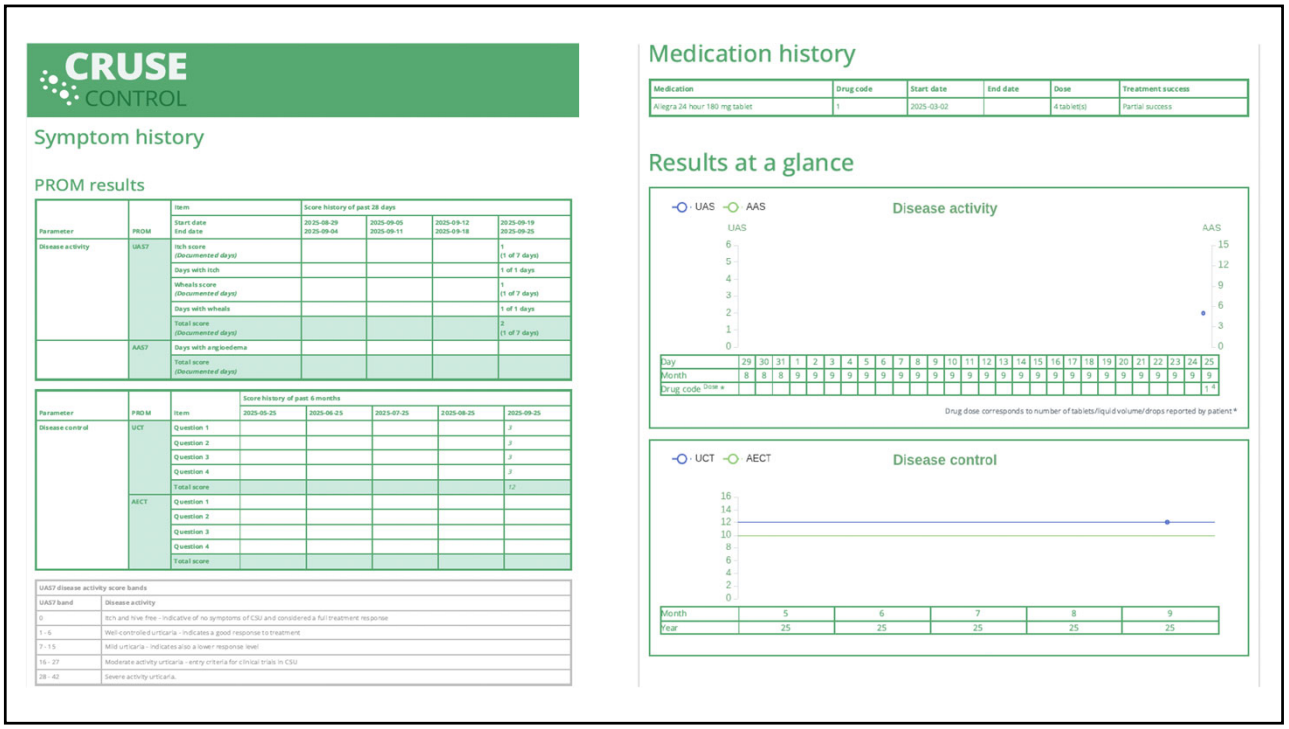

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CU-Q2oL – Chronic Urticaria Quality of Life Questionnaire

- 2 week recall period
- 23-item PROM
- Scoring 0 to 100
  - > 20 = impairment in QoL
- 6 Domains
  - Pruritus
  - Sleep
  - Looks
  - Limitations
  - Impact
  - Swelling

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RETURN TO AGENDA

"But I don't have time to complete a questionnaire like this in clinic"

Then **JUST ASK** how they are doing in each domain!!!

We will never know if we don't ask.

25

Podium to Practice

Assessing QoL and Disease Severity is important for patient care, drug approval and monitoring response to treatment

If we don't ask, we will likely underestimate the impact CSU has on our patients

Assessing QoL and Disease Severity does NOT have to be difficult – Try the CRUSE App

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RETURN TO AGENDA

Choosing Wisely – The Work-Up of CSU and Using Biomarkers to Predict Outcomes and Future Therapies

David A. Khan, MD
Professor of Medicine and Pediatrics
Allergy & Immunology Program Director

UT SOUTHWESTERN MEDICAL CENTER

1

1

Disclosures

- No relevant disclosures

All medications other than antihistamines and omalizumab and dupiluamb are considered "off-label" for treatment of chronic urticaria

2

2

RETURN TO AGENDA

Diagnostic Evaluation in Urticaria

How Many and What Tests Are Required?

3

3

Original Article

The Diagnostic Workup in Chronic Spontaneous Urticaria—What to Test and Why

Martin Metz, MD[a], Sabine Altrichter, MD[a], Thomas Buttgereit, MD[a], Joachim W. Fluhr, MD[a], Jie Shen Fok, MD[a,b,c], Tomasz Hawro, MD[a], Qingqing Jiao, PhD[d], Pavel Kolkhir, MD[a,e], Karoline Krause, MD[a], Markus Magerl, MD[a], Polina Pyatilova, MD[a,f], Frank Siebenhaar, MD[a], Huichun Su, MD[a,g], Dorothea Terhorst-Molawi, MD[a], Karsten Weller, MD[a], Yi-Kui Xiang, MD[a], and Marcus Maurer, MD[a] *Berlin, Germany; Melbourne, Vic, Australia; Suzhou, Jiangsu and Fuzhou, Fujian, China; and Moscow, Russia*

What to do in every CSU patient

Questions	Physical examination*	Basic tests**	UCT

* Including review of patient photo documentation
** Differential blood count, CRP/Erythrocyte sedimentation rate, IgG-anti-TPO, total IgE

Confirm	Rule out differential diagnoses
Cause	Look for indicators of CSU^{aiTI}, CSU^{aiTIIb}
Cofactors	Identify potential triggers, aggravators
Comorbidities	e.g. check for CIndU, autoimmunity, mental health
Consequences	e.g. identify problems with sleep, distress, sexual health, work and social performance
Components	Assess potential biomarkers or predictors of treatment response
Course	Monitor CSU activity, impact and control

J Allergy Clin Immunol Pract. 2021;9(6):2274-83.

4

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RETURN TO AGENDA

Choosing Wisely
An initiative of the ABIM Foundation

American Academy of Allergy, Asthma & Immunology

American Academy of Allergy Asthma & Immunology

Five Things Physicians and Patients Should Question

I

Don't perform unproven diagnostic tests, such as immunoglobulin G (IgG) testing or an indiscriminate battery of immunoglobulin E (IgE) tests, in the evaluation of allergy.

Appropriate diagnosis and treatment of allergies requires specific IgE testing (either skin or blood tests) based on the patient's clinical history. The use of other tests or methods to diagnose allergies is unproven and can lead to inappropriate diagnosis and treatment. Appropriate diagnosis and treatment is both cost effective and essential for optimal patient care.

Don't order sinus computed tomography (CT) or indiscriminately

3

Don't routinely do diagnostic testing in patients with chronic urticaria.

In the overwhelming majority of patients with chronic urticaria, a definite etiology is not identified. Limited laboratory testing may be warranted to exclude underlying causes. Targeted laboratory testing based on clinical suspicion is appropriate. Routine extensive testing is neither cost effective nor associated with improved clinical outcomes. Skin or serum-specific IgE testing for inhalants or foods is not indicated, unless there is a clear history implicating an allergen as a provoking or perpetuating factor for urticaria.

4

Don't recommend replacement immunoglobulin therapy for recurrent infections unless impaired antibody responses to vaccines are demonstrated.

Immunoglobulin (gammaglobulin) replacement is expensive and does not improve outcomes unless there is impairment of antigen-specific IgG antibody responses to vaccine immunizations or natural infections. Low levels of immunoglobulins (isotypes or subclasses), without impaired antigen-specific IgG antibody responses, do not indicate a need for immunoglobulin replacement therapy. Exceptions include IgG levels <150mg/dl and genetically defined/suspected disorders. Measurement of IgG subclasses is not routinely useful in determining the need for immunoglobulin therapy. Selective IgA deficiency is not an indication for administration of immunoglobulin.

5

Don't diagnose or manage asthma without spirometry.

Clinicians often rely solely upon symptoms when diagnosing and managing asthma, but these symptoms may be misleading and be from alternate causes. Therefore spirometry is essential to confirm the diagnosis in those patients who can perform this procedure. Recent guidelines highlight spirometry's value in stratifying disease severity and monitoring control. History and physical exam alone may over- or under-estimate asthma control. Beyond the increased costs of care, repercussions of misdiagnosing asthma include delaying a correct diagnosis and treatment.

5

5

Practice parameter

The diagnosis and management of acute and chronic urticaria: 2014 update

Chief Editors: **Jonathan A. Bernstein, MD, David M. Lang, MD, and David A. Khan, MD**

Workgroup Contributors: **Timothy Craig, DO, David Dreyfus, MD, Fred Hsieh, MD, Javed Sheikh, MD, David Weldon, MD, and Bruce Zuraw, MD**

Task Force Reviewers: **David I. Bernstein, MD, Joann Blessing-Moore, MD, Linda Cox, MD, Richard A. Nicklas, MD, John Oppenheimer, MD, Jay M. Portnoy, MD, Christopher R. Randolph, MD, Diane E. Schuller, MD, Sheldon L. Spector, MD, Stephen A. Tilles, MD, and Dana Wallace, MD**

Bernstein JA et al. J Allergy Clin Immunol 2014;133:1270-7.

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Diagnostic Testing in CU

- **SUMMARY STATEMENT 28:** After a thorough history and physical examination, **no diagnostic testing may be appropriate** for patients with CU; however, **limited routine lab testing may be performed** to exclude underlying causes. Targeted lab testing based on clinical suspicion is appropriate. **Extensive routine testing** for exogenous and rare causes of CU, or immediate hypersensitivity skin testing for inhalants or foods, is **not warranted.**

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Routine Labs

- **Summary Statement 28** (cont'd): **Routine laboratory testing** in patients with CU, whose history and physical examination lack atypical features**, rarely yields clinically significant findings**.[C]

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Task Force Labs in CU Consensus

Laboratory Evaluation

- **Routine evaluation. Testing should be selective. There is an honest difference of opinion concerning the appropriate tests that should routinely be performed for patients with CU in the absence of etiologic considerations raised by a detailed history and careful physical exam.**
- **A majority of members of the Practice Parameters Task Force expressed a consensus for the following routine tests in managing a patient with CU without atypical features:**
  - Complete blood count with differential
  - Erythrocyte sedimentation rate and/or C-reactive protein
  - Liver enzymes
  - Thyroid stimulating hormone

The utility of performing the above tests routinely for CU patients has not been established.

9

9

Additional Labs in CU

- **Additional evaluation may be warranted based upon patient circumstances, and may include but not be limited to the diagnostic tests listed below. A thorough history and meticulous physical exam is essential for determining whether these additional tests are appropriate:**
  - Skin biopsy
  - Physical challenge tests
  - Complement system: e.g. C3, C4, and CH_{50}
  - Stool analysis for ova and parasites
  - Urinalysis
  - Hepatitis B and C serologies
  - Chest radiograph and/or other imaging studies
  - Antinuclear antibody (ANA)
  - Rheumatoid factor, anti-citrullinated protein
  - Cryoglobulin levels
  - Serologic and/or skin testing for immediate hypersensitivity
  - Thyroid autoantibodies
  - Serum protein electrophoresis

  More detailed laboratory testing and/or skin biopsy merits consideration if urticaria is not responding to therapy as anticipated.

  Additional laboratory testing may be required prior to initiation of certain medications, e.g. glucose-6-phosphate dehydrogenase (G6PD)

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GUIDELINES

Allergy WILEY

The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria

What routine diagnostic measures should be performed in chronic spontaneous urticaria?

We **recommend** limited investigations. Basic tests include differential blood count, CRP and/or ESR, and in specialized care total IgE and IgG anti-TPO, and more biomarkers as appropriate.

We **recommend** performing further diagnostic measures based on the patient history and examination, especially in patients with long-standing and/or uncontrolled disease.

[1]>75% agreement

Consensus[1]

Expert consensus

Zuberbier T et al. Allergy. 2022;77(3):734-66.

11

11

Original Article

Cost-Utility of Routine Testing in Chronic Urticaria/ Angioedema: A Cohort Study

Ismael Carrillo-Martin, MD[a], Matthew G. Dudgeon, MD, MBA[a], Natalia Chamorro-Pareja, MD[b], Daniela A. Haehn, MD[c], Maritza G. Rivera-Valenzuela, MD[b], Aaron C. Spaulding, PhD[d], Michael G. Heckman, MS[e], Nancy N. Diehl[e], Joan M. Irizarry-Alvarado, MD[f], Haytham Helmi, MD, MPH, CPH[a], and Alexei Gonzalez-Estrada, MD[b] *Jacksonville, Fla*

Patient outcome if testing was performed (N = 543)	
Tests led to no change in outcome	538 (99.1)
Tests led to change in outcome	5 (0.9)
Alternative diagnoses found if testing was performed (N = 543)	
Cushing's syndrome	1 (0.1)
Hashimoto's thyroiditis	1 (0.1)
Iron-deficiency anemia	1 (0.1)
Cold-induced urticaria	1 (0.1)
Scabies	1 (0.1)
Small-vessel vasculitis	1 (0.1)
Urticarial vasculitis	1 (0.1)
Vasculitis	1 (0.1)

- 75% of patients had ≥ 1 test performed, the mean cost was $569/patient
- In only 3 cases, (all skin biopsies showing vasculitis) test results influenced management (0.5%)
- Cost of tests did not change before or after the U.S. practice parameters were published though there were some differences in tests ordered, but not consistent with guideline recommendations.

Carrillo-Martin I, et al. JACI In Practice 2019;7(8):2823-32.

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RETURN TO AGENDA

Original Article

Optimizing Value in the Evaluation of Chronic Spontaneous Urticaria: A Cost-Effectiveness Analysis

Marcus Shaker, MD, MS[a,b,c], John Oppenheimer, MD[d], Dana Wallace, MD[e], David M. Lang, MD[f], Todd Rambasek, MD[g], Mark Dykewicz, MD[h], and Matthew Greenhawt, MD, MBA, MSc[i] *Lebanon and Hanover, NH; Newark, NJ; Fort Lauderdale, Fla; Cleveland and Sandusky, Ohio; St. Louis, Mo; and Aurora, Colo*

- Cost-effective modeling to assess value of routine laboratory screening in CSU
- Average cost was $572
- Screening tests with multiple simulations were not cost-effective
- **Since "benefit of testing is extraordinarily low" routine lab testing is not cost effective**
- Further evidence for not doing routine lab testing in CSU patients with normal histories and physical exams

TABLE II. Laboratory tests (and costs) used in chronic urticaria testing

Test	Frequency ordered	Cost range	Distributed laboratory screening cost
CBC	73.0%	$67-$215	$48.93-$157.02
Basic metabolic panel	71.3%	$46-$57	$32.82-$40.67
Helicobacter pylori ab	6.2%	$70-$186	$4.33-$11.49
ESR	59.8%	$147	$87.95
CRP	5.1%	$29-$156	$1.47-$7.89
TSH	73.6%	$24-$90	$17.66-$66.24
Thyroglobulin ab	35.7%	$45-$177	$16.05-$63.14
Microsomal ab	49.4%	$36-$230	$17.80-$113.71
Tryptase*	11.5%	$200-$263	$23.03-$30.29
ANA	37.4%	$173-$295	$64.63-$110.21
IgE	5.6%	$16-$147	$0.90-$8.26
SPEP	12.1%	$266	$32.13
U/A	38.8%	$163	$63.19
Serum-specific IgE†	4.2%	$320-$1420	$13.48-$59.83
Skin prick test†	5.9%	$760	$44.83
Skin biopsy	0.8%	$317-$610	$2.67-$5.14
Total			$471.88-$673.89
Average			$572.88

Shaker M et al. J Allergy Clin Immunol Pract. 2020;8(7):2360-9.e1.

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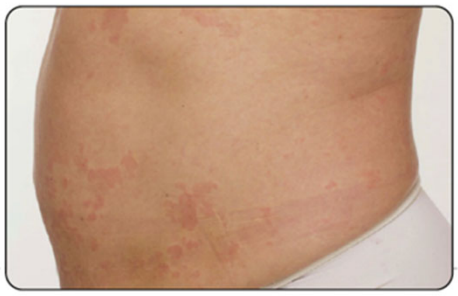
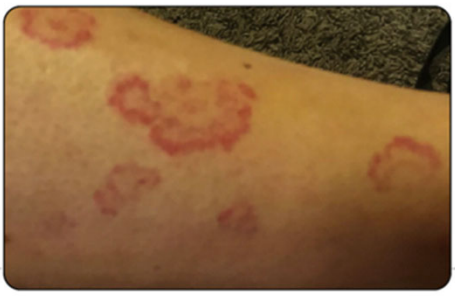
URTICARIA MIMIC – Case Two



Widespread urticarial plaques involving the abdomen.



Resolved urticarial plaques with residual ecchymotic arcuate and semi-arcuate patches.

B

Peter J et al. J Allergy Clin Immunol Pract 2021;9(6):2220-8.

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"Urticaria" Red Flag Symptoms

- Wheals are persistent > 24 hours
- Wheals leave marks
- Overlying skin changes
- Fevers and systemic symptoms

Red flag symptoms are atypical for CSU and skin biopsy and other laboratory investigations may be appropriate

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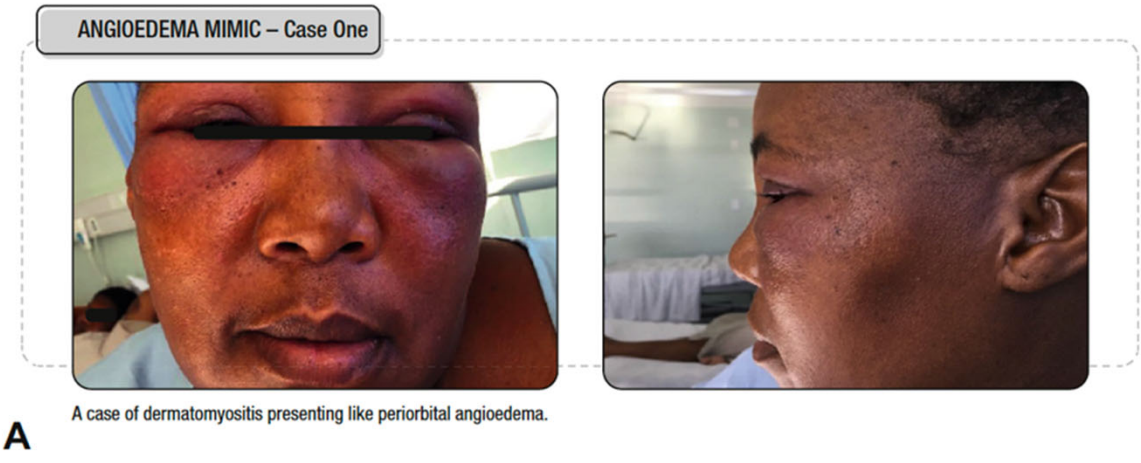

Peter J et al. J Allergy Clin Immunol Pract 2021;9(6):2220-8.

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"Angioedema" Red Flag Symptoms

- Single location
- Persistent swelling
- Pain and burning > itching
- Systemic symptoms

These Red flag symptoms are atypical for angioedema and biopsy and other laboratory investigations may be appropriate

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Urticaria Practice Parameter Project updates

• Leukotriene antagonists	JACI
• Topical corticosteroids	Annals
• Systemic steroids	JACI IP
• Systemic treatments	JACI
• Antihistamines	Under review
• Acupuncture	Finishing analysis
• V&P	Accepted, online in next month
• Occult disease	Distribution September
• Treatment response predictive factors	Distribution planned October
• Problematic trials in allergy	JACI IP (first draft one)

Guideline Meeting

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RETURN TO AGENDA

June 18, 2025

Progress Update

Screening for Occult Disease

WHAT WE'VE COMPLETED

100%

451
records extracted

58 cancer studies
reviewed to restrict those with dedicated cancer screening

Preliminary Analysis

POPULATION CHARACTERISTICS

1,158,303
patients

54
countries

63%
female

NUMBER OF STUDIES BY OUTCOME

12
reporting prevalence of **cancer***

reporting prevalence of **autoimmune diseases**

88
reporting prevalence of **parasitic infections**

WHAT WE'RE WORKING ON

Subgroup Analyses
by age, sex, type of CU

Certainty of Evidence Assessment

Manuscript Draft
Discussion section

19

Biomarkers in CSU

In Search of the Holy Grail

20

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GUIDELINES

Allergy WILEY

The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria

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Consensus[1]

Expert consensus

[1]>75% agreement

Zuberbier T et al. Allergy. 2022;77(3):734-66.

Ann Allergy Asthma Immunol 134 (2025) 408–417

Contents lists available at ScienceDirect

ELSEVIER

Annals of Allergy, Asthma & Immunology

Review

Endotypes, phenotypes, and biomarkers in chronic spontaneous urticaria

Evolving toward personalized medicine

David M. Lang, MD*; Javed Sheikh, MD†; Shyam Joshi, MD‡; Jonathan A. Bernstein, MD§

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† *Department of Clinical Immunology and Allergy, Kaiser Permanente Southern California, Los Angeles, California*
‡ *Department of Medicine, Section of Allergy and Immunology, Oregon Health & Science University, Portland, Oregon*
§ *Division of Rheumatology, Allergy and Immunology, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio*

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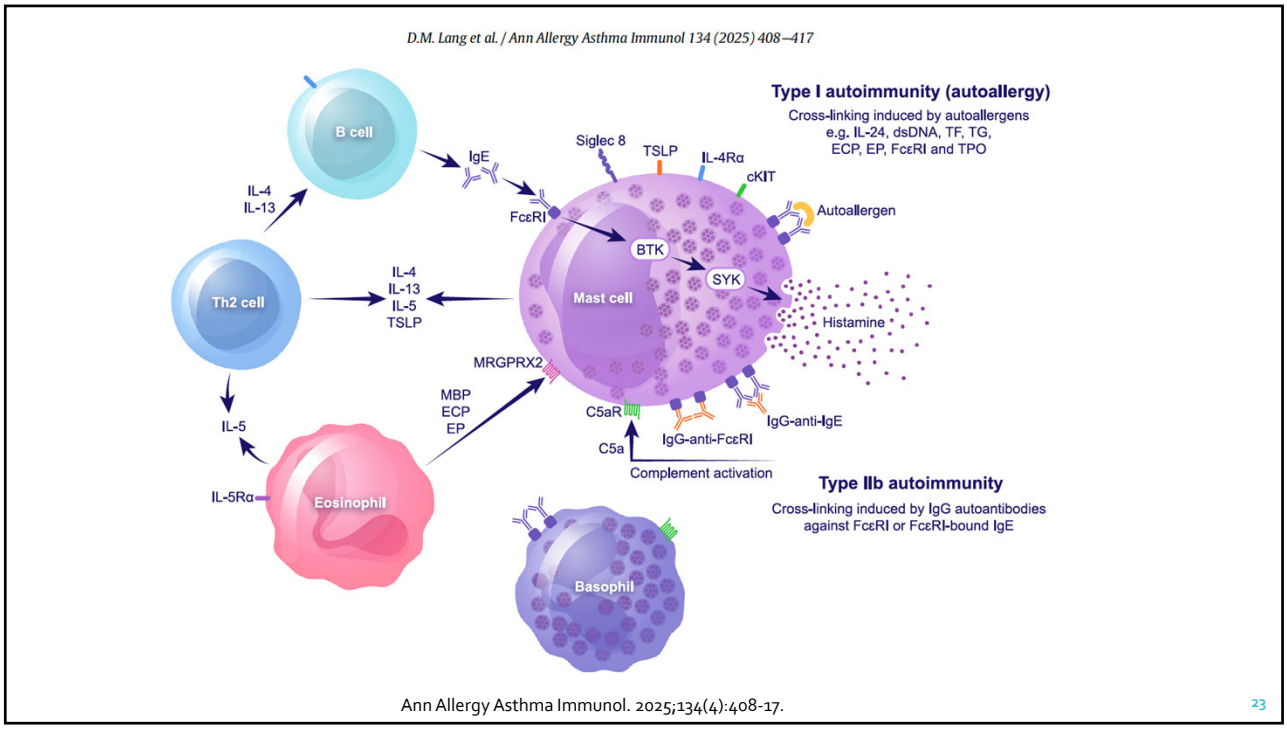

Ann Allergy Asthma Immunol. 2025;134(4):408-17.

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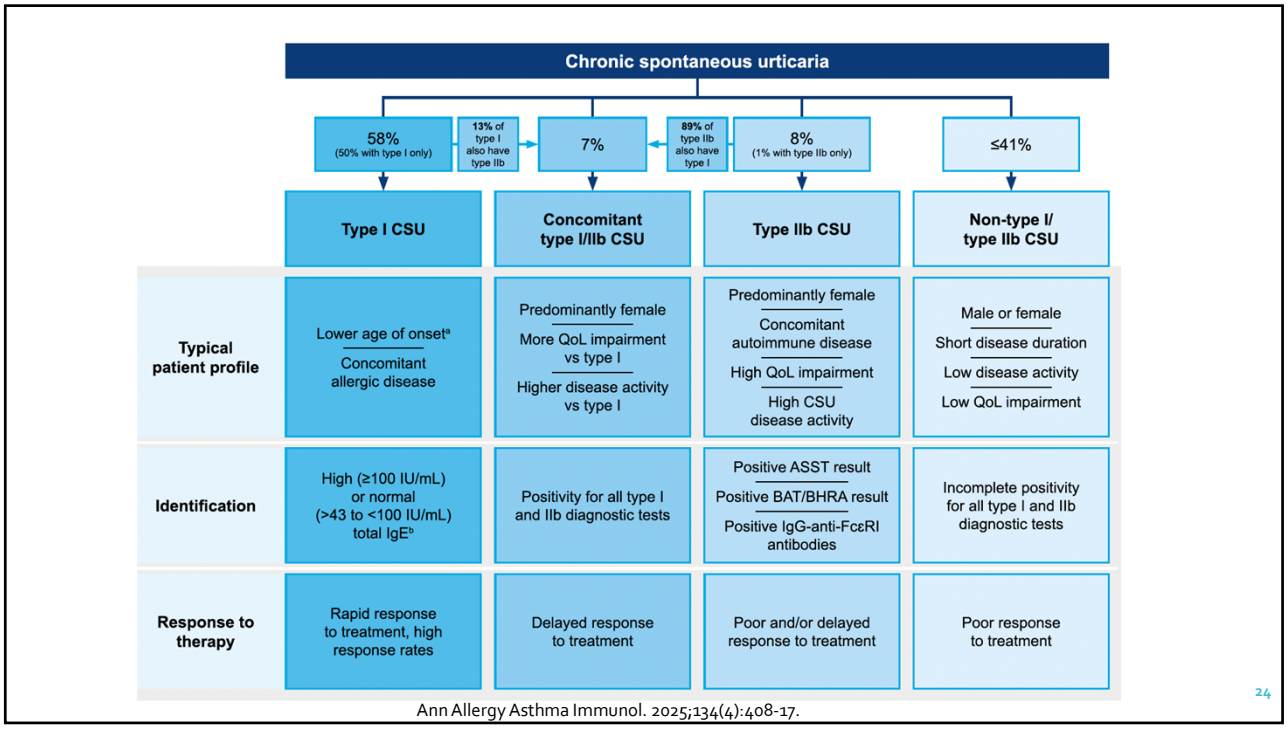

Ann Allergy Asthma Immunol. 2025;134(4):408-17.

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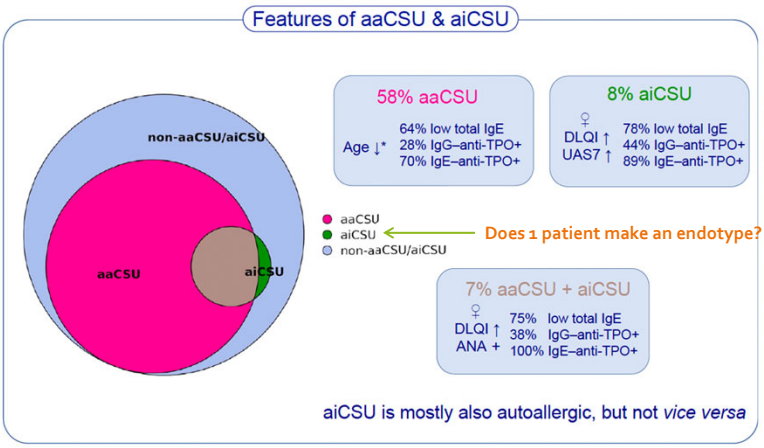
Original Article

Most Patients With Autoimmune Chronic Spontaneous Urticaria Also Have Autoallergic Urticaria, but Not *Vice Versa*

Yi-Kui Xiang, MD[a,b], Pavel Kolkhir, MD[a,b], Jörg Scheffel, PhD[a,b], Merle Sauer, MD[a,b], Carolina Vera, MD[a,b], Stefan Frischbutter, PhD[a,b], Karoline Krause, MD[a,b], Frank Siebenhaar, MD[a,b], Martin Metz, MD[a,b], Marcus Maurer, MD[a,b], and Sabine Altrichter, MD[a,b,c] *Berlin, Germany; and Linz, Austria*



- Retrospective study to evaluate autoimmune and autoallergic markers in 111 CSU patients
- Autoallergic (aaCSU)
  - IgE-antiTPO or IgE-anti-IL-24
- Autoimmune (aiCSU)
  - +ASST or +BAT plus +IgG or IgE-antiFcεRI
- 58% had autoallergic CSU
- 8% had autoimmune CSU
  - **All but 1 also was autoallergic**
- **Raises the question of how distinct these 2 endotypes really are**

J Allergy Clin Immunol Pract. 2023;11(8):2417-25. 25

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Biomarkers That Can Potentially Distinguish Between Different CSU Endotypes and Phenotypes[a]

Category	Potential use	Biomarker	Featured in guidelines as potentially useful for distinguishing between different endotypes and phenotypes[4]
Identification	Marker for type IIb CSU	Low total IgE[b]	✔
		High IgG-anti-TPO	✔
Disease severity and duration	Associated with severe disease	Basopenia ($<0.01\times10^9$/L)	✔
		Positive BAT result[c]	✔
		Positive BHRA result	
		Eosinopenia ($<0.05\times10^9$/L)	✔
		Upregulated cytokines (interferon gamma, TGFβ, IL-23, IL-6, and TNF-α)	
		High C3 and C4 levels	
		High D-dimer	
		High CRP	✔
		High SAA-1	

Ann Allergy Asthma Immunol. 2025;134(4):408-17. 26

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Biomarkers That Can Potentially Distinguish Between Different CSU Endotypes and Phenotypes[a]

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		Upregulated cytokines (interferon gamma, TGFβ, IL-23, IL-6, and TNF-α)	
		High C3 and C4 levels	
		High D-dimer	
		High CRP	✔
		High SAA-1	

Biomarkers and Disease Severity

- Ann Allergy Asthma Immunol. 2025;134(4):408-17.

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Treatment response	Associated with poor omalizumab response	Low baseline serum total IgE[b]	✔
		High IgE- and IgG-anti-TF antibodies	
		High IgG-anti-TPO (kU/L) to total IgE (IU/mL) ratio	✔
		Low basophil FcεRI expression	
		Basopenia ($<0.01\times10^9$/L)	✔
		Eosinopenia ($<0.05\times10^9$/L)	✔
		Positive ASST result[d]	✔
		Positive BHRA result	
	Associated with poor antihistamine response	High total IgE[b]	✔
		High CRP (≥5.0 mg/L)	✔
		High platelet-activating factor	
		Eosinopenia ($<0.05\times10^9$/L)	✔
	Associated with good cyclosporine response	Low total IgE[b]	✔
		Positive BHRA result	
		Positive ASST result[d]	✔

Biomarkers and Treatment Response

- Ann Allergy Asthma Immunol. 2025;134(4):408-17.

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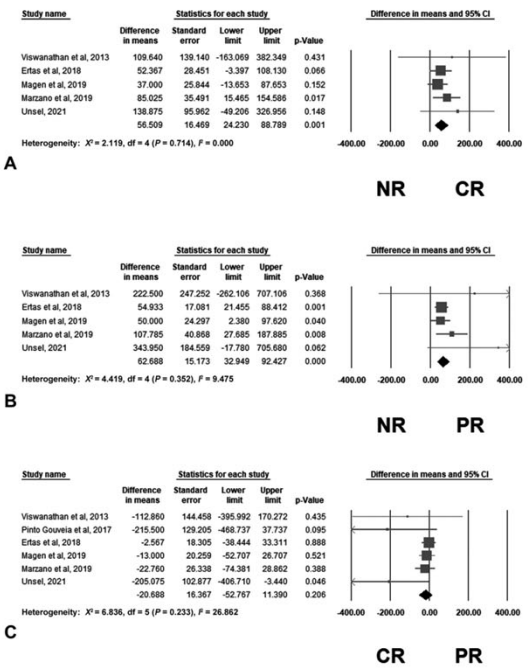
IgE as a Predictor of Omalizumab Response

Original Article

Association Between Serum Total IgE Levels and Clinical Response to Omalizumab for Chronic Spontaneous Urticaria: A Systematic Review and Meta-Analysis

Kai-Wen Chuang, MD[a], Che-Yuan Hsu, MD[b,*], Shiu-Wen Huang, PhD[c,d,e,*], and Hua-Ching Chang, MD, MS[f,g,h]
Taipei, Taiwan; and Sapporo, Japan

- Total IgE levels lower in Non-Responders than Complete or Partial Responders
- IgE levels not different between partial or complete responders



Chuang KW et al. J Allergy Clin Immunol Pract. 2023;11(8):2382-9.e3.

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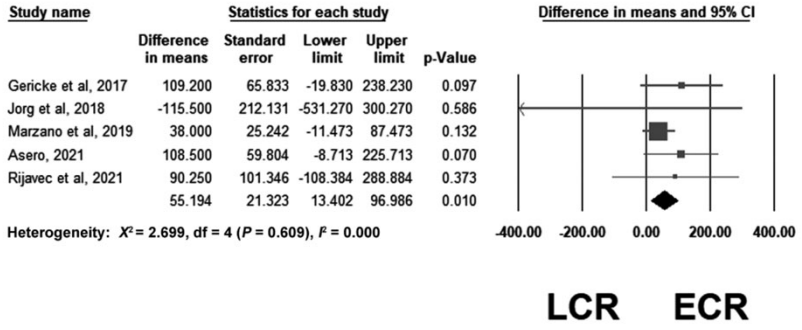
IgE Levels Higher in Early Responders than Late Responders



Chuang KW et al. J Allergy Clin Immunol Pract. 2023;11(8):2382-9.e3.

Editorial

The Crucial Role of IgE as a Predictor of Treatment Response to Omalizumab in Chronic Spontaneous Urticaria

Marcus Maurer, MD[a,b], Pavel Kolkhir, MD[a,b], Sherezade Moñino-Romero, PhD[a,b], and Martin Metz, MD[a,b]
Berlin, Germany

- A standardized range and threshold for baseline IgE levels would be of great help
  - to implement personalized treatment strategies
  - manage patient expectations
  - individualize dosage and treatment intervals

J Allergy Clin Immunol Pract. 2023;11(8):2390-1.

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Limitations of Meta-Analysis

- Most studies not randomized
- Sample size small in many studies
- Most all studies from Europe and may not be generalizable
- Minimum and maximum levels of IgE for predicting response still unclear

Chuang KW et al. J Allergy Clin Immunol Pract. 2023;11(8):2382-9.e3.

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Anti-thyroperoxidase Antibodies as a Predictor of Omalizumab Response

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Chen et al. World Allergy Organization Journal (2021) 14:100501
http://doi.org/10.1016/j.waojou.2020.100501

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Omalizumab treatment and outcomes in Chinese patients with chronic spontaneous urticaria, chronic inducible urticaria, or both

Yudi Chen[a,b,c,d], Miao Yu[b,c,d,e], Xiaojie Huang[f], Ping Tu[b,c,d], Peikun Shi[g], Marcus Maurer[h,**,1] and Zuotao Zhao[b,c,d,*,1]

Characteristics	Responders (n = 120)	Non-responders (n = 18)	*P* value
Demographic features			
Sex: female, n (%)	79 (65.8)	13 (72.2)	0.592
Age (y), mean ± SD	39.59 ± 13.41	39.83 ± 13.85	0.943
Clinical features			
Types of CU, n (%)			
CSU	75 (62.5)	12 (66.7)	0.760
ClndU	30 (25.0)	3 (16.7)	
CSU+ClndU	15 (12.5)	3 (16.7)	
Disease duration (mo), median (IQR)	24 (12-51)	39 (18-81)	0.084
Concomitant angioedema, n (%) [a]	39 (32.5)	10 (55.6)	0.057
Baseline UCT, median (IQR)	3.0 (1.0-4.8)	1.5 (0.0-3.0)	0.120
Baseline UAS7, median (IQR) [b]	28.0 (24.0-31.0)	30.0 (23.5-35.0)	0.249
Treatment period (mo), median (IQR)	6.0 (4.0-12.0)	4.5 (3.8-5.5)	**0.035**
Immunological features			
Total IgE (kU/L), median (IQR)	121.5 (62.5-320.3)	35.0 (12.7-86.5)	**<0.001**
Elevated total IgE, n (%)[c]	59 (53.6)	2 (11.1)	**0.001**
Low total IgE, n (%) [d]	16 (14.5)	11 (61.1)	**<0.001**
Elevated thyroid autoantibodies, n (%) [e]	20 (23.0)	9 (50.0)	**0.041**
Elevated IgG-anti-TPO, n (%) [f]	13 (14.9)	8 (44.4)	**0.012**
Elevated IgG-anti-TG, n (%) [g]	15 (17.2)	6 (33.3)	0.219
IgG-anti-TPO: total IgE, median (IQR)	0.09 (0.03-0.23)	1.22 (0.26-5.48)	**<0.001**
Positive ASST, n (%) [h]	39 (51.3)	8 (66.7)	0.322

- Retrospective analysis of 138 patients treated with omalizumab
- 13 (9%) had elevated IgG anti-TPO Abs
- Response rate lower in those with elevated TPO Abs
  - 44% non-responder
  - 15% responder
- Limitations
  - Small sample size
  - Retrospective study
  - Single center from China

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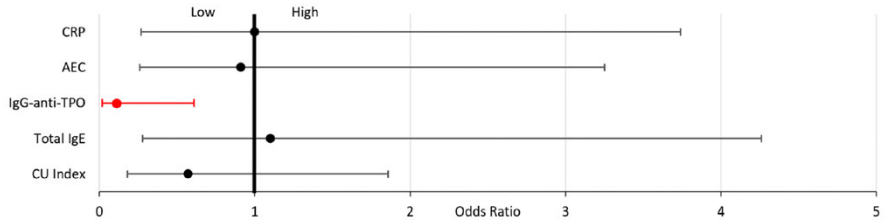
Utility of serum biomarkers in real-world practice for predicting response to omalizumab therapy in patients with chronic spontaneous urticaria

Check for updates

Wesley V. Cain, DO,[a] Roman A. Jandarov, PhD,[b] Mohana Priya, SRP, MPH,[b] Marepalli Rao, PhD, MS,[b] and Jonathan A. Bernstein, MD[a] *Cincinnati, Ohio*



- Retrospective analysis of 46 CSU patients treated with omalizumab
- Multiple biomarkers assessed
- IgE levels not predictive
- High IgG-anti-TPO associated with lower complete response to omalizumab
  - 1/12 vs. 12/28
- Limitations
  - Validated urticaria specific tool not used to assess response
  - Very small sample size
  - Retrospective

J Allergy Clin Immunol Glob. 2025;4(1):100386.

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Clinical Communications

Anti-thyroid peroxidase antibody (anti-TPO antibodies) is higher in children with chronic urticaria who require omalizumab

Zainab Alsaffar, MD[a,*], Roy Khalaf[b,*], Abdulaziz Alrafiaah, MD[c,*], Sarah D. Mohamed[b], Elena Netchiporouk, MD[d], Michael Fein, MD[e], John Sampalis, PhD[f], and Moshe Ben-Shoshan, MD[a]

Clinical Implication

This study suggests that anti–thyroid peroxidase positivity in pediatric chronic spontaneous urticaria predicts a severe form associated with higher likelihood of requiring omalizumab.

- Retrospective analysis of 205 children with CU
- 18 (8.7%) had elevated IgG anti-TPO Abs
- UCT scores not different
- 5/18 (28%) with TPO Abs treated with omalizumab vs 15/187 (8%)
- Very small sample size of anti-TPO patients
- Unclear if response rate to omalizumab different

Characteristics	Elevated anti-TPO level n = 18 n (%)	Nonelevated anti-TPO level n = 187 n (%)	*P* value*
Age (y), median (IQR)	14.5 (8.9–14.9)	8.4 (4.5–13.2)	**.01**
Male sex	6 (33.3)	89 (47.6)	.23
Allergic comorbidities			
Asthma	2 (11.1)	23 (12.3)	.99
Allergic rhinitis	1 (5.6)	8 (4.3)	.57
Atopic dermatitis	2 (11.1)	20 (10.7)	.99
Anaphylaxis	1 (5.6)	4 (2.1)	.37
Food allergy	3 (16.7)	16 (8.6)	.22
Insect sting allergy	0	4 (2.1)	.99
Hay fever	1 (5.6)	12 (6.4)	.99
No allergies	7 (38.9)	83 (44.4)	.81
Other	0	21 (11.2)	.23
Autoimmune disease	0	3 (1.6)	.99
Inflammatory bowel disease	1 (5.6)	3 (1.6)	.31
Cholinergic induced	1 (5.6)	6 (3.2)	.48
Solar induced	0	1 (0.53)	.99
Pressure induced	0	1 (0.53)	.99
Treatment			
Antihistamines	15 (83.3)	155 (82.9)	.99
First-generation antihistamines	3 (16.7)	53 (28.3)	.41
Second-generation antihistamines	14 (77.8)	86 (46.0)	**.02**
Steroids	0	12 (6.4)	.61
Other	1 (5.6)	18 (9.6)	.99
No treatment given	2 (11.1)	16 (8.6)	.66
Omalizumab	5 (27.8)	15 (8.0)	.02

J Allergy Clin Immunol Pract. 2025;13(9):2496-8.

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June 18, 2025

Progress Update

Prognostic factors of treating CU

SCREENING

7962 Titles & Abstracts → 543 Full Texts → 85 Included Records

SOME PROGNOSTIC FACTORS IDENTIFIED

Age	Age of onset of CU	Smoking
Sex	Angioedema	Stress
BMI	CU duration	Anti-TPO antibody positivity

WHAT WE'VE COMPLETED

Title and Abstract Screening after Citation Analysis

Full-text Screening and Data Extraction

WHAT WE'RE WORKING ON

85 Records extracted → IPD data cleaning is ongoing

Data Cleaning & Analysis

Manuscript Draft

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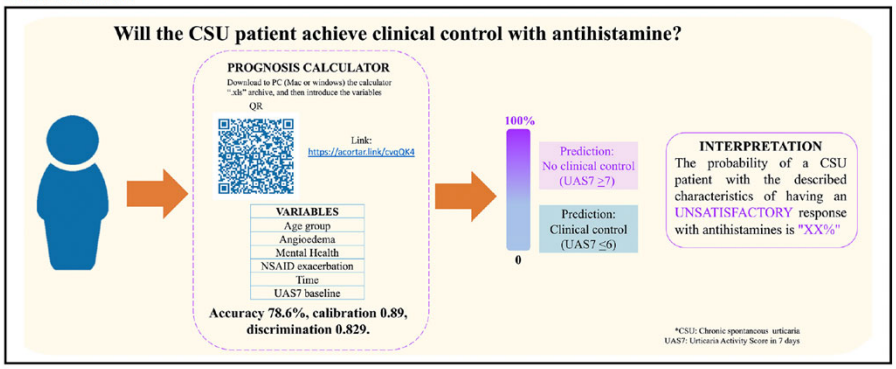
Original Article

Prognostic Calculator of the Clinical Response to Antihistamines in Chronic Urticaria: External Validation

Jorge Sánchez, MD, MSc, EAC, PhD[a], Ana Caraballo, MD[a], Ivan Cherrez, MD, MSc, PhD[b,c,d], Elizabeth García, MD, EAC[e], Jose-Ignacio Larco, MD[f], German Ramon, MD[g], Margarita Velasquez, MD, PhD[h], and Fabian Jaimes, MD, MSc, PhD[i]
Medellín and Bogotá, Colombia; Guayaquil, Ecuador; Berlin, Germany; Lima, Perú; and Buenos Aires, Argentina

VISUAL SUMMARY



- Retrospective study of 542 CSU patients
- Treated with high dose antihistamines
- Outcome UAS 7 ≤6 after 1 month

J Allergy Clin Immunol Pract. 2025;13(9):2361-9.

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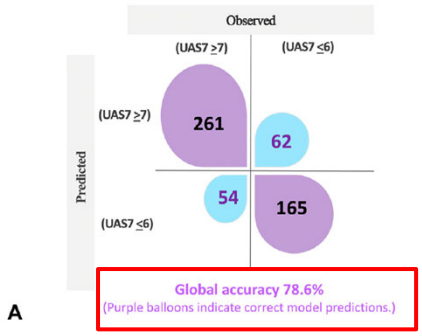

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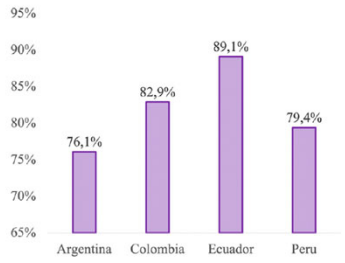

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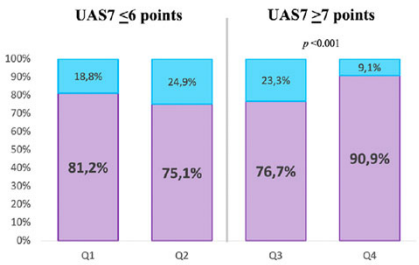

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J Allergy Clin Immunol Pract. 2025;13(9):2361-9.

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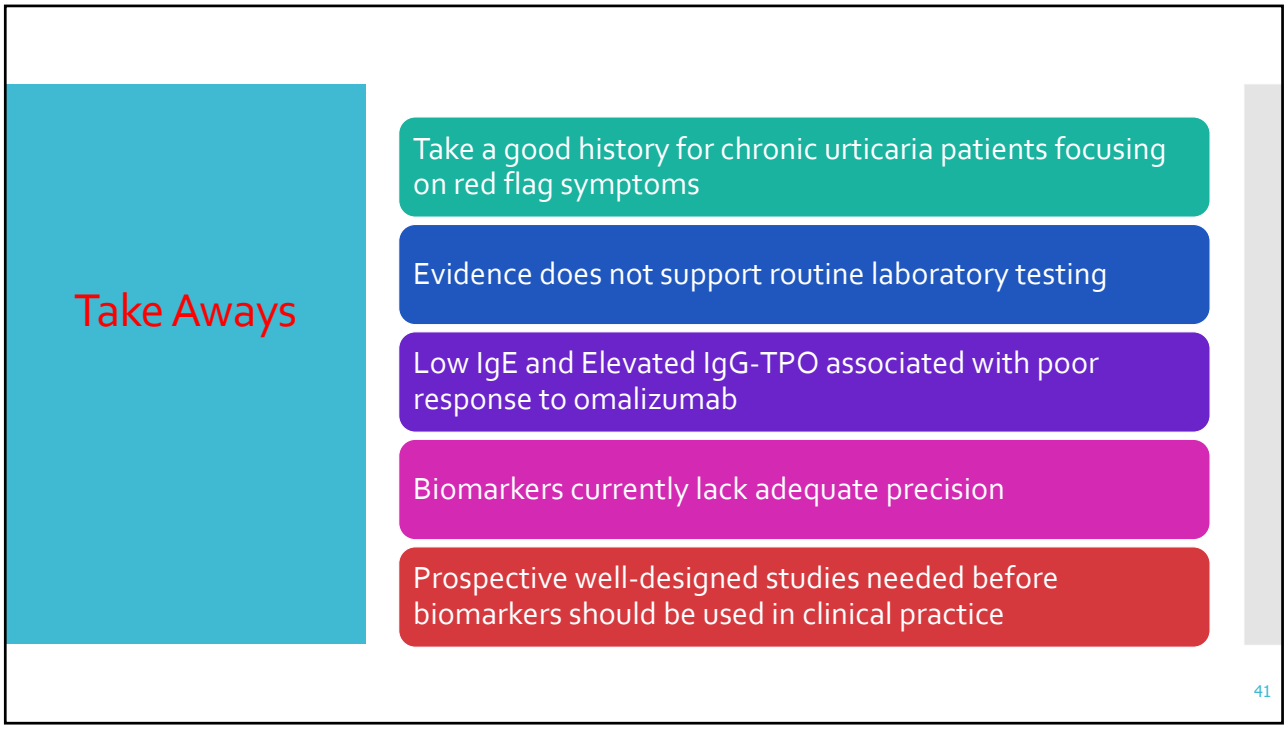

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New and ExcitingTreatments for CSU

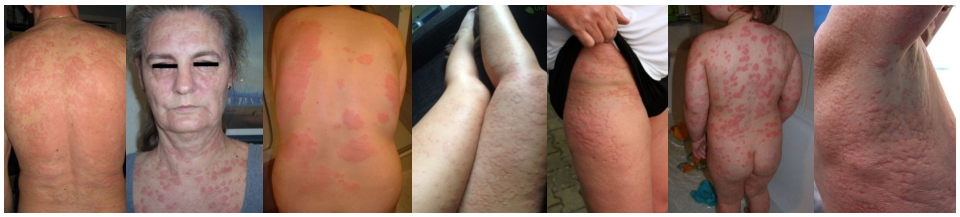
Martin Metz | November 6th, 2025

Institute of Allergology,
Charité - Universitätsmedizin Berlin

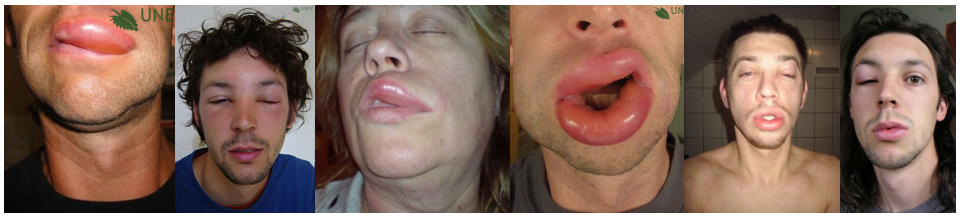
Fraunhofer Institute of Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin

1

Chronic spontaneous urticaria (CSU)



Itchy wheals



Angioedema

The (still) current treatment algorithm

2020 EAACI/GA²LEN/EuroGuiDerm/APAAACI Urticaria Guideline

1. **Start with standard dose 2nd generation H1-Antihistamine**
   if needed:
   Increase 2nd generation AH dose (up to 4x)*

   ↓ **If inadequate control on high dose:** after 2-4 weeks or earlier, if symptoms are intolerable

2. **Add on to 2nd generation AH: Omalizumab**
   if needed:
   Increase dose or shorten intervall*

   ↓ **If inadequate control :** within 6 months or earlier, if symptoms are intolerable

3. **Add on to 2nd generation AH: ciclosporin***

Consider referral to specialist

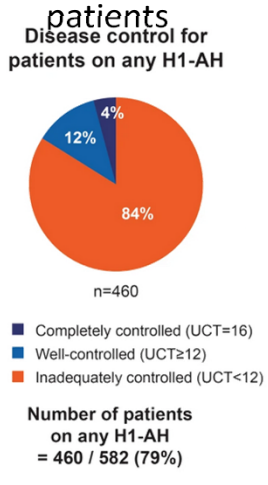
Should be performed under the supervision of a specialist

* Not approved for the treatment of CSU; Zuberbier et al., Allergy. 2022;77:734-766

3

What are the current problems in adequate CSU patient care?

1. Insufficient control by antihistamines in the majority of patients



Urticaria voices study

CHARITÉ | Institute of Allergology

Bernstein et al., Dermatol Ther (Heidelb). 2025;15:2201-15

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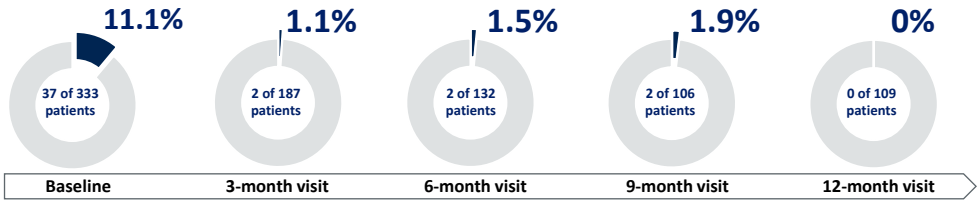
What are the current problems in adequate CSU patient care?

1. Insufficient control by antihistamines in the majority of patients
2. Too few patients receive recommended, approved and indicated treatments (i.e. 2nd generation AH, up-dosing of AHs, omalizumab)

Data from the **AWARE** study (a European based RWE study)

Proportion of patients escalated to biologic treatment following insufficient response to up-dosed H_1-AHs, %



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Based on Laires et al., EAACI Congress 2023, Hamburg, Germany. Poster TP-C105

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What are the current problems in adequate CSU patient care?

1. Insufficient control by antihistamines in the majority of patients
2. Too few patients receive recommended, approved and indicated treatments (i.e. 2nd generation AH, up-dosing of AHs, omalizumab)

→ Patient preference (i.e. needle phobia)

→ Physician‘s fear of adverse events (anaphylaxis)

→ Patients receive AH, but disease control is not monitored

→ Severity of disease is not sufficiently recognized

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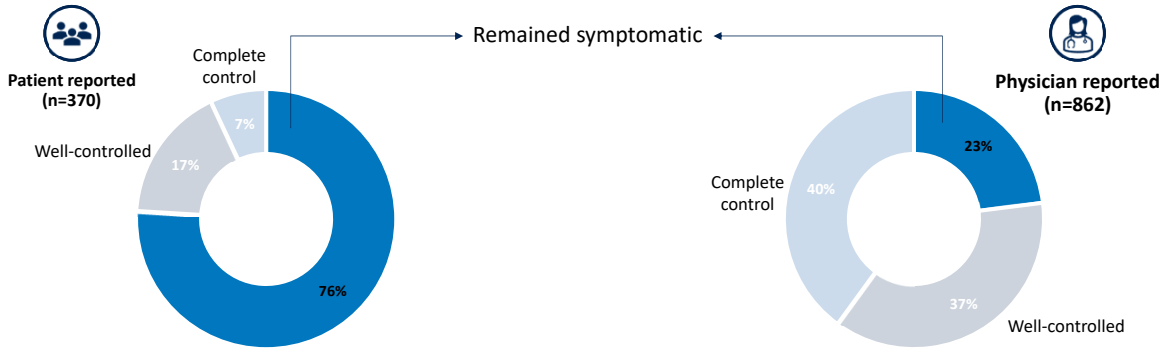
Perception of diseases control by AH differs between patients and physicians

Urticaria Voices Study **(survey; self-reported)**

Independently Evaluated Patient And Physician Perceptions Of CSU Disease Control With Standard Dose Second-generation H_1-AHs



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Based on Laires et al., EAACI Congress 2023, Hamburg, Germany. Poster TP-C105

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Perception of diseases control by AH differs between patients and physicians

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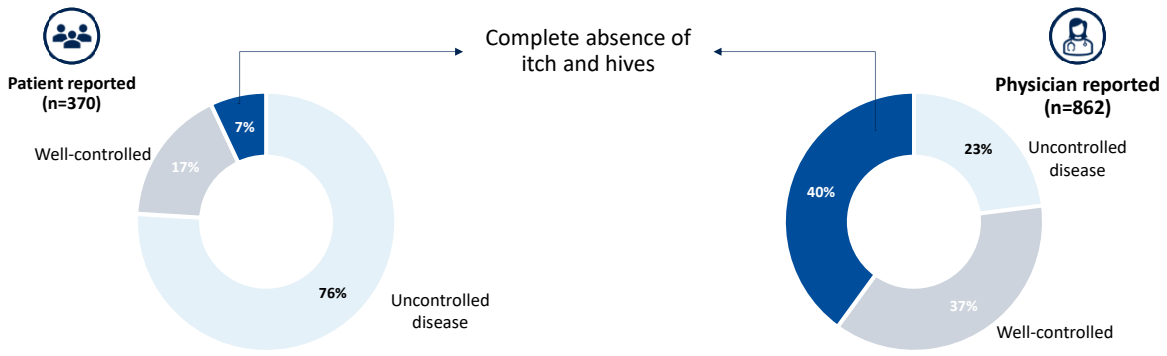
Independently Evaluated Patient And Physician Perceptions Of CSU Disease Control With Standard Dose Second-generation H_1-AHs



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Based on Laires et al., EAACI Congress 2023, Hamburg, Germany. Poster TP-C105

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What are the current problems in adequate CSU patient care?

1. Insufficient control by antihistamines in the majority of patients
2. Too few patients receive recommended, approved and indicated treatments (i.e. 2nd generation AH, up-dosing of AHs, omalizumab)
3. Not all patients respond to omalizumab

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Individual time to response to omalizumab

Institute of Allergology

Maurer et al., EAACI 2016

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The (still) current treatment algorithm

2020 EAACI/GA²LEN/EuroGuiDerm/APAAACI Urticaria Guideline

1 **Start with standard dose 2nd generation H1-Antihistamine**
if needed:
Increase 2nd generation AH dose (up to 4x)

There is a need for new treatment options!

2 **Add on to 2nd generation AH: Omalizumab**
if needed:
Increase dose or shorten intervall

If inadequate control : within 6 months or earlier, if symptoms are intolerable

3 **Add on to 2nd generation AH: ciclosporin**

Consider referral to specialist

Should be performed under the supervision of a specialist

Zuberbier et al., Allergy. 2022;77:734-766

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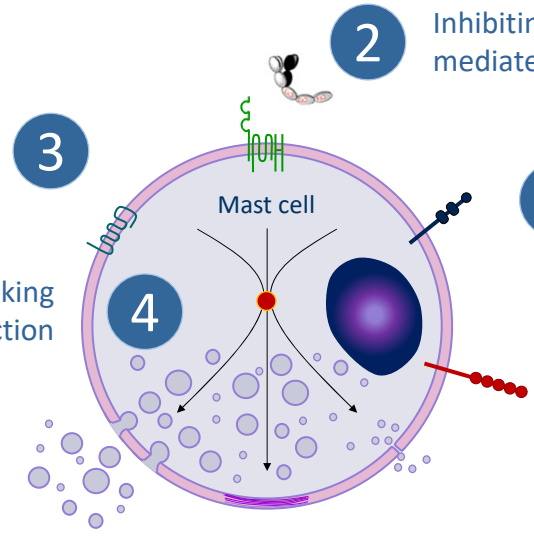
Therapeutical approaches in CSU



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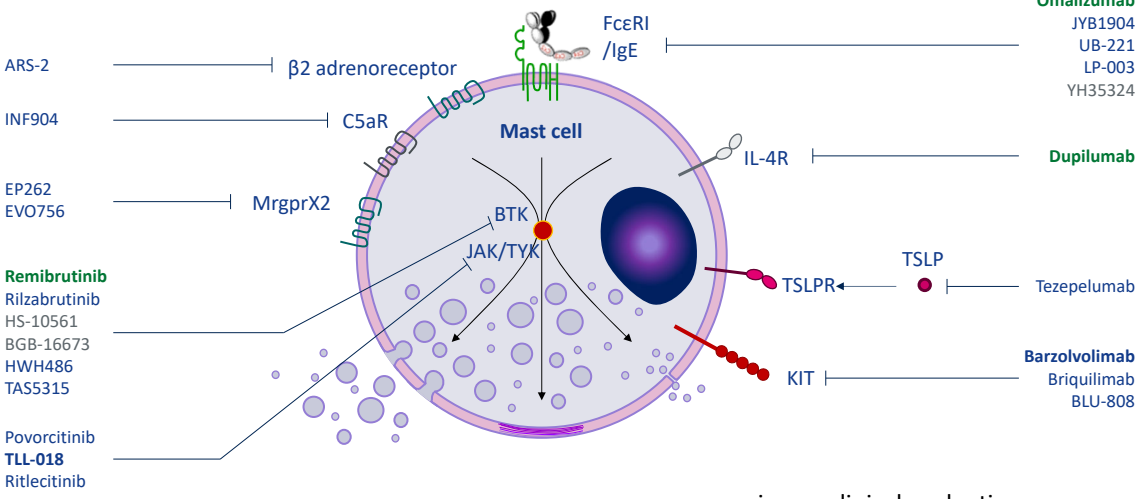
Targets currently under development in CSU

Approved/Ph 3 available
In Phase 3
In Phase 2
In Phase 1b



…more in pre-clinical evaluation

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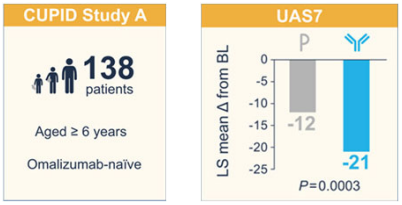
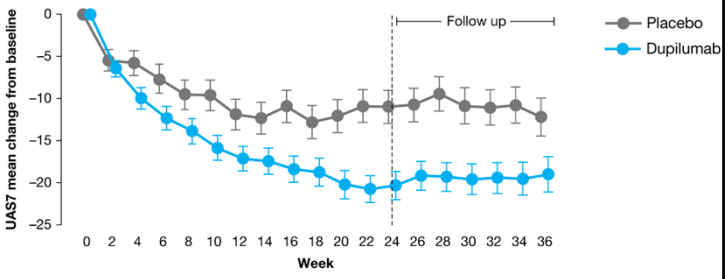
Based on ClinicalTrials.gov, accessed 15 September 2025

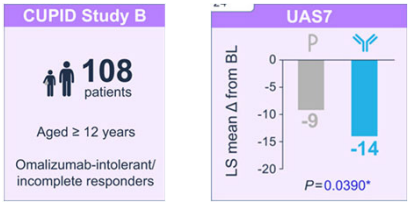
13

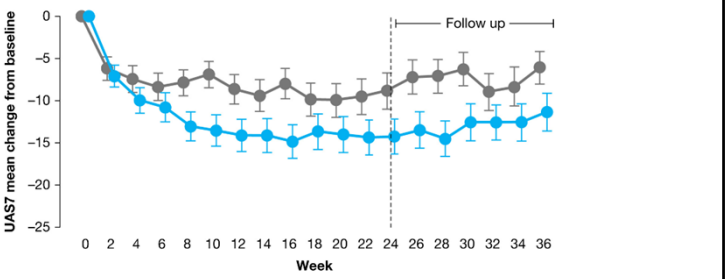
Efficacy of dupilumab in CSU

Results of the LIBERTY-CSU (CUPID) trials, two phase 3 studies









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Maurer et al., J Allergy Clin Immunol 2024; 2024;154:184-194

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Safety of dupilumab in CSU

Combined reported safety data of the LIBERTY-CSU (CUPID) trials

	Safety Outcomes Pooled for CUPID A and CUPID B 24 Weeks of Treatment	
Patients, n (%)	Dupilumab (n=124)	Placebo (n=122)
TEAE	71 (57.3)	69 (56.6)
Severe TEAE	3 (2.4)	5 (4.1)
Treatment-emergent SAE	5 (4.0)	7 (5.7)
TEAE leading to death*	0	1 (0.8)
TEAE leading to permanent study intervention discontinuation	2 (1.6)	4 (3.3)
TEAEs with frequency ≥5% in any treatment group		
CSU	10 (8.1)	9 (7.4)
Nasopharyngitis	2 (1.6)	7 (5.7)
Injection-site erythema	3 (2.4)	7 (5.7)

CUPID C: Overall rates of participants with TEAEs were the same for both groups (~53%)

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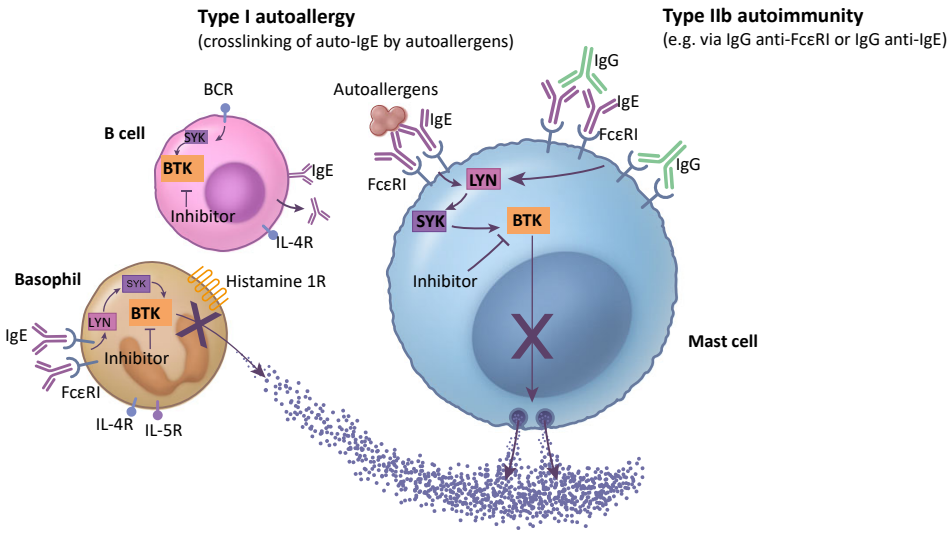
Maurer et al., J Allergy Clin Immunol 2024; 2024;154:184-194
Casale T, et al. Ann Allergy Asthma Immunol. 2024;133(6):S2-S4

15

Inhibition of Bruton's tyrosine kinase (BTK) in CSU



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Maurer, et al. Clin Exp Allergy 2019;49:655-62; Angst et al. J Med Chem 2020;63:5102-18; Neys et al. Front Cell Dev Biol 2021;9:668131; Maurer et al. J Allergy Clin Immunol 2022;150:1498-506; Gimeno et al. Clin Transl Allergy 2023;13:e12227

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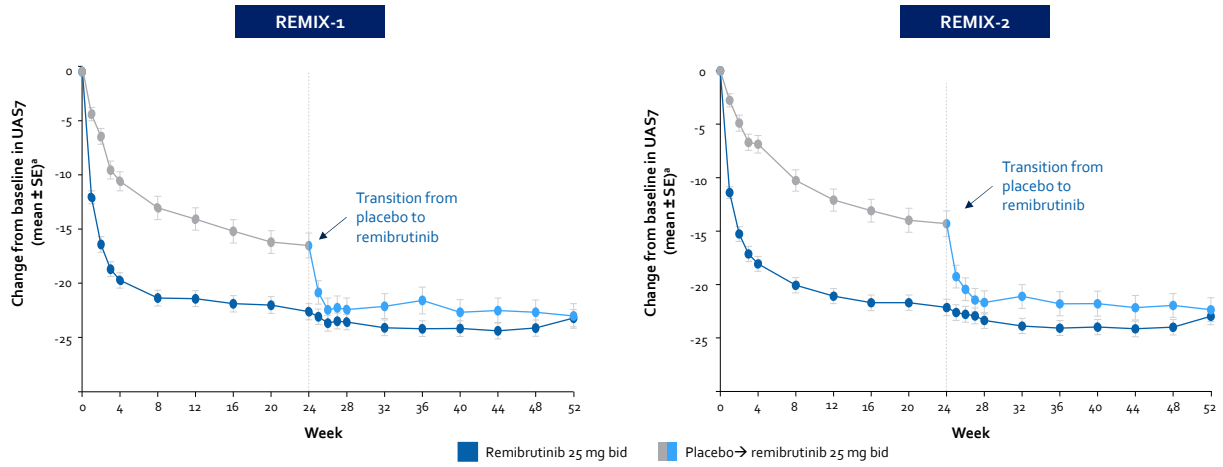
* Remibrutinib is not approved for CSU

Efficacy of Remibrutinib in CSU*

Results of the REMIX 1 & 2 trials, two phase 3 studies



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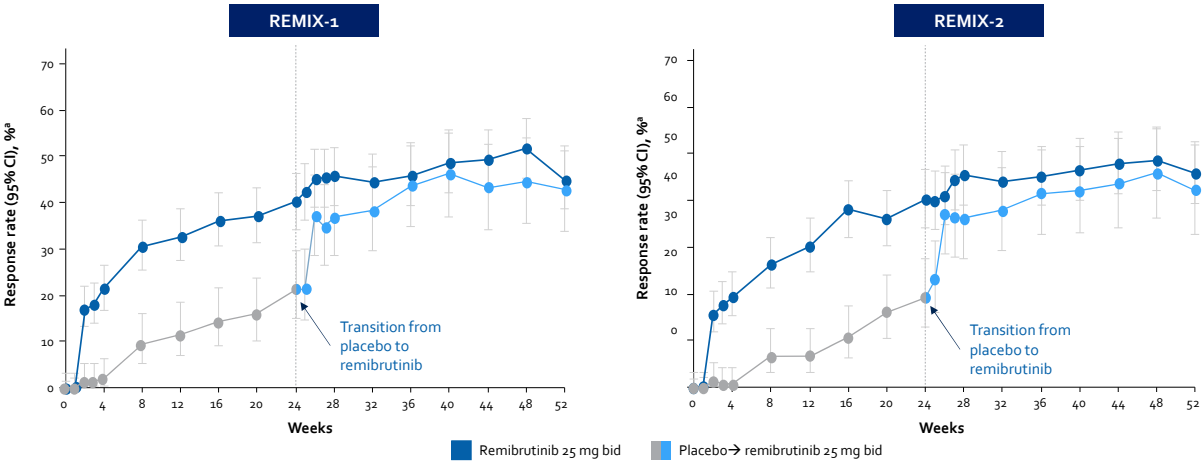
Metz et al., N Engl J Med. 2025 Mar 6;392(10):984-994
Metz et al., oral presentation L-OAS-CT 01, EAACI 2024, Valencia, Spain

17

* Remibrutinib is not approved for CSU

Complete Responses (UAS7=0) With Remibrutinib in CSU*



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Metz et al., N Engl J Med. 2025 Mar 6;392(10):984-994
Metz et al., oral presentation L-OAS-CT 01, EAACI 2024, Valencia, Spain

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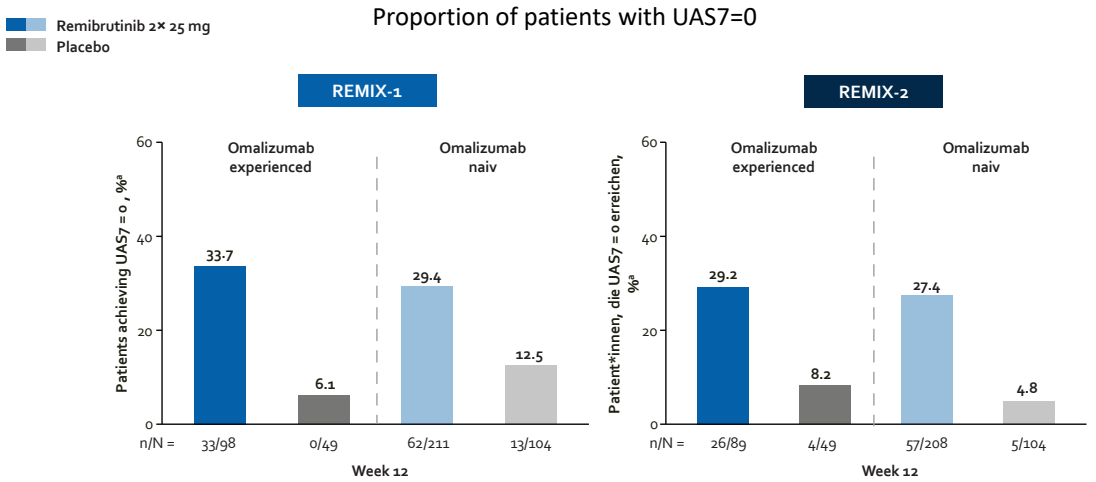
* Remibrutinib is not approved for CSU

Remibrutinib is effective in patients with or without prior exposure to omalizumab*



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Mosnaim, AAAAI 2024, Poster L28

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Adverse events – 52 week data

	Double-blind period[a]		Entire study period[a]	Open label[a]
	Remibrutinib (n=606)	Placebo (n=306)	Remibrutinib (n=606)	Transitioned to remibrutinib (n=262)
Median exposure, weeks	**24**	**24**	**52.1**	**28.1**
COVID-19, n (%), [EAIR]	65 (**10.7**), [26.0]	35 (**11.4**), [28.0]	94 (**15.5**), [19.0]	19 (**7.3**), [14.1]
Nasopharyngitis, n (%), [EAIR]	40 (**6.6**), [15.7]	14 (**4.6**), [10.9]	55 (**9.1**), [10.7]	9 (**3.4**), [6.5]
Headache, n (%), [EAIR]	38 (**6.3**), [15.0]	19 (**6.2**), [14.8]	47 (**7.8**), [9.0]	4 (**1.5**), [2.8]
Upper respiratory tract infection, n (%), [EAIR]	18 (**3.0**), [6.9]	6 (**2.0**), [4.6]	34 (**5.6**), [6.4]	11 (**4.2**), [7.9]
Urinary tract infection, n (%), [EAIR]	19 (**3.1**), [7.3]	8 (**2.6**), [6.1]	28 (**4.6**), [5.2]	4 (**1.5**), [2.8]
Petechiae, n (%), [EAIR]	23 (**3.8**), [8.9]	1 (**0.3**), [0.8]	24 (**4.0**), [4.5]	7 (**2.7**), [5.0]
Urticaria, n (%), [EAIR]	15 (**2.5**), [5.7]	15 (**4.9**), [11.7]	20 (**3.3**), [3.7]	7 (**2.7**), [5.0]

	Double-blind period[a]		Entire study period[a]	Open label[a]
	Remibrutinib (n=606)	Placebo (n=306)	Remibrutinib (n=606)	Transitioned to remibrutinib (n=262)
Median exposure, weeks	**24**	**24**	**52.1**	**28.1**
ALT or AST >3x ULN, n (%)	8 (**1.3**)	4 (**1.3**)	9 (**1.5**)	3 (**1.2**)
ALT or AST >20x ULN, n (%)	0	0	0	0
ALT or AST >3x ULN and TBL >2x ULN (Biochemical Hy's Law), n (%)	0	0	0	0

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Metz et al., oral presentation, EAACI 2024, Valencia, Spain

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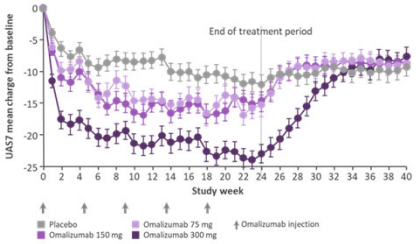
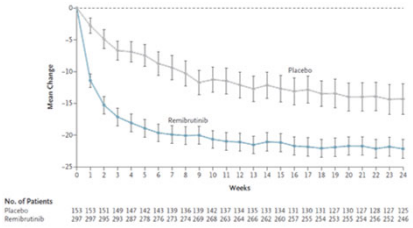
Comparison of efficacy over time between phase 3 studies in CSU

Note: Different patients, different times, no direct comparison possible



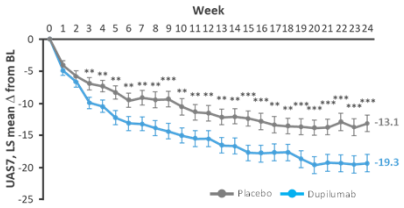
Omalizumab ASTERIA 1

Saini et al. J Invest Dermatol. 2015;135(1):67-75.



Remibrutinib REMIX-2

Metz et al., New Engl J Med. 2025, 392: 984-994



Dupilumab Pooled CUPID A + C:

Bernstein et al. Eastern Allergy Conference (EAC) 2025; Palm Beach, FL, USA.

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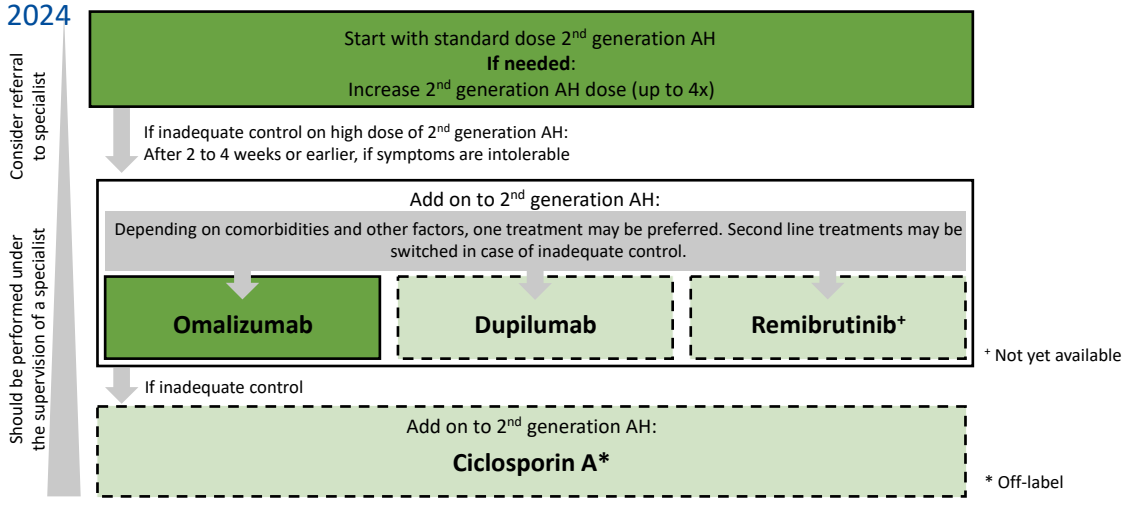
The (potential) future treatment algorithm of the international Guideline for the Definition, Classification, Diagnosis and Management of Urticaria - 2024



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Adapted consented version, based on Urticaria Guideline Meeting Dec 06th 2024, Berlin

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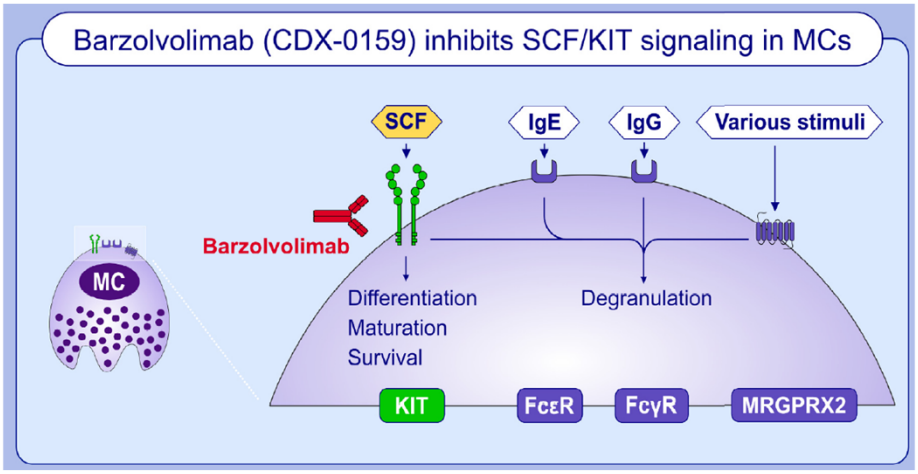
Targeting KIT – a novel approach to achieve complete control of signs & symptoms



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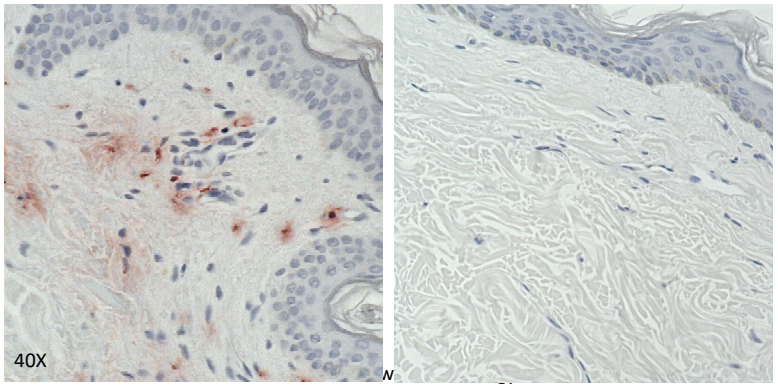
Terhorst-Molawi et al., Allergy. 2023;78:1269-79

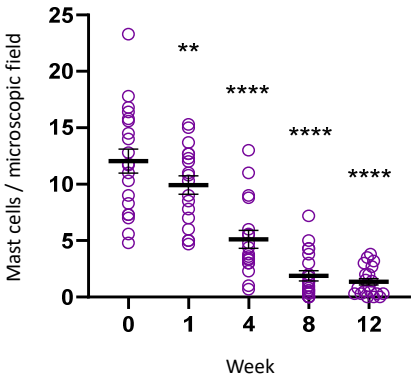
23

Barzolvolimab depletes mast cells

Tryptase staining in patients with CINDU (cold urticaria and symptomatic dermographism)



Baseline Week 12



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Terhorst-Molawi et al., Allergy. 2023;78:1269-79

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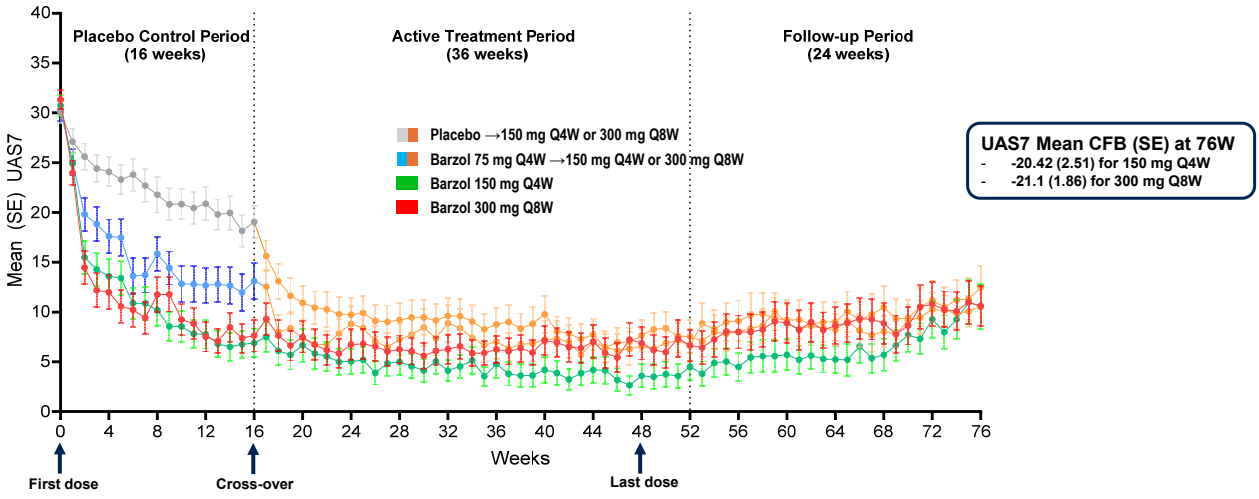
* Barzolvolimab is not approved for CSU

Change in UAS7 with barzolvolimab for 52 weeks, including 28 follow-up*

Results of a phase 2 study: early and sustained responses



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Metz et al., EAACI 2025 Glasgow, oral late breaker

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Phase 2 safety data of Barzolvolimab

- Most events were grade 1 (mild), mechanism-related (KIT) and expected to be reversible
- Adverse events were not dose dependent
- No association between infections and neutropenia/decreased neutrophil counts

	Placebo Controlled Period (16 weeks)		Full Treatment Period (52 weeks)	Placebo → Barzolvolimab (36 weeks)
Patients, n (%)	**Barzolvolimab (N= 156)**	**Placebo (N= 51)**	**Barzolvolimab (N= 156)**	**Transitioned to Barzolvolimab (N=48)**
At least one AE	103 (66)	20 (39)	139 (89)	32 (67)
Treatment Related SAEs	0	0	2 (1)	0
Most frequent AEs by Preferred Term (≥10% of patients in any treatment group)				
Hair color changes	22 (14)	0	40 (26)	8 (17)
Neutropenia / Neutrophil Count Decreased	14 (9)	0	26 (17)	2 (4)
Urticaria	15 (10)	5 (10)	23 (15)	3 (6)
Skin hypopigmentation	2 (1)	0	21 (13)	9 (19)
Nasopharyngitis	6 (4)	3 (6)	15 (10)	4 (8)

All dose levels (75mgQ4W, 150mgQ4W, 300mgQ8W) combined

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Maurer & Metz et al., EADV 2024 Amsterdam, oral late breaker

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Takeaways

- Too few patients with CSU receive effective treatment!
- Novel effective and safe treatment options are/will be available
- Possibility for personalized treatment in the future – faster and more effective treatment
- Room for shared-decision making (i.e. oral vs. Injectable; efficacy vs. adverse event)
- „no more signs and symptoms“ and „treat the disease until it is gone!“

Marcus Maurer

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SCAN ME

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Pruritus: Nerves and the Immune System

Timothy Berger

1

Agenda

- Measuring Itch
- Classifying Itch
- Sensitization
- Treating Pruritus

2

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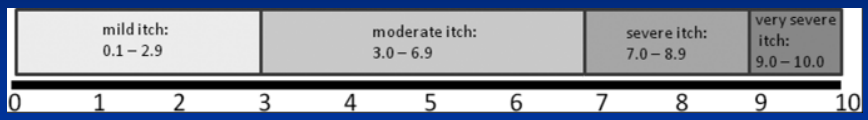
Measure Itch

Numerical Rating Scale (NRS)



NRS > 7 severely impacts QOL

Decrease of NRS is measure of efficacy of drugs

(% patients achieving NRS decrease of 4)

Placebo effect is 25%

Figure 1 Acta Derm Vernerol 2013; 93:511

3

Neuroanatomy of Pruritus

- Unique set of non-myelinated C fibers
- Extend into the epidermis
- Cell body in Dorsal Root Ganglion (DRG)
- NON-HISTAMINERGIC
- Itch is a disorder of the nervous system

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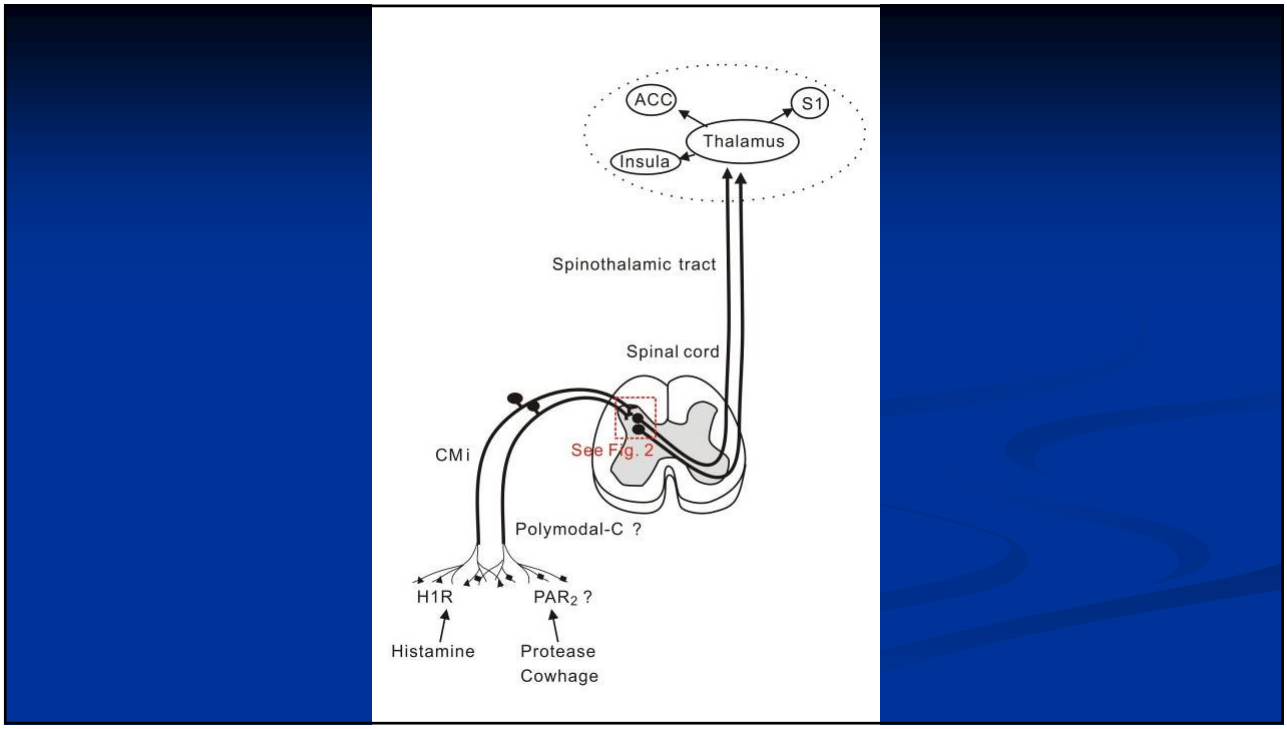

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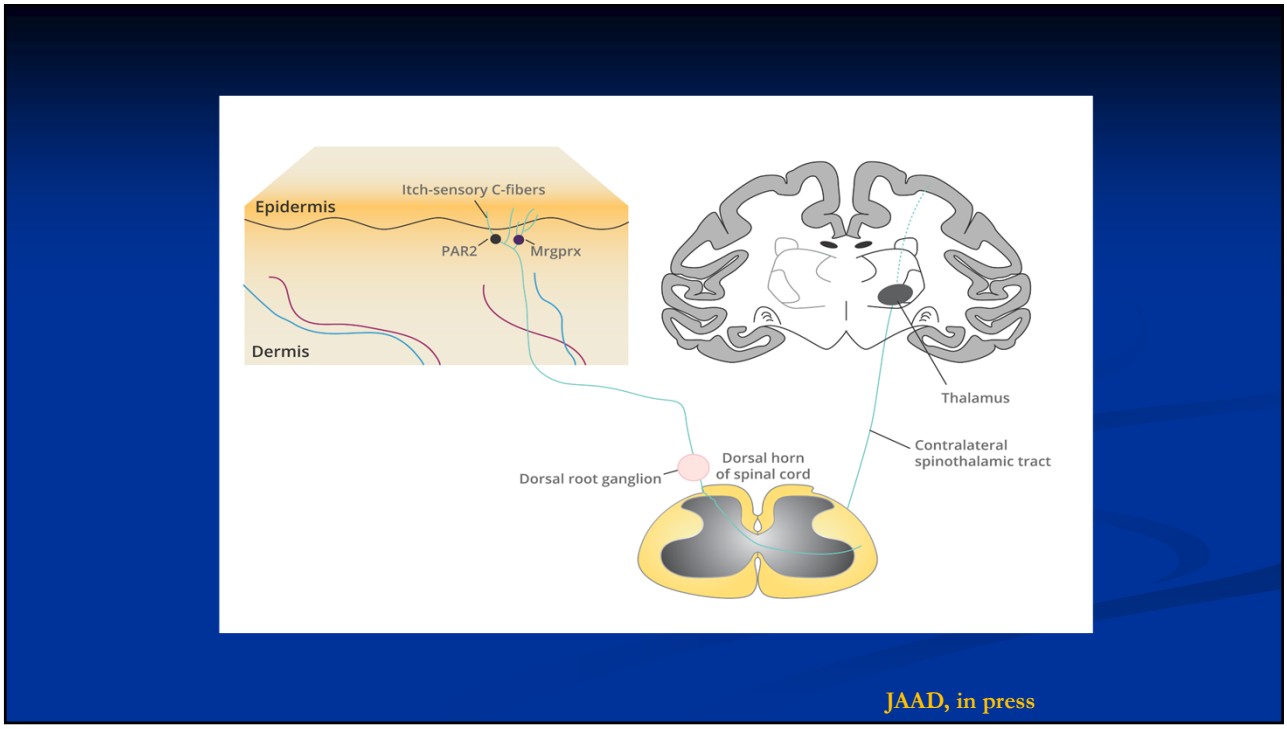

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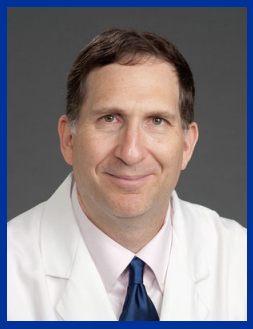
IFSI Classification of Pruritus

Acta Derm Vener 2007;87:291

- Group I: Pruritus on diseased Skin
- Group II: Pruritus on non-diseased Skin
- Group III: Chronic scratch lesions



Dr. Gil Yosipovitch

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Itch Evaluation: Step 1

- Does the patient have an inflammatory dermatosis? Type I Pruritus?

Itch

Rash No Rash

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Four Cornerstones of Treatment of Adult Pruritic Rashes

1. Treat the BARRIER
2. Treat the INFLAMMATION
3. Treat the ITCH (Nerves)
4. Avoid environmental triggers (exogenous)

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Itchy Inflammatory Rashes

- Many (? Most) inflammatory (rashy) dermatoses are Th2 mediated
- Treatment with immunosuppressives (MTX, CSA, MMF, new biologics) is effective
- Scratching damages skin barrier enhancing inflammation
- Itch nerves produce cytokines worsening rash and itch
- TREAT BOTH THE RASH AND THE ITCH

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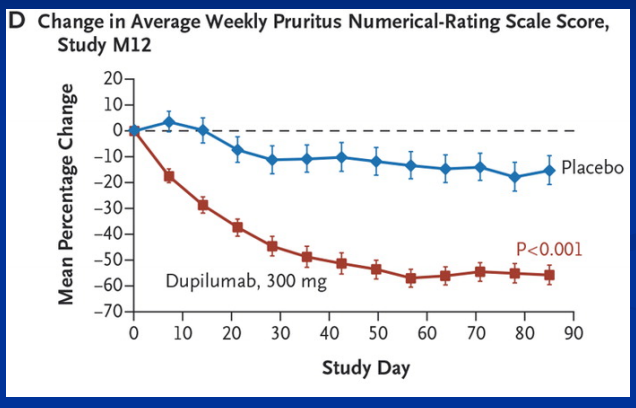
Biologics for Rashes

- Dupilumab (4, 13), Tralokinumab (13), Lebrikizumab (13)
- Nemolizumab (IL-31) (ITCH:+/- RASH)
- Upadacitinib (JAK) >Cibinqo (JAK)
- Opzelura (ruxolitinib, topical JAK)
- Response can be delayed (up to 6 months)
- Usually need supplementary topical anti-inflammatories (TCS/TCI)

11

Beck LA et al. N Engl J Med 2014;371:130-139.



IL 4 blockade

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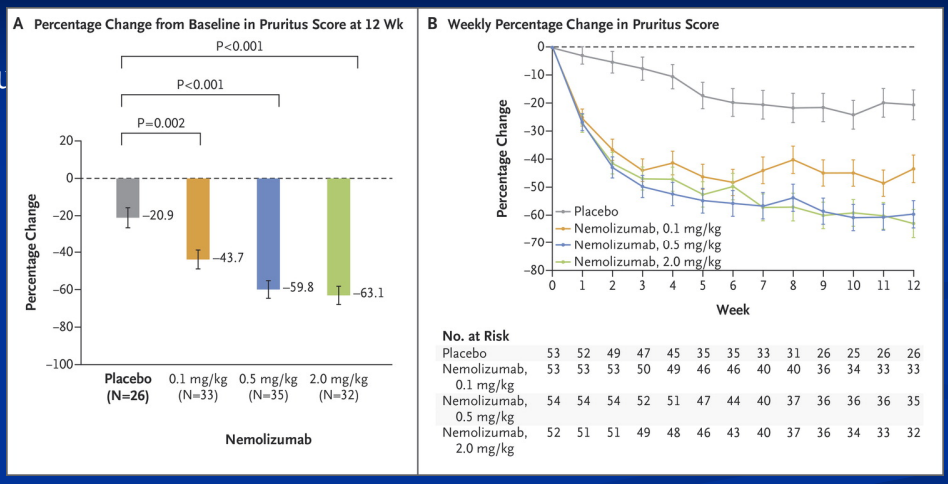
IL 31 blockade: Change in Pruritus Scores.

- Figu



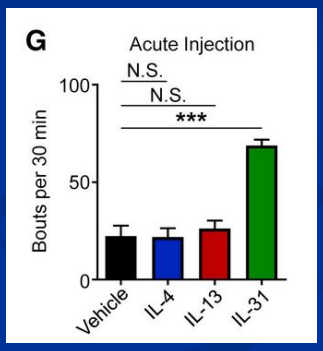
Ruzicka T et al. N Engl J Med 2017;376:826-835.

13

How do itch cytokines mediate itch?

Oetjen et al., 2017 Cell 171, 1-12

- IL-31 and IL-4/13 receptors are found on itch sensing neurons
- IL-31 activates itch specific neurons
- IL-5R is NOT found on itch sensing neurons
- IL4/13 do NOT activate itch neurons



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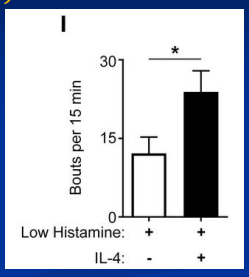
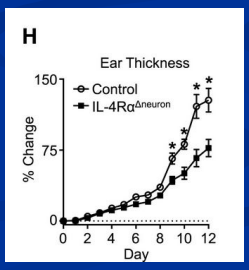
How do T2 cytokines mediate itch?

Oetjen et al., 2017 Cell 171, 1-12

- **IL-4/13 SENSITIZE itch specific neurons to many pruritogens**

- **Deleting IL4Ra in itch specific neurons results in less pruritus and less skin inflammation.**





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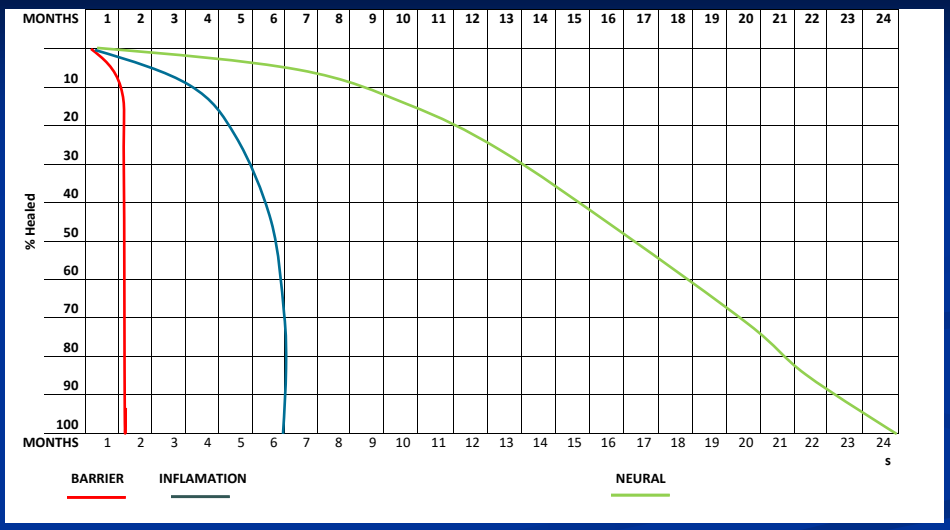

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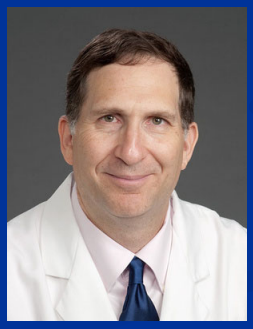
IFSI Classification of Pruritus

Acta Derm Vener 2007;87:291

- Group I: Pruritus on diseased Skin
- Group II: Pruritus on non-diseased Skin
- Group III: Chronic scratch lesions



Dr. Gil Yosipovitch

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Group 2 Itch

- Most common causes of Group 2 pruritus are metabolic disease (DM2, hepatic, renal, etc) and meds (CCB's), usually diagnosed by standard labs.
- CBC (ferritin**), HbA1C, HBV, HCV, LFT's, Thyroid functions, Renal function, Ca, P

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When/How to look for Cancer Causing Pruritus

- 1. Good PE and up to date and appropriate cancer screening.
- 2. Order CBC with Diff
- 3. Treat patient's pruritus
- 4. Refractory Pruritus (>7/10)
- 5. Excluded Scabies/Medication/BP/CTCL/SS with appropriate evaluations.
- 6. Order T cell panel, LDH, TCR
- 7. Chest X-ray or CT (chest, abd, pelvis)
- 8. Heme/Onc referral for ? BM biopsy

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Group 2 Pruritus

- Most common cause of Group 2 pruritus in my Referral Population is ***Neuropathic*** itch.

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Neuropathic Itch

J Diabetes Investig
2017; 8: 646-655

- Three types:
  - 1. Generalized: Diabetes (prediabetic neuropathy), small fiber neuropathy, MS
  - 2. Localized: Impingements
    - Cervical: Brachioradial Pruritus
    - Thoracic: Notalgia Paresthetica
    - Lumbosacral: Genital Pruritus (men)
  - 3. Multilevel Symmetric Neuropathic Pruritus

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IFSI Classification of Pruritus

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- Group III: Chronic itch-scratch lesions

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Group III Pruritus
Itch Scratch Cycle (Sensitization)

- Begins usually with either
- Neuropathic Itch OR
- Chronic Type I Pruritus (inflammatory itch)

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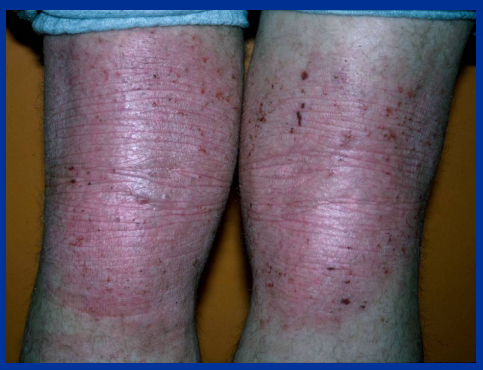
Sensitization



- "My son just scratches and scratches his rash, and it doesn't hurt. He says it feels good. "

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Sensitization

- Itch is "learned"
- Both peripheral and central processes are involved.

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Pruritus and "Sensitization"

1. Peripheral: sensory nerves are hyperactive/hypersensitive (little stimulus causes big response); spontaneous discharge of itch neurons; mediator responses are altered
2. Central: Dorsal Root Ganglion "reprograms" to enhance the itch signal (touch triggers itch)

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IFSI Classification of Pruritus

Acta Derm Vener 2007;87:291

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- MANY FORMS OF PRURITUS ARE "NEURAL"

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Topical Treatment of Itch (treat the nerves!)

- 1. Menthol/Camphor
- 2. Pramoxine
- 2a. Strontium (Dermeleve)
- 3. Topical Doxepin (genitalia)
- 4. Capsaicin
- 5. Lidocaine patch
- 6. Amitriptyline/Ketamine
- 7. Botox
- 8. Repeated (Q month) injections with lidocaine/bupivacaine/Kenalog (3.3mg/cc)

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RETURN TO AGENDA

Antihistamines

1st generation: Hydroxyzine
2nd generation:
Fexofenodine, Loratadine,
Cetirizine

Neural Agents

Gabapentin/Pregabalin
Doxepin
Mirtazipine/sertraline
Amitriptyline (TCA's)
Mexilitine
Aprepitant
Duloxetine

Cannabinoids

Marinol (THC)

Photo-Therapy

nb-UVB
bb-UVB (renal)
PUVA

Opiate Pathway

Naltrexone
Butorphanol
Kappa-Agonist
(Nalfurefine)
Difelikefalin

29

Min, JW et al. Kidney Res Clin Pract 35(2): 107-113

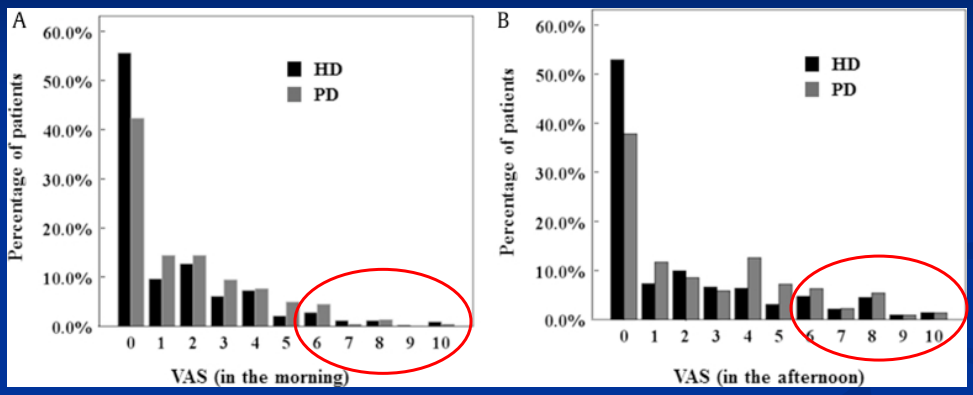

Fig1. Distribution of patients in each range of VAS scores in HD and PD patients. VAS in the morning (A) and VAS in the afternoon (B) are shown. HD, hemodialysis; PD, peritoneal dialysis; VAS, visual analog scale.

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RETURN TO AGENDA

Initial Pruritus Treatment

- Gabapentin-safe (in elderly), effective
- Start with a small dose at 4-6 PM and about twice that dose at bedtime
- Example: 300 mg 4PM, 600 mg bedtime
- Not immediately as sedating, so the PM dose is actually controlling itch to aid sleep initiation.
- May prevent "sensitization"

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Pruritus
Gabapentinoid Treatment

- Gabapentin 100mg – 600 mg at night AND
- 100-300 mg at 4-6 PM (just before the itch starts)
- Escalate to 900-1200 at night and 600 at 4PM
- Pregabalin if Gabapentin not tolerated
- Start at 25-100mg at bedtime and increase as needed
- Max dose: gabapentin 3600 mg/pregabalin 200 mg TID

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RETURN TO AGENDA

Gabapentin for Pruritus

- Escalate to total daily dose of 1,200mg to 1,800 mg as tolerated. Max dose 3,600 mg
- In the elderly can start with 100 mg capsules
- Side effect compared to placebo: dizziness (19% vs 5%), peripheral edema (7% vs 2.2%), and ataxia or gait disturbances (8.8% vs 1.1%).
- Dreams are more vivid

33

Antipruritics in Older Age

J Am Geriatr Soc. 2019 April ; 67(4): 674-694.

- American Geriatrics Society develops Beers Criteria for Potentially Inappropriate Medication Use in Older Adults
- Drugs that have high potential for CNS side effects, falls, etc which happen more frequently in older age.

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RETURN TO AGENDA

"Avoid" Antipruritics in the Elderly

- Hydroxyzine
- Diphenhydramine
- Chlorpheniramine
- Doxepin > 6 mg
- Amitriptyline

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Acceptable Oral Antipruritics in the Elderly

- Gabapentin (safety literature from PHN trials)
- Doxepin up to 6mg
- Mirtazapine, paroxetine, sertraline
- Opiate Agonists/Antagonists
- Aprepitant
- Cannabanoids
- Don't forget, most patients have an inflammatory skin disease—IL4, 13, 31 blockade

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Step 2

Add:

- Doxepin, Amitriptyline, sertraline, mirtazepine, Duloxetine OR
- Naltrexone, OR
- Mexiletine, OR
- Dronabinol

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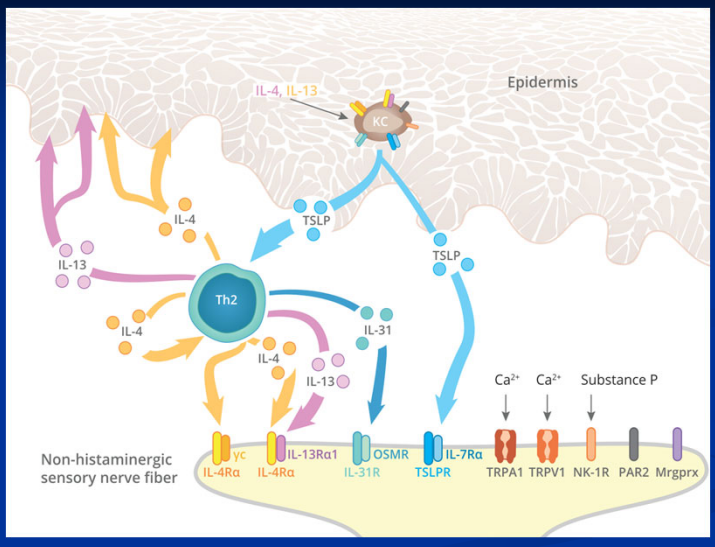

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Important Points

- Itch is mediated by a special family of nonhistaminergic nerves
- New biologics are effective but can have delayed onset and may need supplemental anti-inflammatories and antipruritics initially
- Measure itch using NRS (>4; 50% decrease significant)

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- **Thank You**

40

RETURN TO AGENDA

Back to the Basics: Moisturizers, Bathing, and Wet Wraps

Peter Lio, MD

1

A Heterogeneous Disease

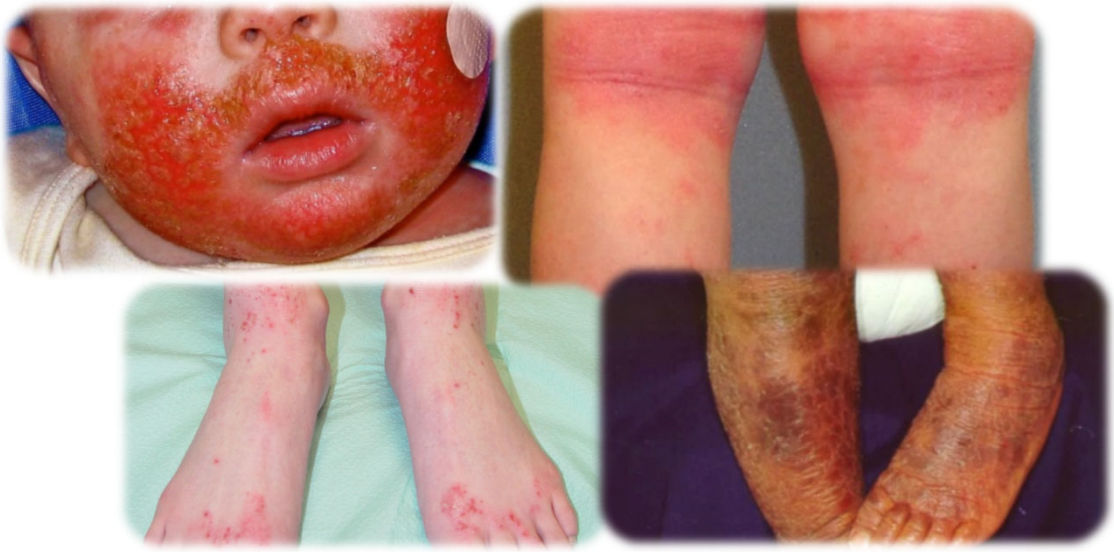

Photo courtesy of Peter Lio, MD (Consent on file)

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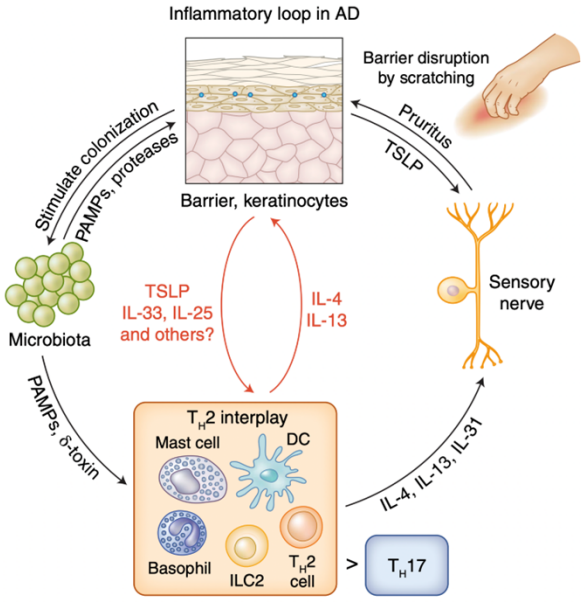
Loops



Dainichi T, et al. *Nat Immunol*. 2018;19(12):1286-1298

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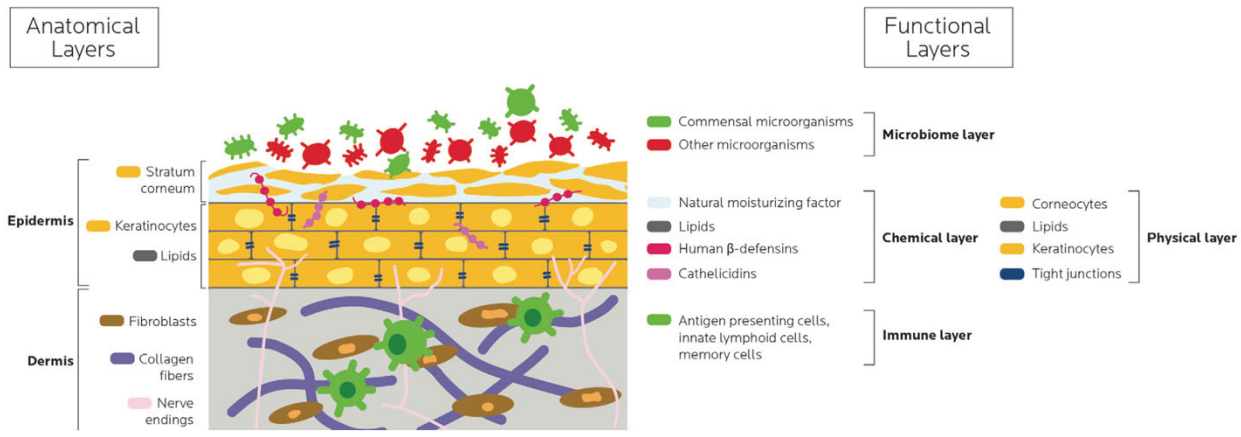


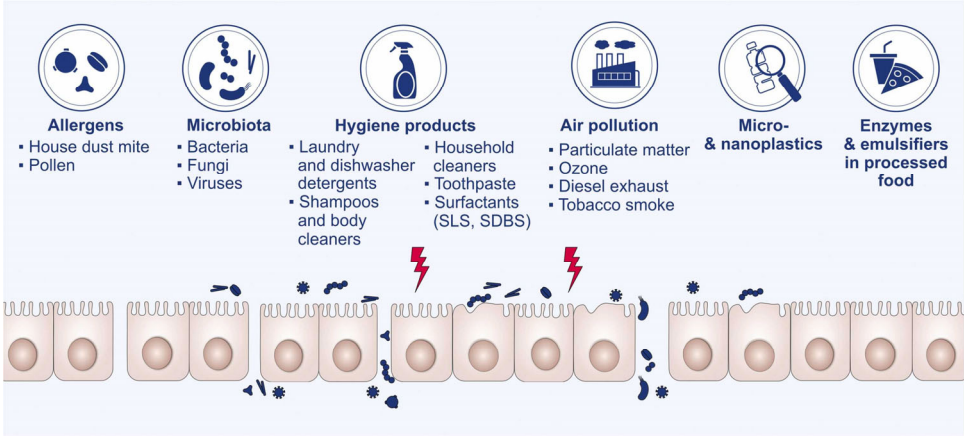
Strugar TL, Kuo A, Seité S, Lin M, Lio P. Connecting the Dots: From Skin Barrier Dysfunction to Allergic Sensitization, and the Role of Moisturizers in Repairing the Skin Barrier. Journal of drugs in dermatology: JDD. 2019 Jun;18(6):581-.

4

RETURN TO AGENDA

Epithelial Barrier Hypothesis

- Industrialization, urbanization and Westernized lifestyle have a devastating impact on the epithelial barriers of the skin, airways, and gut mucosa as proposed by the Epithelial Barrier Theory



- Yazici D, et al. *Semin Immunol*. 2023;70:101846.

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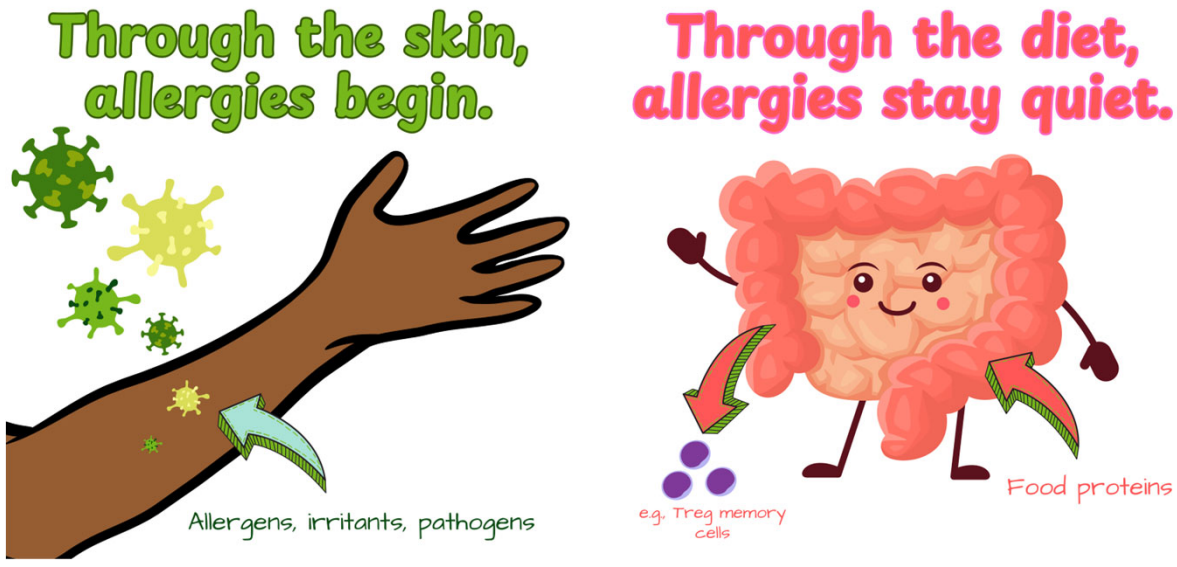

- Figures: originals by Peter Lio, MD. Quote attributed to Ruchi Gupta, MD

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Topical Steroids and Barrier

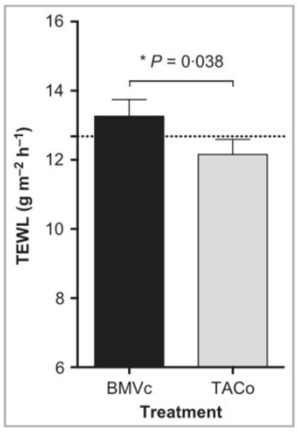

Fig 1. The effect of betamethasone valerate cream (BMVc) and tacrolimus ointment (TACo) on skin barrier function. Transepidermal water loss (TEWL) was significantly different post-treatment, accounting for baseline measurements (one-way ANCOVA, $P = 0{\cdot}038$). The dashed line indicates mean TEWL before treatment.

Danby SG, Chittock J, Brown K, Albenali LH, Cork MJ. The effect of tacrolimus compared with betamethasone valerate on the skin barrier in volunteers with quiescent atopic dermatitis. Br J Dermatol. 2014 Apr;170(4):914-21.

7

Either Way…

The Barrier Problem is here to stay

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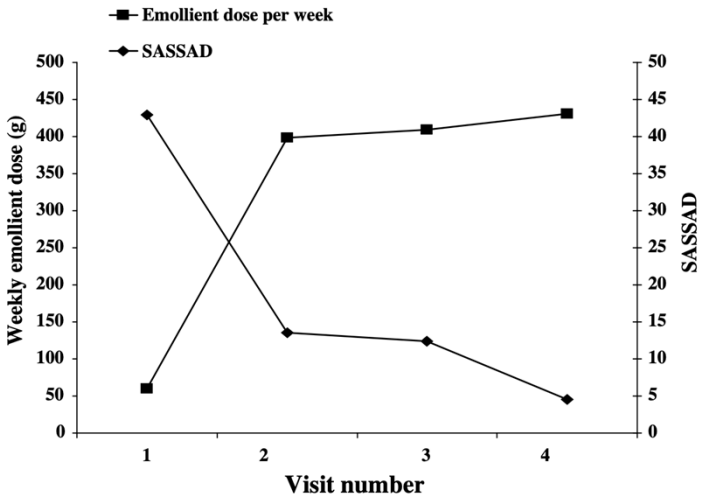
More Moisturizer = Less Eczema!



- SASSAD = six area, six sign atopic dermatitis severity score.
  Cork MJ, et al. *Br J Dermatol*. 2003;149(3):582-9.

9

MOISTURIZERS WORK!

"In this review, 17 studies were identified that examined the effects of various moisturiers in pediatric patients with AD.

…[C]ompared to no treatment, moisturizers of any type are very beneficial on a wide variety of outcomes considered in this review.

Across all studies comparing moisturizer use to no moisturizer use, significantly improved AD outcomes were seen in treatment groups.

Determining the most suitable moisturizer for a particu-
lar patient or circumstance remains unanswered…"

Osher GR, Madkins K, Lio P. Efficacy of Over-the-Counter Moisturizers in Pediatric Atopic Dermatitis: An Update to a Systematic Review. Current Dermatology Reports. 2024 Dec;13(4):236-47.

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RETURN TO AGENDA

MOISTURIZERS WORK!

Table 1 Characteristics of included studies

Author	Country	Design (duration)	Age (range)	Intervention (*n*) Control (*n*)	Outcome Measures	Results	References
Alexopoulos et al.	Greece	Observer-blind, multicenter, clinical rct (4 weeks)	6.67 (2–18)	Intervention (35): (ECZAID®) cream (1% ectoine and 0.1% hyaluronic acid) x 2 Control (35): vehicle x 2	SCORAD, IGA, pt judgment of pruritus	Significant improvement in SCORAD, IGA, and pruritus score compared to control ($p < 0.001$).	[2]
Ridd et al.	UK	Multi-center, individually randomized, parallel-group superiority trial with nested qualitative study (52 weeks)	4 (0.5–12)	Intervention: lotion (137) x 2 + or cream (140) x 2 + or gel (135) x 2 + or ointment (138) x 2 + *list of approved products in each category Control: NA	POEM, EASI, ADQoL, CHU9D, well-controlled weeks	No significant differences in POEM, EASI, ADQL, CHU9D, or well-controlled weeks between groups.	[19]
Allen et al.	UK	Multi-center, individually randomized, parallel-group superiority trial with nested qualitative study (52 weeks)	4 (0.5–12)	Intervention: lotion (137) x 2 + or cream (140) x 2 + or gel (135) x 2 + or ointment (138) x 2 + *list of approved products in each category Control: NA	Emollient Satisfaction Questionaire	Patients significantly less satisfied with ointments ($p < 0.001$), otherwise no significance between groups.	[3]
Bianchi et al.	Italy/Romania	Open rct (28 days)	2.5 (1–4)	Intervention (28): Avene Xeracalm Balm (glycerin, mineral oil) x 2 Control (26): no treatment	SCORAD, TEWL	Improvement in SCORAD and xerosis in treatment group were significant, pruritus score was reduced but insignificant ($p = 0.06$). Significant improvement in TEWL on D15, but not D28 compared to control.	[4]
Dwiyana et al.	Indonesia	Double blind rct (4 weeks)	9.05 (7–12)	Intervention (9): 20% Sunflower seed oil cream x 2 Control (11): common commercial moisturizer x 2	TEWL, SCORAD	SCORAD improvement and TEWL reduction in both groups, data insignificant.	[6]
Gupta et al.	India	Randomized, double-blind, comparative study (6 months)	8.2 (< 18)	Intervention: paraffin-based moisturizer (26) x 2 or ceramide-based moisturizer x 2 Control: NA	SCORAD, CDLQI/IDLQI, time to remission, disease-free duration, TEWL	Insignificant improvement in SCORAD in both groups. No significant differences in CDLQI/IDLQI or TEWL.	[8]

Osher GR, Madkins K, Lio P. Efficacy of Over-the-Counter Moisturizers in Pediatric Atopic Dermatitis: An Update to a Systematic Review. Current Dermatology Reports. 2024 Dec;13(4):236-47.

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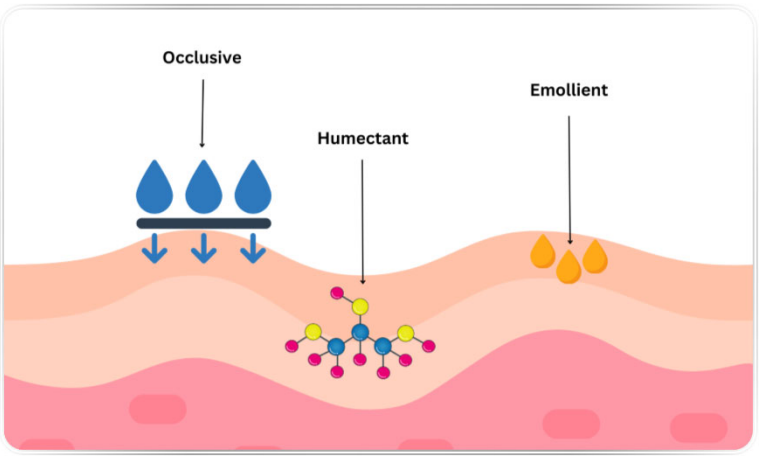
Defining Moisturizing Properties



Original figure by Peter Lio, MD

The principles of occlusion, humectancy, and emolliency are central to SC maintenance

- Occlusives minimize the evaporation of water
- Humectants attract moisture from the dermis to the epidermis
- Emollients are oils and lipids that spread easily on the skin and provide partial occlusion

Rawlings AV et al. *Derm Ther* 2004;17:49-56

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RETURN TO AGENDA

May 2012 633 Volume 11 • Issue 5
Copyright © 2012 ORIGINAL ARTICLES Journal of Drugs in Dermatology

A Comparison of Physicochemical Properties of a Selection of Modern Moisturizers: Hydrophilic Index and pH

Vivian Y. Shi BS,[a] Khiem Tran PhD,[b] and Peter A. Lio MD[c]

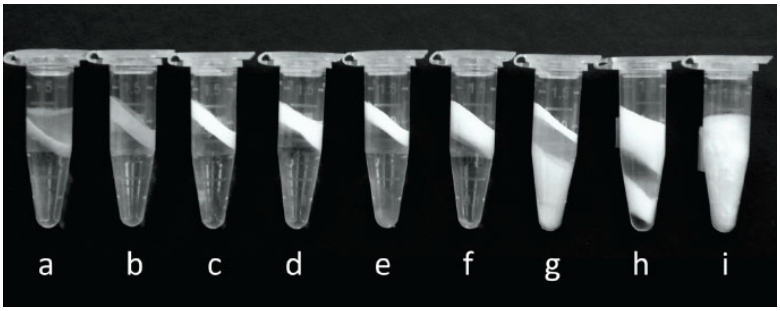

FIGURE 1. Separation of hydrophobic and hydrophilic layers after centrifugation. The most translucent (aqueous) layer is extracted. **a)** Motor Oil; **b)** Aquaphor® Ointment; **c)** Eucerin® Original Dry Skin Therapy Cream; **d)** Eucerin® Original Dry Skin Therapy Lotion; **e)** Cetaphil® Restoraderm Skin Restoring Moisturizer; **f)** Aveeno® Advanced Care Moisturizing Cream; **g)** Dove® Day Lotion (SPF15); **h)** CeraVe® Moisturizing Cream; **i)** Neosalus® Cream.

Shi VY, Tran K, Lio PA. A comparison of physicochemical properties of a selection of modern moisturizers: hydrophilic index and pH. Journal of drugs in dermatology: JDD. 2012 May 1;11(5):633-6.

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The Golden Ratio

"Cholesterol, ceramides, and essential / nonessential free fatty acids (FFAs) in an equimolar ratio allows normal barrier recovery, whereas any 3:1:1:1 ratio of these four ingredients accelerates barrier recovery."

Zettersten EM, Ghadially R, Feingold KR, Crumrine D, Elias PM. Optimal ratios of topical stratum corneum lipids improve barrier recovery in chronologically aged skin. J Am Acad Dermatol. 1997 Sep;37(3 Pt 1):403-8.

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RETURN TO AGENDA

Ceramides Play a Key Role in Barrier Function

- Ceramides are the most common constituent among SC lipids
- Ceramide levels in the SC are regulated by a balance of enzymes, ceramidase, sphingomyelinase and β-glucoscerebrosidase
- Ceramide 1 and 3* levels are reduced and the quantity of ceramide 3 were significantly correlated with TEWL impairment in AD subjects

**There is a new nomenclature for ceramides… but it's a bit cumbersome and most of the original landmark studies used these older terms…*

Choi MJ, Maibach HI. *Am J Clin Dermatol*. 2005;6:215-223. Pilgram GS et al. *J Invest Dermatol*. 2001;117:710-717. Di Nardo A, et al. *Acta Derm Venereol*. 1998;78:27-30. Chamlin S, et al. *J Am Acad Dermatol*. 2002;47:198-208.

*Ceramides Nomenclature

Structural characteristics and proposed designation for skin ceramides

Spot	Previous code (Ref. 5)	LCB	Fatty acid	Ester linkage	New code	Legend
a	Cer 1	Sphingosine	ω-OH (long chain)	present	Cer[EOS]	E: ester-linked fatty acids O: ω-OH fatty acids S: sphingosine
b	Cer 2	Sphingosine	non-OH	absent	Cer[NS]	N: non-OH fatty acids S: sphingosine
c		Phytosphingosine	non-OH (mainly C24-C26)	absent	Cer[NP]	N: non-OH fatty acids P: phytosphingosine
d		Phytosphingosine	non-OH (mainly C16-C18)	absent		
e	Cer 4/5	Sphingosine	α-OH	absent	Cer[AS]	A: α-OH fatty acids S: sphingosine
f	Cer 6I	Phytosphingosine (mainly C18)	α-OH (mainly C24-C26)	absent	Cer[AP]	A: α-OH fatty acids P: phytosphingosine
g	Cer 6II	Phytosphingosine (mainly C22)	α-OH (mainly C18-C20)	absent		

Motta S, Monti M, Sesana S, Caputo R, Carelli S, Ghidoni R. Ceramide composition of the psoriatic scale. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 1993 Sep 8;1182(2):147-51.

RETURN TO AGENDA

Expensive Moisturizing Device Study

- Clinical trial of 121 patients with moderate AD (6 months to 18 years)
- No statistically significant difference in efficacy between EpiCeram and fluticasone cream at day 28
- At days 14 and 28, EpiCeram had comparable efficacy to fluticasone in decreasing pruritus (P > .05)

POSTER ABSTRACT
Pediatric Dermatology. 25(6):667-668, November/December 2008.
Sugarman, Jeffrey L. ; Eichenfield, Larry ; Simpson, Eric

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But if It Works…

- Study by Miller et al. (2011 AAD Annual Meeting, Poster P1303) compared OTC-petroleum, EpiCeram, and Atopiclair in 39 subjects, aged 2-17, with mild-mod AD
- Applied TID x 3 weeks

Miller DW, Koch SB, Yentzer BA, Clark AR, O'Neill JR, Fountain J, Weber TM, Fleischer Jr AB. An over-the-counter moisturizer is as clinically effective as, and more cost-effective than, prescription barrier creams in the treatment of children with mild-to-moderate atopic dermatitis: a randomized, controlled trial. Journal of drugs in dermatology: JDD. 2011 May 1;10(5):531-7.

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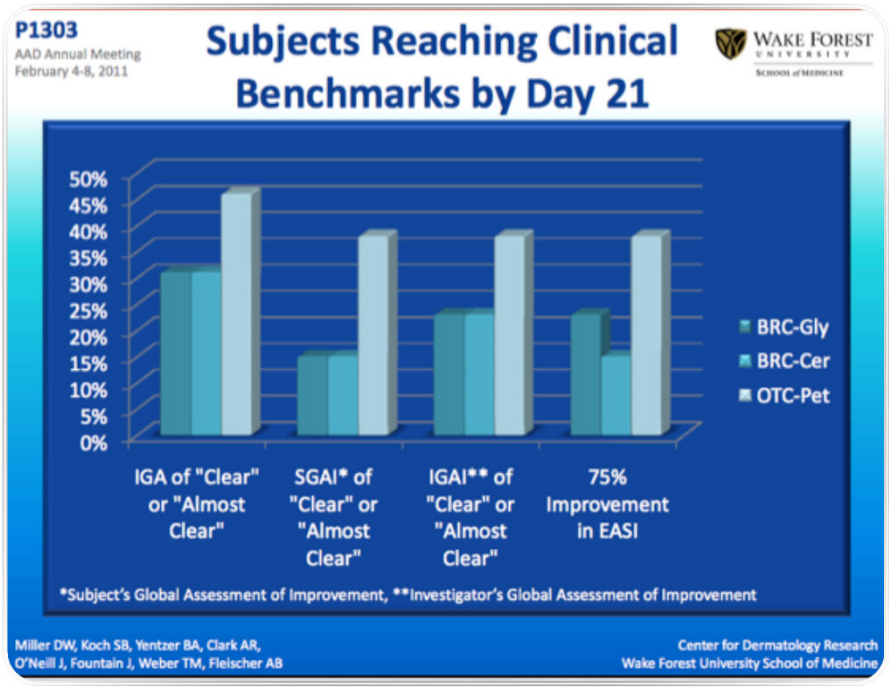

ONLY the Petroleum group showed significant improvement in all assessments by day 21 ($p<.05$)

Miller DW, Koch SB, Yentzer BA, Clark AR, O'Neill JR, Fountain J, Weber TM, Fleischer Jr AB. An over-the-counter moisturizer is as clinically effective as, and more cost-effective than, prescription barrier creams in the treatment of children with mild-to-moderate atopic dermatitis: a randomized, controlled trial. Journal of drugs in dermatology: JDD. 2011 May 1;10(5):531-7.

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And the Killer . . .

- OTC-Pet was found to be at least 47 times more cost-effective than BRC-Gly or BRC-Cer

	BRC-Gly	BRC-Cer	OTC-Pet
Cost per 100 gm	$121.45	$89.44	$3.41
% improvement in EASI by Day 21	43%	21%	64%
Cost-efficacy (cost per % improvement)	**$2.82**	**$2.35**	**$0.05**

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Miller DW, Koch SB, Yentzer BA, Clark AR, O'Neill JR, Fountain J, Weber TM, Fleischer Jr AB. An over-the-counter moisturizer is as clinically effective as, and more cost-effective than, prescription barrier creams in the treatment of children with mild-to-moderate atopic dermatitis: a randomized, controlled trial. Journal of drugs in dermatology: JDD. 2011 May 1;10(5):531-7.

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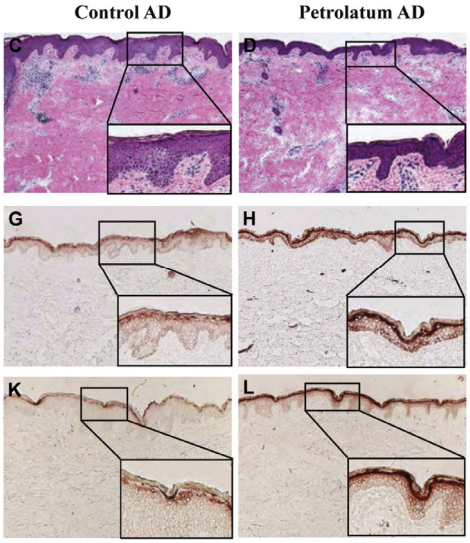
RETURN TO AGENDA

Good Old Petrolatum

- "Petrolatum robustly modulates antimicrobials and epidermal differentiation barrier measures."
- "AD skin shows parakeratosis and focal disruptions of the granular layer…with restoration of orthokeratosis with petrolatum…"
- "Weak and discontinuous LOR (G) and FLG (K) staining was observed in control AD skin, with increased intensity and restoration of continuous expression of both markers after occlusion with petrolatum." (Histologic magnification x10)



- LOR = loricrin; FLG = filaggrin.
  Czarnowicki T, et al. *J Allergy Clin Immunol*. 2016;137(4):1091-1102.e7.

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Select bioactive ingredients of moisturizers and their intended function

Bioactive ingredients	Intended functions
Cannabinoids	Mitigate itch and inflammation, stimulate lipid production
Petroleum	Occlusion, decreasing TEWL; strengthen lipid lattice, stimulate AMP production
Ceramides	Restore SC lipid matrix, water permeability and barrier function
Antioxidants	Prevent oxidative damage by decreasing ROS
Niacinamide	Improve epidermal barrier function by decreasing TEWL, increasing ceramides, and thickening the stratum corneum. Anti-inflammatory
Pre/Probiotics	Improve skin barrier by decreasing TEWL and increasing ceramide levels

Chandan N, Rajkumar JR, Shi VY, Lio PA. A New Era of Moisturizers. Journal of Cosmetic Dermatology. 2021 May 12.

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RETURN TO AGENDA

Antimicrobial Enzymes

- A European product uses extracted natural phage endolysins specific to targeting S. aureus
- This product has two promising features in treating AD patients:
  - Selective degradation of specific bacteria
  - Limited likelihood of emerging resistance
- Case report of 3 adults with positive effect
- But…

Totte JE, van Doorn MB, Pasmans SG. Successful treatment of chronic Staphylococcus aureus-related dermatoses with the topical endolysin Staphefekt SA. 100: a report of 3 cases. Case reports in dermatology. 2017;9(2):19-25.

Antimicrobial Enzymes

- DB-RCT in 100 adult patients with moderate-to-severe AD
- Randomly 1:1 to a 12-week intervention with either topical endolysin against S. aureus or a vehicle twice daily
- There was no statistically significant difference in the probability of TCS use per day between the groups in the intention-to-treat and per-protocol analyses and in the subgroup of S. aureus–positive patients
- Essentially no statistically significant differences were found in the secondary outcomes after both intention-to-treat and per-protocol

de Wit J, Totté JE, van Mierlo MM, van Veldhuizen J, van Doorn MB, Schuren FH, Willemsen SP, Pardo LM, Pasmans SG. Endolysin treatment against Staphylococcus aureus in adults with atopic dermatitis: A randomized controlled trial. Journal of Allergy and Clinical Immunology. 2019 Sep 1;144(3):860-3.

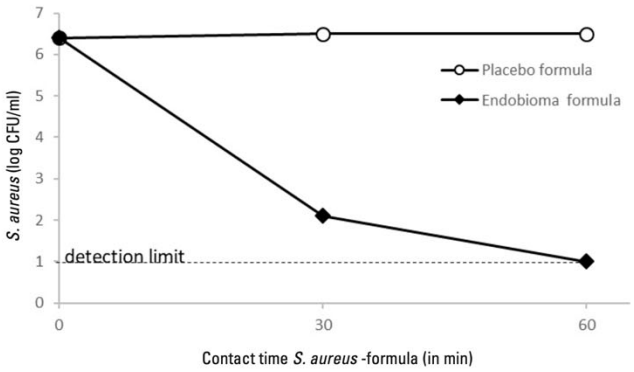
RETURN TO AGENDA

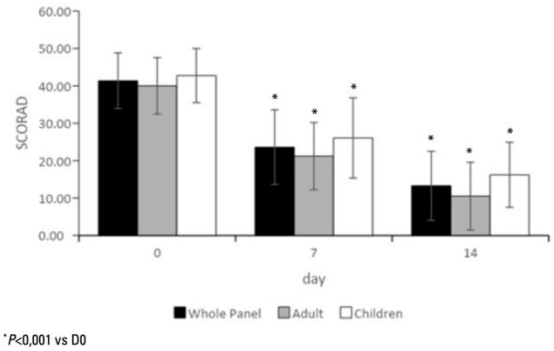
Antimicrobial Enzymes

- They conclude:
  - "Our results are in accordance with data from a Cochrane review showing no significant effect of short-term anti–S. aureus therapy in patients with noninfected AD…"
  - "Our data suggest that endolysin treatment has no effect on S. aureus *in vivo.* However, patients might have been recolonized with S. aureus from the nose because 73% of them were nasal carriers…"
  - In conclusion, long-term targeted endolysin treatment against S. aureus in this study was well tolerated but had no TCS-sparing effect in patients with AD.

de Wit J, Totté JE, van Mierlo MM, van Veldhuizen J, van Doorn MB, Schuren FH, Willemsen SP, Pardo LM, Pasmans SG. Endolysin treatment against Staphylococcus aureus in adults with atopic dermatitis: A randomized controlled trial. Journal of Allergy and Clinical Immunology. 2019 Sep 1;144(3):860-3.

Antimicrobial Enzymes: New Study

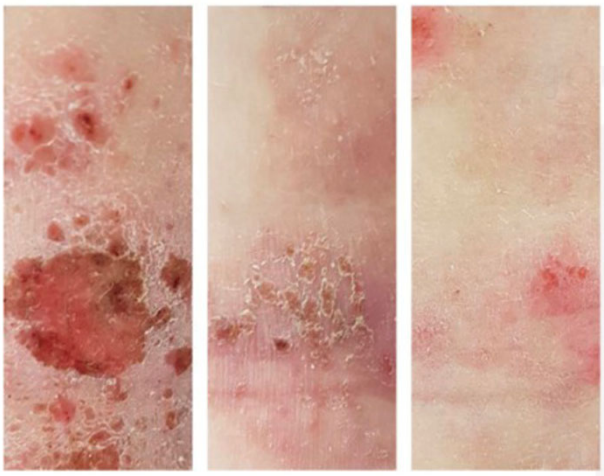




Moreau M, Seité S, Aguilar L, Da Cruz O, Puech J, Frieling J, Demessant A. Topical S. aureus-Targeting Endolysin Significantly Improves Symptoms and QoL in Individuals With Atopic Dermatitis. Journal of drugs in dermatology: JDD. 2021 Dec 1;20(12):1323-8.

RETURN TO AGENDA

Antimicrobial Enzyme: Baseline, Day 7, and Day 14



Moreau M, Seité S, Aguilar L, Da Cruz O, Puech J, Frieling J, Demessant A. Topical S. aureus-Targeting Endolysin Significantly Improves Symptoms and QoL in Individuals With Atopic Dermatitis. Journal of drugs in dermatology: JDD. 2021 Dec 1;20(12):1323-8.

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Antimicrobial Enzymes

- They conclude:
  - "This study showed that S. aureus-targeting … cream monotherapy produced a statistically and clinically significant reduction of AD severity scores… in both adults and children."

Moreau M, Seité S, Aguilar L, Da Cruz O, Puech J, Frieling J, Demessant A. Topical S. aureus-Targeting Endolysin Significantly Improves Symptoms and QoL in Individuals With Atopic Dermatitis. Journal of drugs in dermatology: JDD. 2021 Dec 1;20(12):1323-8.

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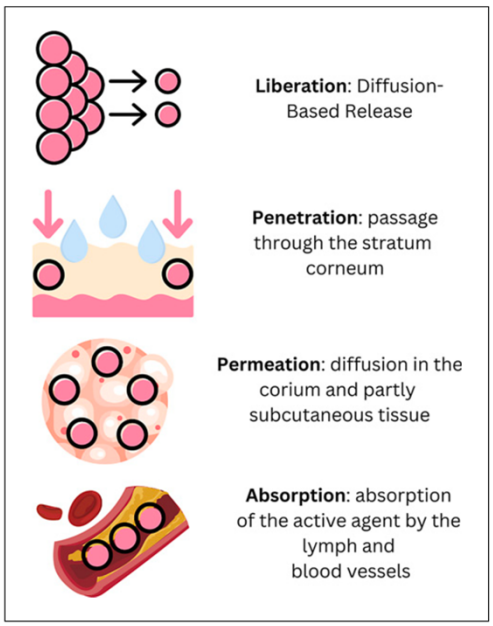

Fig. 2. Major steps in active transport of a drug. The figure depicts the four major steps involved in active transport of an agent from penetration into skin to systemic absorption.

Ahuja K, An M, Lio P. A brief review of vehicles for topical therapies. Skin Pharmacology and Physiology. 2025 Feb 12;37(4-6):104-8.

Fig. 1. Schematic of topical agents. The figure depicts the classification of topical agents based on chemical properties.

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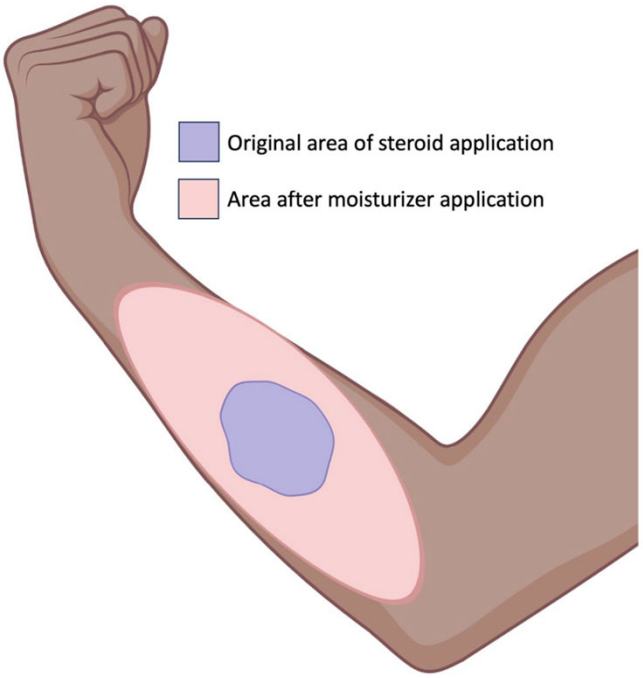
ORDER OF TOPICALS

Undesirable spreading. When a topical steroid is focally applied, even after waiting 30 min, the subsequent application of a lipophilic moisturizer can spread the drug far beyond the intended area.



Ahuja K, Lio PA. Topical steroids or emollients: does order matter?. Archives of Dermatological Research. 2024 Mar 15;316(4):104.

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RETURN TO AGENDA

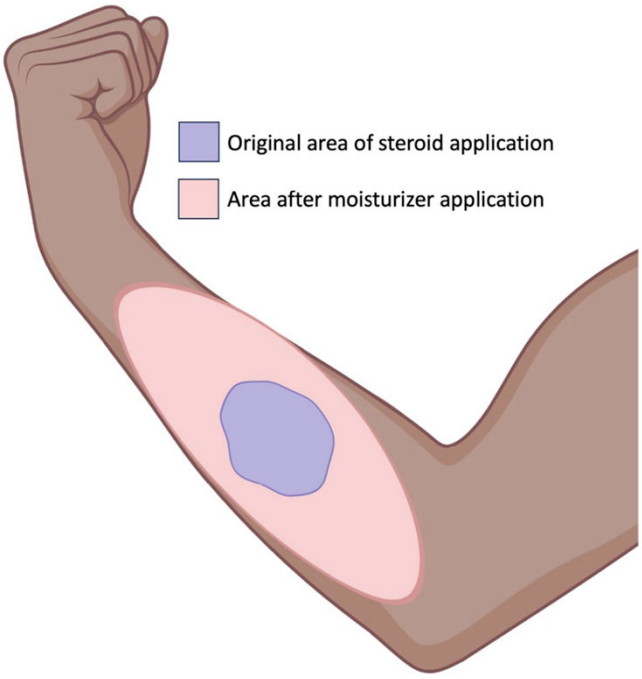
ORDER OF TOPICALS

"…Highly credible sources as well as current randomized controlled trial practices, sway towards topical corticosteroids being applied first.

However, compelling arguments exist for applying moisturizer first:
• Minimizing unwanted distribution of medications
• Helping alleviate stinging and burning of SSAs.

Additional research assessing varying sequences of application and time intervals with different medications and moisturizers is needed to understand this issue fully."

Ahuja K, Lio PA. Topical steroids or emollients: does order matter?. Archives of Dermatological Research. 2024 Mar 15;316(4):104.



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Moisturizer Tips

- If they find it too cold: have them "float" the jar in the tub while the patient takes a bath to warm it up
- If the skin is hot and it makes it feel hotter/itchier: keep it in the refrigerator (not freezer)
- If infection is a problem: use a clean spoon to dispense the cream (instead of fingers)

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RETURN TO AGENDA

Maximizing Things with Wet Wraps

Follow these 4 steps:

1. Take one pair of onesies, pajamas, gloves, and/or socks and soak it in warm water.

2. Wring out the onesies, pajamas, gloves, or socks until they are only slightly damp.

3. Put the damp onesies, pajamas, gloves, or socks on. Then put the dry onesies, pajamas, gloves, or socks on top of the damp layer.

4. Make sure the room is warm enough before you go to sleep.

https://chicagoeczema.com/wet-wrap-therapy/

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STUDY

Soak and Smear

A Standard Technique Revisited

Ari Benjamin Gutman, MD; Albert M. Kligman, MD, PhD; Joslyn Sciacca, MD; William D. James, MD

- "Hydration for 20 minutes before bedtime followed by ointment application to wet skin and alteration of cleansing habits is an effective method for caring for several common skin conditions."

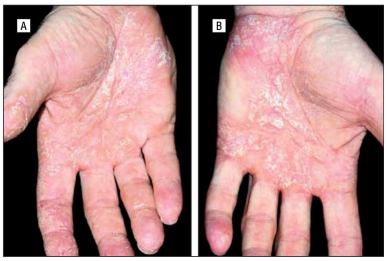

Figure 1. A patient with psoriatic hand involvement before treatment (A and B). The patient was using clobetasol ointment at night with vinyl glove occlusion and frequent moisturization and cream in the morning.

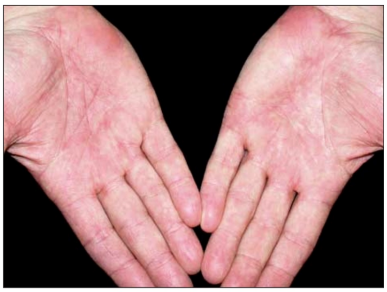

Figure 2. Same patient as in Figure 1 four weeks after treatment. The only change to the patient's regimen was to add a 20-minute plain water soak before the nighttime ointment application.

- Gutman AB, et al. *Arch Dermatol*. 2005;141(12):1556 9.

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RETURN TO AGENDA

What about Bathing?

- Water loss is fundamental, so bathing should be important
- Balneotherapy is ancient, but modern practices began in Europe in the 1800s

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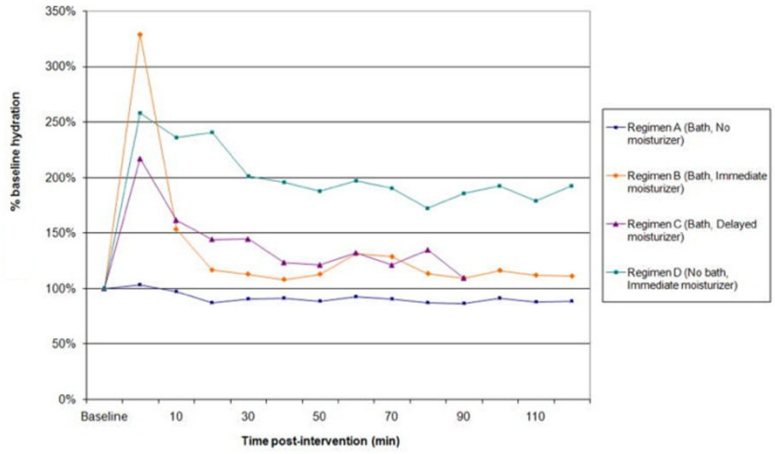
Bathtubs



- Chiang C, Eichenfield LF. *Pediatr Dermatol*. 2009;26(3):273-8.

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RETURN TO AGENDA

"Soak and Seal"

- Randomized crossover trial: Frequent vs infrequent baths
- Children 6m-11y with moderate-to-severe AD
- Randomized 1:1 into 2 groups
  - Group 1 underwent twice-weekly soak and seal (SS) baths for 10-minutes or less over 2-weeks ("dry method," DM) followed by twice-daily SS baths for 15-20 minutes, over 2-56 weeks ("wet method," WM)
  - Group 2 did the inverse
- Primary outcome: SCORAD
- Of the 63 children screened, 42 fulfilled inclusion criteria and were randomized
- WM decreased SCORAD significantly more than DM (p<0.0001)

- SCORAD = SCORing Atopic Dermatitis Index.
  Cardona ID, et al. *J Allergy Clin Immunol Pract*. 2020;8(3):1014-1021.

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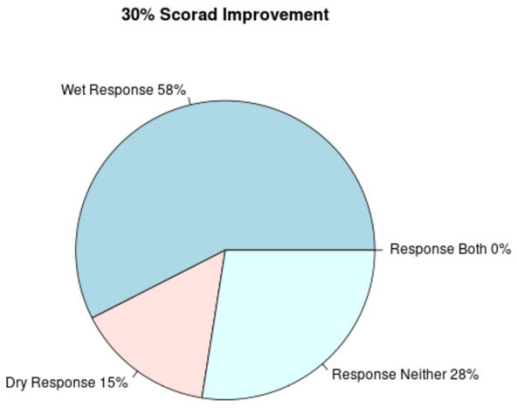
More Frequent Bathing Is Better!



- Cardona ID, et al. *J Allergy Clin Immunol Pract*. 2020;8(3):1014-1021.

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RETURN TO AGENDA

What about Spa Therapy?

- Data can be a bit messy since mineral water baths also involve
  - Warm weather (climatotherapy)
  - Sunshine (heliotherapy)
  - A vacation setting (relaxation)

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Balneotherapy

- There is solid data that children and adults with moderate-to-severe AD generally improve with balneotherapy/spa therapy
- But it's
  - Expensive
  - Time-consuming
  - Temporary

- Farina S, et al. *J Dermatolog Treat*. 2011;22(6):366-71. Cacciapuoti S, et al. *J Clin Med*. 2020;9(9):3047.

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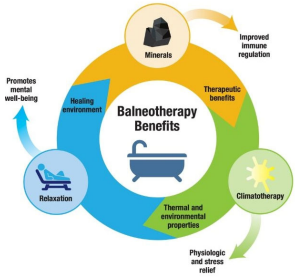
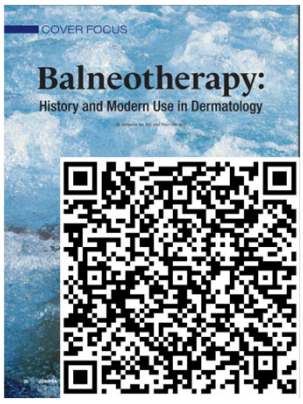
TABLE 1. SELECTED CLINICAL STUDIES

References (year)	Study Design	Disease	Total no. of patients	Treatment(s) (duration)	Results
Alder-Cohen et al. (2012)[22]	Treatment study	Atopic dermatitis	49	Climatotherapy at the Dead Sea (two years)	Post-treatment, disease severity decreased by 39 points, measured by the Scoring Atopic Dermatitis (SCORAD) value ($P < 0.001$). Quality of life improved by a mean value of 33 points on the Skindex-29 score ($P < 0.001$).
Proksch et al. (2005)[23]	Randomized, double-blind	Atopic dermatitis	30	5% Dead Sea salt bath solution vs. tap water (6 weeks)	Salt solution bathing was well tolerated, enhancing stratum corneum hydration and significantly reducing skin roughness, redness, and inflammation. Also significantly improved skin barrier function compared to tap water in groups with elevated baseline transepidermal water loss.
Peroni et al. (2008)[24]	Clinical trial	Chronic plaque psoriasis	300	Balneotherapy + narrowband UVB vs. balneotherapy (2 weeks)	Scores for Psoriasis Area and Severity Index (PASI), self-administered PASI (SAPASI), and Skindex-29 significantly decreased in both groups, with notable decline in photobalneotherapy group in the second week. ($P < 0.001$). All treatments were well tolerated.
Tabolli et al. (2009)[25]	Observational prospective study	Chronic plaque psoriasis	111	Balneophototherapy + UVB (BPT) vs. balneotherapy (BT) (2 weeks)	Self-administered PASI score significantly decreased in both groups, with greater reduction in BPT group than BT group. General health questionnaire (GHQ-12) notably improved in BPT group. No adverse events in either group.
Peter et al. (2017)[26]	Clinical trial	Psoriatic vulgaris	80	Spa therapy, sulfuric water (3 weeks)	Post-treatment, significant reduction in the PASI score ($P < 0.001$) and a decrease in C-reactive protein levels ($P = 0.026$).
Golubin et al. (2015)[27]	Randomized controlled clinical trial	Plaque psoriasis	60	Mineral baths + hot packs + calcipotriol vs. calcipotriol (21 days)	Treatment group saw significantly decreased PASI score (59.45%) ($P < 0.05$), decreased desquamation ($P < 0.001$), and improved therapeutic efficacy at the end of treatment and on day 30 compared to calcipotriol group.
Baros et al (2014)[28]	Randomized controlled clinical trial	Psoriasis	60	(G1) Standard therapies vs. (G2) balneotherapy vs. (G3) balneotherapy + standard therapy (3 weeks)	G3 had a significantly longer remission duration compared to G1 ($P = 0.019$) and G2 ($P = 0.032$).
Tsourelli-Nikita et al. (2002)[29]	Clinical trial	Symmetric, bilateral psoriasis	10	Leopoldine spa water vs. double-distilled water immersion (4 weeks)	Compared to control, Leopoldine treatment improved PASI scores (85.9%), significantly reduced number of epidermal CD4+ cells, and decreased CD8+ T cell, CD1a+ Langerhans cells, and epidermal keratinocyte expression of intercellular adhesion molecule-1 and IL-8 along with dermal expression of CD4+ and CD8+ T cells. All treatments were well tolerated.
Benevento-Italy (2015)[30]	Randomized, double-blind, placebo-controlled pilot study	Plaque psoriasis	58	Topical + balneotherapy vs. balneotherapy (2 weeks)	PASI, Dermatology Life Quality Index (DLQI), and reactive oxygen metabolites (ROMI) ($P < 0.05$) significantly decreased in two groups compared to before treatment. Well tolerated, no adverse reactions.
Sitepu (2012)[31]	Clinical trial	Atopic dermatitis	40	Balneotherapy vs. no intervention (2 weeks)	After treatment, balneotherapy group experienced significant reduction in itching ($P < 0.05$) compared to no intervention.
Farina et al. (2011)[32]	Randomized clinical trial	Atopic dermatitis (children)	104	Topical corticosteroids (TCS) vs. balneotherapy (2 weeks)	By month 4, balneotherapy group showed significant reduction in number and duration of relapses compared to TCS group ($P < 0.0001$). At two weeks, improvements in investigator global assessment (IGA), patients' self-global assessment (PSGA), children's DLQI, and family dermatitis impact questionnaire (FDIQ) were similar between both groups. All treatments were well tolerated, no adverse events.
Brockow et al. (2007)[33]	Randomized controlled trial	Psoriasis	143	Spa therapy with saline water + UVB vs. UVB (6 weeks)	Balneotherapy group showed a reduction of PASI by 50% (PASI-50) scores compared to the UVB group. No adverse events.
Léauté et al. (2001)[34]	Randomized controlled trial	Psoriasis vulgaris	71	Group A: spa water Group B: UVB Group C: spa water + UVB (21 days)	PASI decreased by 29% in GA with minor therapeutic effect compared with GB and GC ($P < 0.001$). No significant changes in electrolytes in any group. GA and GC experienced more adverse reactions, though not significantly.
Gálvez-Galve et al. (2012)[35]	Randomized controlled trial	Psoriasis vulgaris	46	Sulfurous mineral water spray vs. distilled water (15 days)	PASI improved in both groups after intervention, with no significant differences between them. Control group with significant DLQI improvement by the end of treatment. No adverse reactions noted.
Dawe et al. (2003)[36]	Randomized controlled trial	Chronic plaque psoriasis	60	Dead Sea solution + narrowband-UVB (NB-UVB) vs. NB-UVB (8 weeks)	Balneophototherapy showed marginally smaller average psoriasis plaque area and slightly higher improvement in Scaling, Erythema and Induration (SEI) score compared to NB-UVB treatment alone. Minor side effects reported for balneophototherapy.
Gambichler et al. (2001)[37]	Randomized controlled trial	Chronic plaque psoriasis	10	24% NaCl + UVB vs. tap water + UVB (30 treatments)	After 30 treatments, no significant reduction in baseline score.





https://digitaleditions.walsworth.com/article/Balneotherapy%3A+History+and+Modern+Use+in+Dermatology/4844255/829572/article.html

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RETURN TO AGENDA

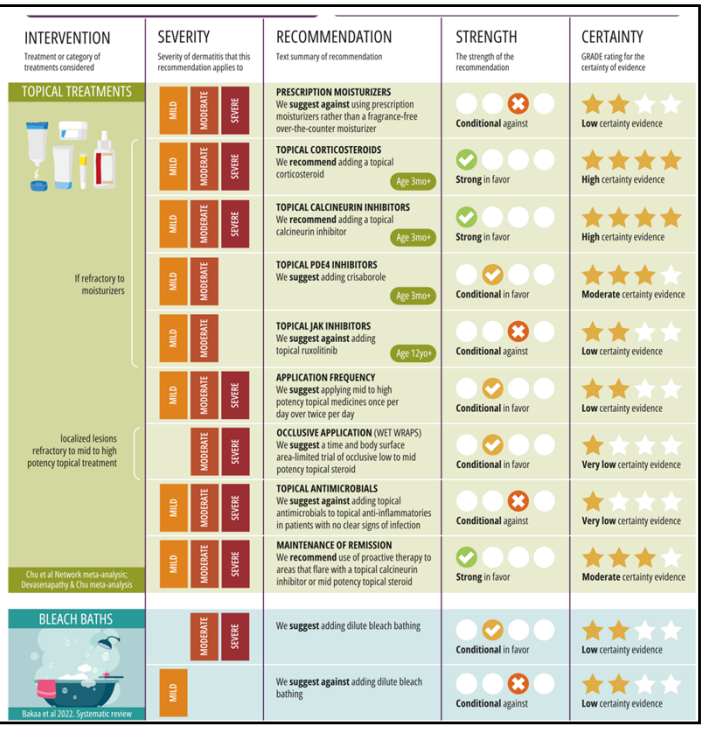
Water Softener?

- Paradox: Balneotherapy studies show improvement with mineral-rich water = “hard” water
- Randomized trial of 336 children found, at 12 weeks, no significant difference in eczema improvement with and without a water “softener” (removes minerals)

Thomas KS, et al. *PLoS Med*. 2011;8(2):e1000395.

45

JTF Guidelines



Chu DK, Schneider L, Asiniwasis RN, Boguniewicz M, De Benedetto A, Ellison K, Frazier WT, Greenhawt M, Huynh J, Kim E, LeBovidge J. Atopic dermatitis (eczema) guidelines: 2023 American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force on Practice Parameters GRADE–and Institute of Medicine–based recommendations. Annals of Allergy, Asthma & Immunology. 2023 Dec 18.

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JTF Guidelines

Chu DK, Schneider L, Asiniwasis RN, Boguniewicz M, De Benedetto A, Ellison K, Frazier WT, Greenhawt M, Huynh J, Kim E, LeBovidge J. Atopic dermatitis (eczema) guidelines: 2023 American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force on Practice Parameters GRADE–and Institute of Medicine–based recommendations. Annals of Allergy, Asthma & Immunology. 2023 Dec 18.

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Dilute bleach bath?

	Bleach ($n = 26$)	Water ($n = 26$)
Change in *S. aureus* growth (n (%)+)		
Better	5 (19.2)	10 (38.5)
Same	13 (50.0)	10 (38.5)
Worse	8 (30.8)	6 (23.1)

- Conclusion: "This study demonstrated that a four-week, twice-weekly regime of diluted bleach baths may not be useful in reducing S. aureus colonization/infection and improving AD. Instead, regular water baths would be a more efficacious alternative for AD."

Hon KL, Tsang YC, Lee VW, et al. Efficacy of sodium hypochlorite (bleach) baths to reduce Staphylococcus aureus colonization in childhood onset moderate-to-severe eczema: A randomized, placebo-controlled cross-over trial. J Dermatolog Treat. 2016;27(2):156-62.

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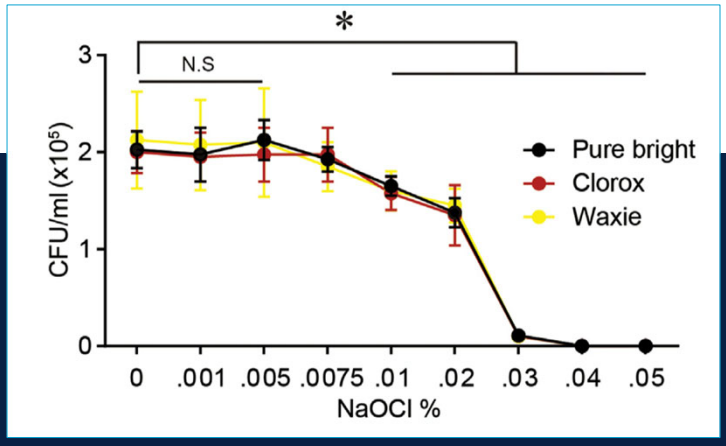
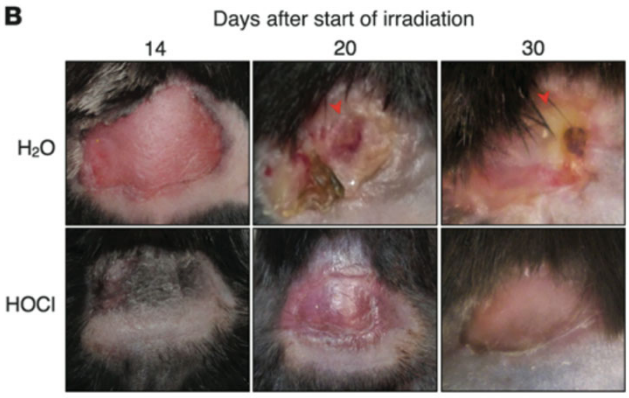
Bleach:
Not Antimicrobial



Sawada Y, Tong Y, Barangi M, Hata T, Williams MR, Nakatsuji T, Gallo RL. Dilute bleach baths used for treatment of atopic dermatitis are not antimicrobial in vitro. Journal of Allergy and Clinical Immunology. 2019 May 1;143(5):1946-8.

49

Bleach is anti-inflammatory



HOCl attenuates acute radiation dermatitis

Leung TH, Zhang LF, Wang J, Ning S, Knox SJ, Kim SK. Topical hypochlorite ameliorates NF-κB-mediated skin diseases in mice. J Clin Invest. 2013 Dec;123(12):5361-70.

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It may be also work via TEWL and itch reduction:

- This study suggests that the benefit observed with bleach baths is likely mediated by improvement in skin barrier function (TEWL and SC cohesion) and reduction in itch intensity but not in normalization of the skin microbiome or systemic Th2 inflammation.

*Perez-Nazario, N and Yoshida, T and Fridy, S and De Benedetto, A and **Beck, LA**. Bleach baths significantly reduce itch and severity of atopic dermatitis with no significant change in S. aureus colonization and only modest effects on skin barrier function. JOURNAL OF INVESTIGATIVE DERMATOLOGY. 2016, May. Vol. 135, pp. S37-S37.*

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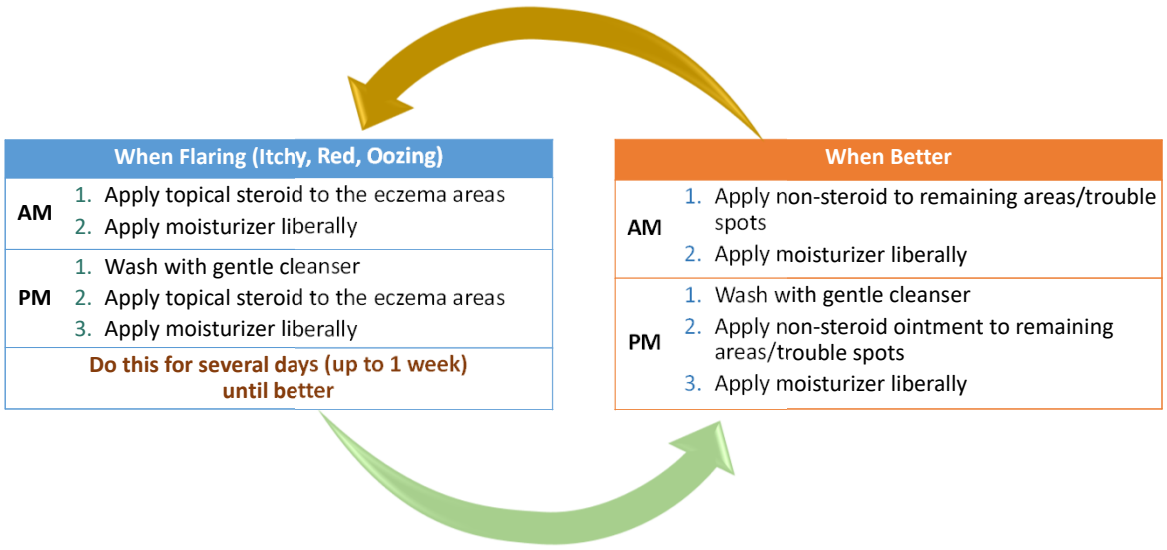
Eczema Action Plan



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RETURN TO AGENDA

Podium to Practice Takeaways

1) Moisturizers are foundational to AD care
2) There is no “perfect” moisturizer for everyone
3) There is still quite a bit of science to bathing and moisturizing that may be underutilized

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Thank you!

peterlio@gmail.com

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RETURN TO AGENDA

ACAAI 2025
Spotlight on Allergic Conditions of the Skin

Current and Emerging Biologics for Atopic Dermatitis

Mark Boguniewicz, MD
Professor, Division of Allergy-Immunology
Department of Pediatrics
University of Colorado School of Medicine

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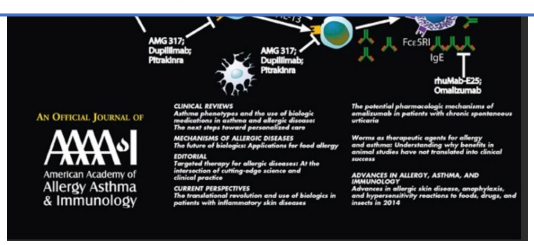
Editorial

Targeted therapy for allergic diseases: At the intersection of cutting-edge science and clinical practice

Mark Boguniewicz, MD, and Donald Y. M. Leung, MD, PhD *Denver, Colo*



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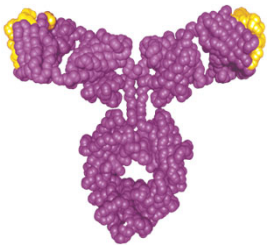
RETURN TO AGENDA

A (very) brief history of monoclonal antibodies

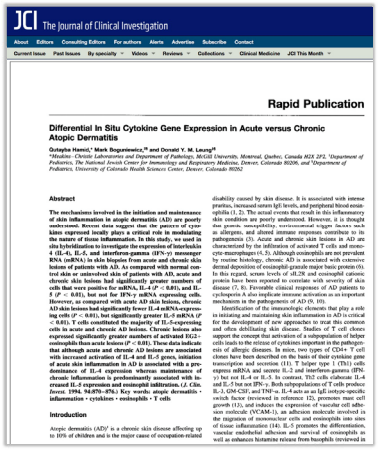
- In 1975, seminal work of Köhler and Milstein to create hybridomas (fusion of myeloma cell line and B cells that produced antibodies specific to known antigens and that were immortalized) ushered in a new era of biologic therapy and led to a Nobel Prize in 1984
- In 1988, Winter and his team pioneered techniques to humanize monoclonal antibodies
- Fully human mAb created with phage display or transgenic mice
  - e.g. Regeneron's VelocImmune technology



Köhler G, Milstein C. Nature 1975;256:495; Jones PT, et al. Nature 1986;321:522; Murphy AJ, et al. PNAS 2014;111:5153

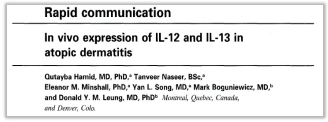
3

Type 2 cytokines & AD…

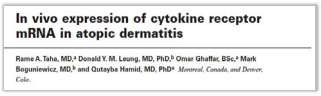

JCI The Journal of Clinical Investigation

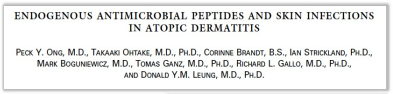
Rapid Publication

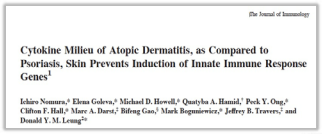
Differential In Situ Cytokine Gene Expression in Acute versus Chronic Atopic Dermatitis

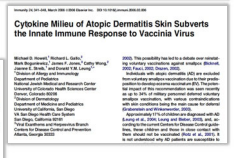

Rapid communication

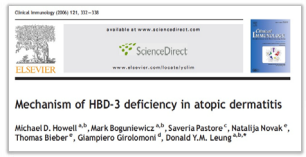
In vivo expression of IL-12 and IL-13 in atopic dermatitis


In vivo expression of cytokine receptor mRNA in atopic dermatitis

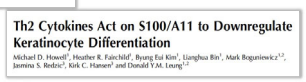

ENDOGENOUS ANTIMICROBIAL PEPTIDES AND SKIN INFECTIONS IN ATOPIC DERMATITIS

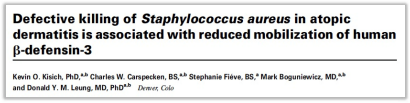

Cytokine Milieu of Atopic Dermatitis, as Compared to Psoriasis, Skin Prevents Induction of Innate Immune Response Genes[1]

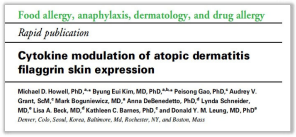

Cytokine Milieu of Atopic Dermatitis Skin Subverts the Innate Immune Response to Vaccinia Virus


Mechanism of HBD-3 deficiency in atopic dermatitis


Loricrin and involucrin expression is down-regulated by Th2 cytokines through STAT-6


Th2 Cytokines Act on S100/A11 to Downregulate Keratinocyte Differentiation


Defective killing of *Staphylococcus aureus* in atopic dermatitis is associated with reduced mobilization of human β-defensin-3


Food allergy, anaphylaxis, dermatology, and drug allergy

Rapid publication

Cytokine modulation of atopic dermatitis filaggrin skin expression

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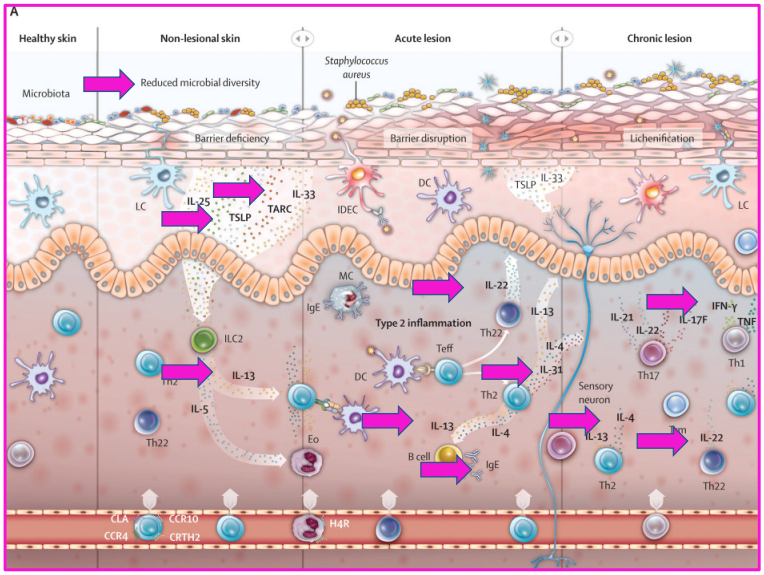
RETURN TO AGENDA

Implications for therapy: Narrow vs broad targeting approach



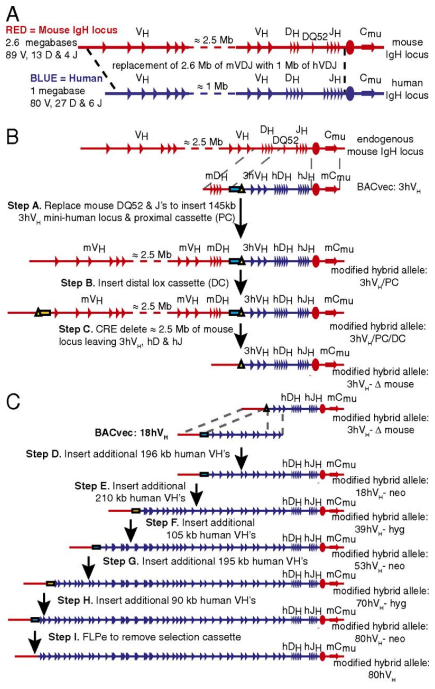
Lancet 2020;396:345-60

5

Human mAb from mice… It's complicated

Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes
Macdonald LE, et al. Proc Nat Acad Sci USA 2014;111:5147

Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice
Murphy AJ, et al. Proc Nat Acad Sci USA 2014;111:5153



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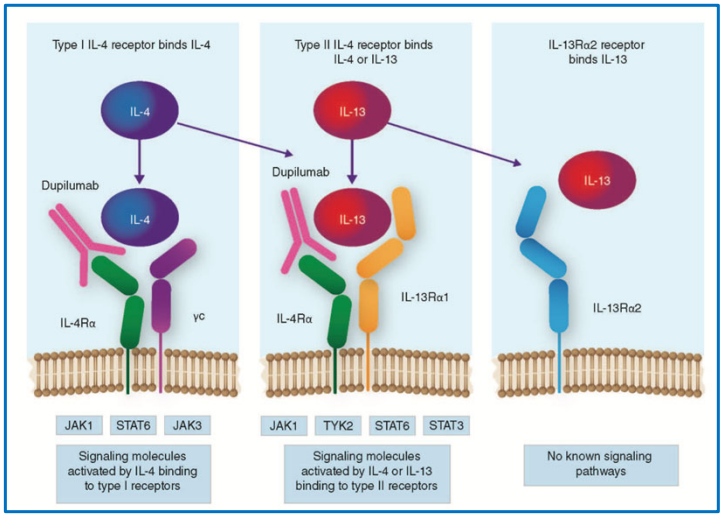
RETURN TO AGENDA

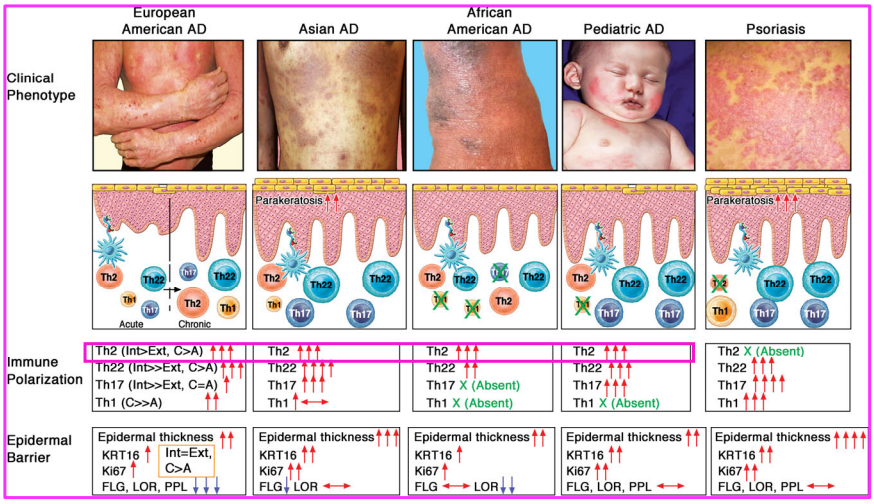
Dupilumab, a fully human monoclonal antibody targeting IL-4 receptor-alpha



Immunotherapy 2015;7:1043

7

AD phenotypes and related endotypes



J Allergy Clin Immunol 2019;143:1

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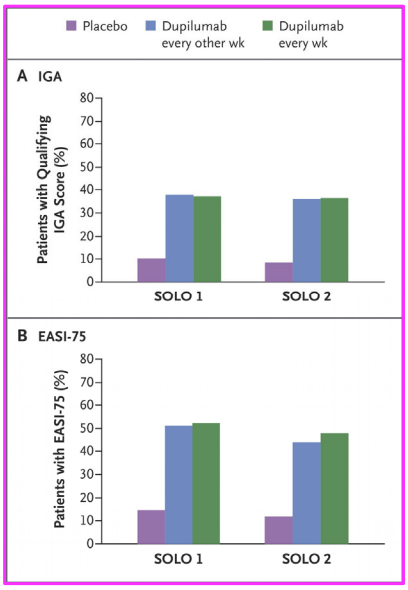
RETURN TO AGENDA

Two phase 3 trials of dupilumab vs placebo in atopic dermatitis

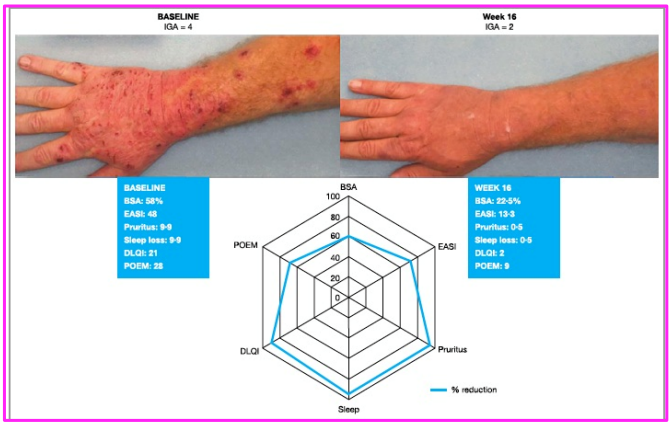


P<0.001 for all dupilumab vs placebo

N Engl J Med 2016;375:2335-48

9

Dupilumab provides important clinical benefits to patients with atopic dermatitis who do not achieve clear or almost clear skin according to the Investigator's Global Assessment: a pooled analysis of data from two phase III trials



Among patients with IGA > 1 at wk 16, dupilumab significantly improved several outcome measures compared with placebo:
- EASI (-48·9% vs. -11·3%, P < 0·001)
- pruritus NRS (-35·2% vs. -9·1%, P < 0·001)
- affected BSA (-23·1% vs. -4·5%, P < 0·001)
- POEM score ≥ 4-point improvement (57·4% vs. 21·0%, P < 0·001)
- DLQI score ≥ 4-point improvement (59·3% vs. 24·4%, P < 0·001)

Br J Dermatol 2019;181:80-87

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Ann Allergy Asthma Immunol 120 (2018) 10–22

Contents lists available at ScienceDirect

Special Article

Atopic dermatitis yardstick: Practical recommendations for an evolving therapeutic landscape

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ABSTRACT

The implementation of treatment guidelines for atopic dermatitis is challenging, in part because of different guidance documents being used by different groups of specialists and in part because the language of guidelines often reflects the evidence base rather than the practical "how to." The Atopic Dermatitis Yardstick is part of a series developed in response to the need to proactively address the loss of disease control for atopic illnesses at all levels of severity. It presents a comprehensive update on how to conduct a sustained step-up in therapy for the patient with inadequately controlled or poorly controlled atopic dermatitis. Patient profiles, based on current guidelines and the authors' combined clinical experience, provide a practical and clinically meaningful guide to aid physicians in helping their patients achieve the goal of clear to almost clear. The intent is not to replace guidelines but to complement their recommendations incorporating the latest research and therapies.

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Disclosures: Dr Boguniewicz is a member of the speakers' bureau and is a consultant for Regeneron and Sanofi-Genzyme and has done clinical research for Regeneron. Dr Farrar has no financial interests to disclose. Dr Fonacier serves on advisory boards for Regeneron and Genentech, is a member of the speakers' bureau for Regeneron, and has research receiving grant support from Baxter, Genentech, and Merck. Dr Guttman-Yassky serves on the boards of Sanofi–Aventis, Regeneron, Stiefel/GlaxoSmithKline, MedImmune, Celgene, Anacor, Leo Pharma, AnaptysBio, Celsus, Dermira, Galderma, Novartis, Pfizer, Vitae, Glenmark, AbbVie, and Asana Biosciences; serves as a consultant for Regeneron, Sanofi Aventis, MedImmune, Celgene, Stiefel/GlaxoSmithKline, Celsus, BMS, Amgen, Drais, AbbVie, Anacor, AnaptysBio, Dermira, Galderma, Leo Pharma, Novartis, Pfizer, Vitae Mitsubishi Tanabe, Eli Lilly, Glenmark, and Asana Biosciences; and receives grant support from Regeneron, Celgene, BMS, Janssen, Dermira, Leo Pharma, Merck, Novartis, and UCB. Dr Ong has no financial interests to disclose. Dr Silverberg serves on advisory boards and as a consultant for AbbVie, Eli Lilly, Galderma, GlaxoSmithKline, Kiniksa, Leo, Menlo, Pfizer, Realm, Roivant, and Regeneron-Sanofi; and has research receiving grant support from GlaxoSmithKline.
Funding Sources: American College of Allergy, Asthma and Immunology, including editorial support and an honorarium for each author.

Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease—one of the most common inflammatory skin diseases worldwide, with an estimated prevalence of up to 25% of children and 7% of adults in the United States.[1-3] AD typically occurs in infancy and early childhood, with an onset in the first year of life reported for 60% to 85% of children and by 5 years of age for at least 85%.[2,4-8] However, AD can present at *any age*; and although most childhood-onset symptoms resolve before adulthood, persistence (albeit some in milder forms) is relatively common.[9-13] Up to 50% of adult patients are first diagnosed in adulthood, and 30% of childhood cases persist into the adult years.[1,14-16] Managing AD at any age can be challenging.

Atopic dermatitis is a diagnosis based on clinical presentation.[9-11,17] Current research detailing the underlying mechanisms of AD (Fig 1; eCommentary 1)[18] holds hope that biomarkers will be available to confirm the diagnosis and possibly differentiate various AD phenotypes (eg, intrinsic vs extrinsic AD, pediatric AD, Asian-origin AD),[19-31] but the current reality is that AD is diagnosed by symptoms and exclusion (Table 1).[3,9,11]

The clinical presentation of AD is characterized by (1) pruritus, (2) eczematous lesions (associated with T-helper cell type [T_H] 2 and T_H22 inflammation), and (3) dry skin (related to epidermal barrier

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Adolescent, pediatric and infant AD trials with dupilumab

JAMA Dermatology | Original Investigation

Efficacy and Safety of Dupilumab in Adolescents With Uncontrolled Moderate to Severe Atopic Dermatitis
A Phase 3 Randomized Clinical Trial

CONCLUSIONS AND RELEVANCE In this study, dupilumab significantly improved AD signs, symptoms, and quality of life in adolescents with moderate to severe AD, with an acceptable safety profile. Placebo-corrected efficacy and safety of dupilumab were similar in adolescents and adults. (JAMA Dermatol 2020;156:44-56)

Dupilumab in children aged 6 months to younger than 6 years with uncontrolled atopic dermatitis: a randomised, double-blind, placebo-controlled, phase 3 trial

Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial

Conclusion: Dupilumab + TCS is efficacious and well tolerated in children with severe AD, significantly improving signs, symptoms, and QOL. (J Am Acad Dermatol 2020;83:1282-93.)

Dupilumab significantly improved AD signs & symptoms vs placebo in children < 6 y. Dupilumab was well tolerated and showed an acceptable safety profile ~ older children and adults. (Lancet 2022;400:908)

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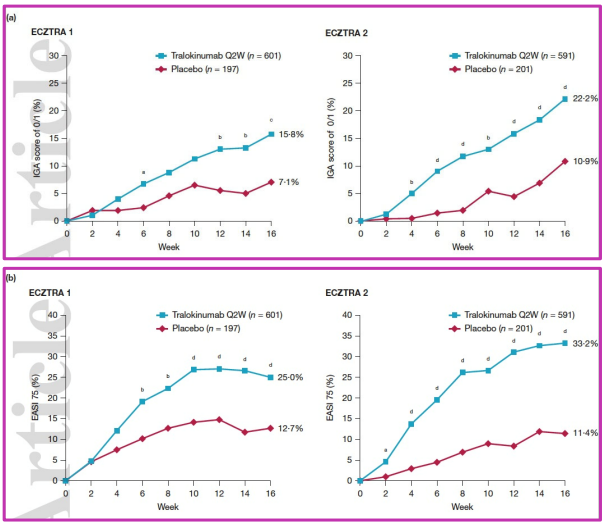
RETURN TO AGENDA

Tralokinumab: direct targeting of IL-13

Achievement of (a) IGA score of 0/1 and (b) EASI 75 in the 16-week initial treatment period in ECZTRA 1 and ECZTRA 2

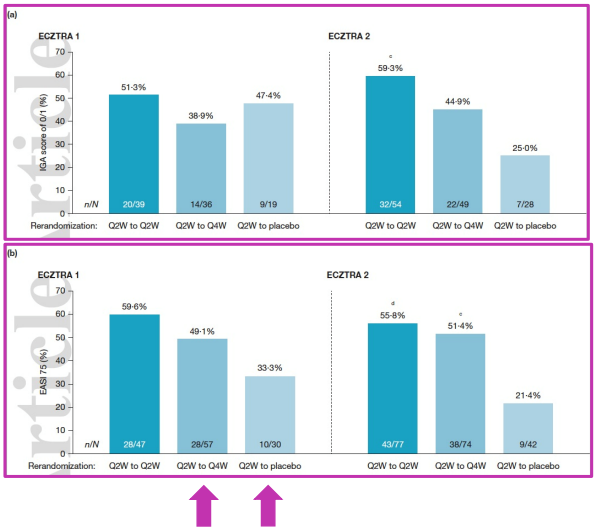


[a]P < 0·05 vs. placebo, [b]P < 0·01 vs. placebo, [c]P = 0·002 vs. placebo, [d]P < 0·001 vs. placebo

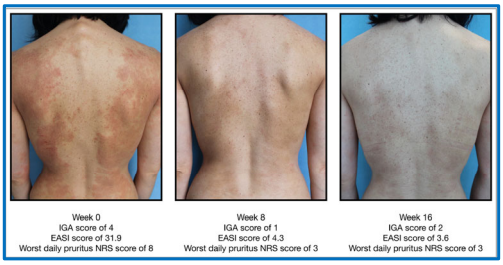
Br J Dermatol 2021;184:437-49

13

Maintenance of (a) IGA score of 0/1* and (b) EASI 75* clinical response at week 52 in ECZTRA 1 and ECZTRA 2



*Assessed in pts achieving W16 primary outcome of IGA or EASI75 score without use of rescue medication after initial randomization to tralokinumab



Br J Dermatol 2021;184:437-49

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RETURN TO AGENDA

Atopic Dermatitis Yardstick Update

- AD Yardstick published in 2018
- 2023 Update addresses:
  - Biologics: dupilumab, tralokinumab
  - JAK inhibitors: ruxolitinib, abrocitinib, upadacitinib
- **Incorporates Expert Commentary from group of allergist-immunologists and dermatologists**
  - **Clinical pearls for real world management**
    - Managing ocular symptoms or facial redness with dupilumab
    - Vaccines in patients on biologic therapy
    - Appropriate screening labs and interval monitoring of patients on sJAKi's

Boguniewicz M, et al. Ann Allergy Asthma Immunol 2023; 130:811

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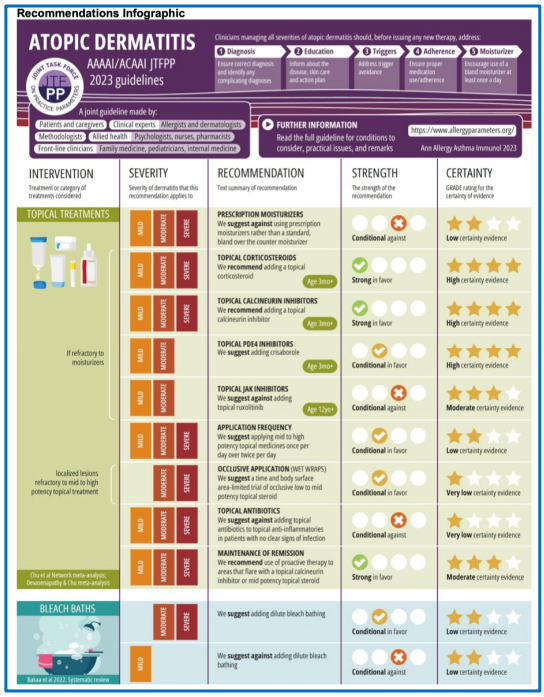

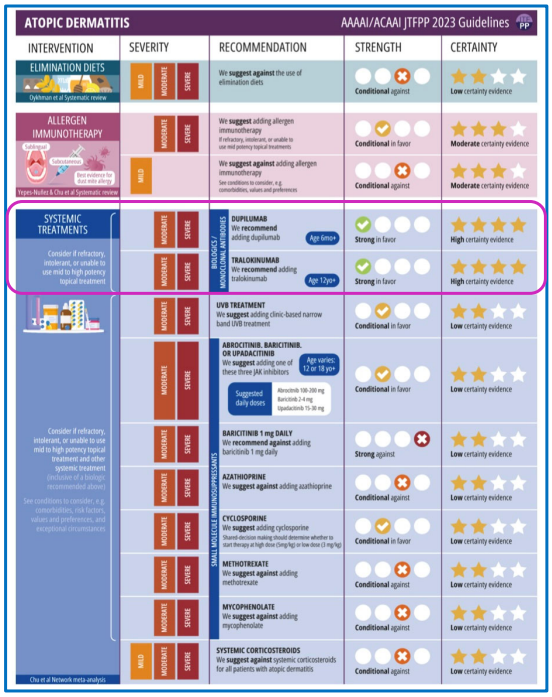

Ann Allergy Asthma Immunol 2024;132:274

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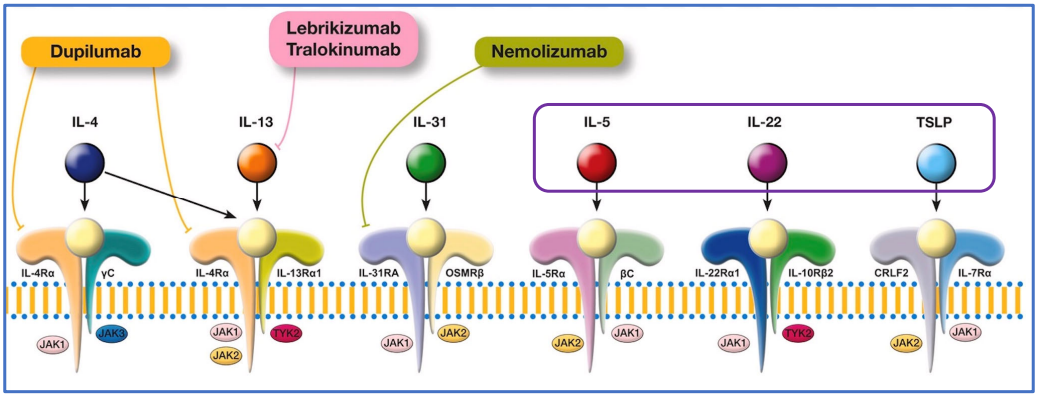
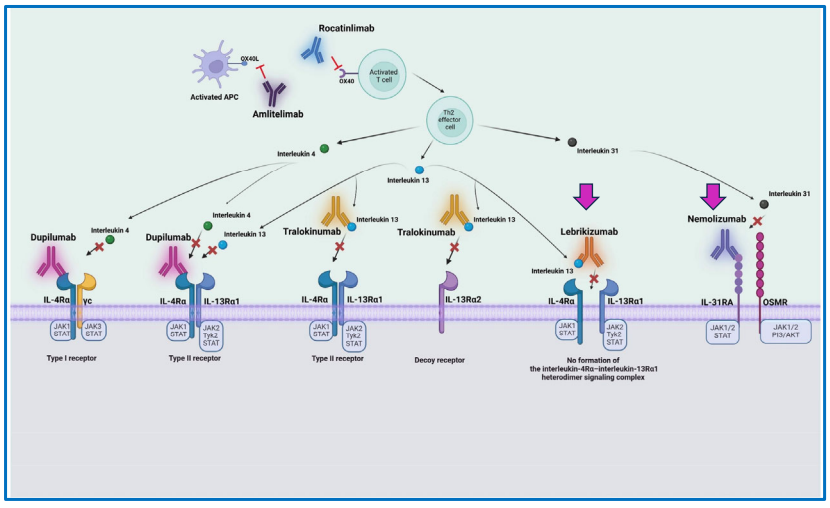
Currently approved mAbs for atopic dermatitis



Modified from J Allergy Clin Immunol Pract 2025; 13:1901

17

Mechanism of action of biologic drugs in atopic dermatitis



J Clin Med 2024;13:4001

18

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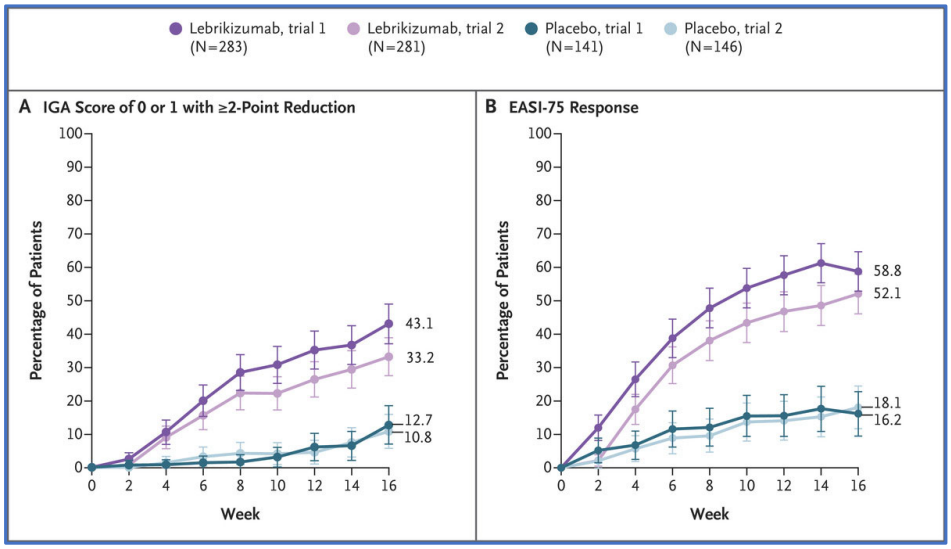
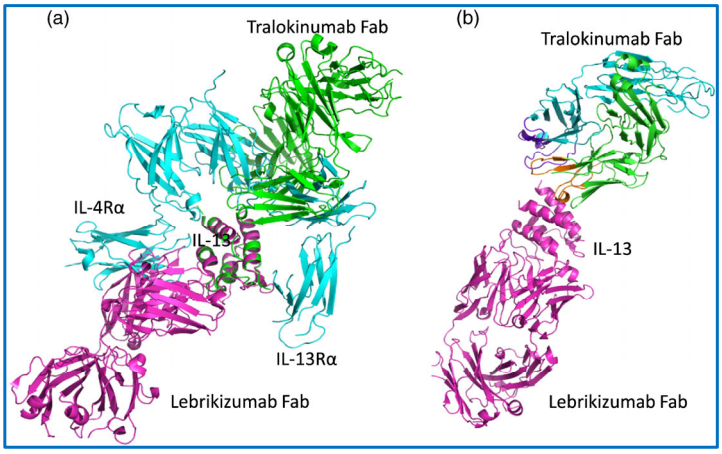
2 Phase 3 Trials of Lebrikizumab for Moderate-to-Severe Atopic Dermatitis



N Engl J Med 2023;388:1080

19

Comparison of the tralokinumab and lebrikizumab binding sites on IL-13



J Mol Biol 2017;429:208

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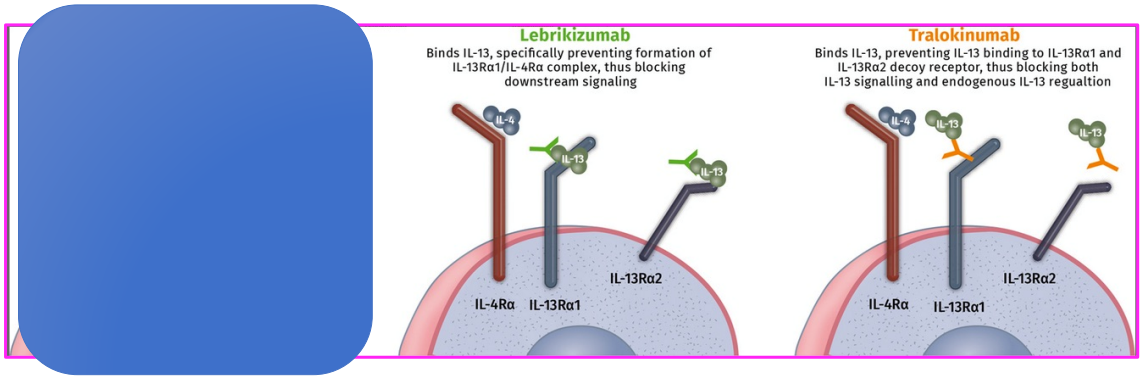
Mechanism of action for biologics targeting the IL-4 and/or IL-13 pathways



Exp Dermatol 2019;28:756

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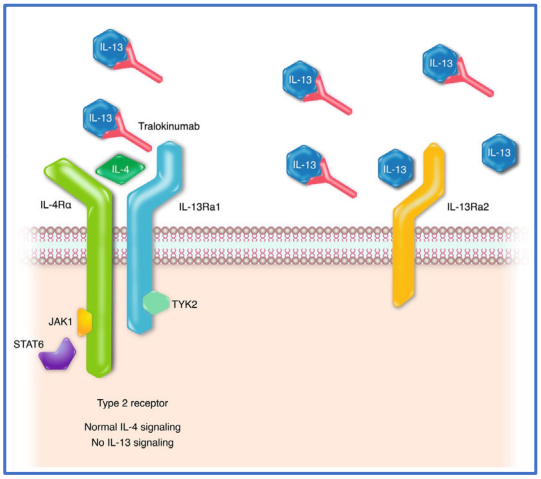
Tralokinumab binds specifically to IL-13 with high affinity at an epitope that overlaps with the binding site of IL-13Rα1 and IL-13Rα2, thereby preventing tralokinumab-bound IL-13 from binding to IL-13Rα1 or IL-13Rα2



- The binding affinity of tralokinumab to IL-13 is 1000-fold greater than the affinity of IL-13 to IL13Rα1
- The binding affinity of tralokinumab to IL-13 is 1000-fold lower than the affinity of IL-13 to IL-13Rα2
- Likely that IL-13Rα2 will out-compete tralokinumab binding to IL-13, and thus IL-13Rα2 is able to function normally and bind any remaining free IL-13, also in the presence of tralokinumab

Allergy 2023;78:2875

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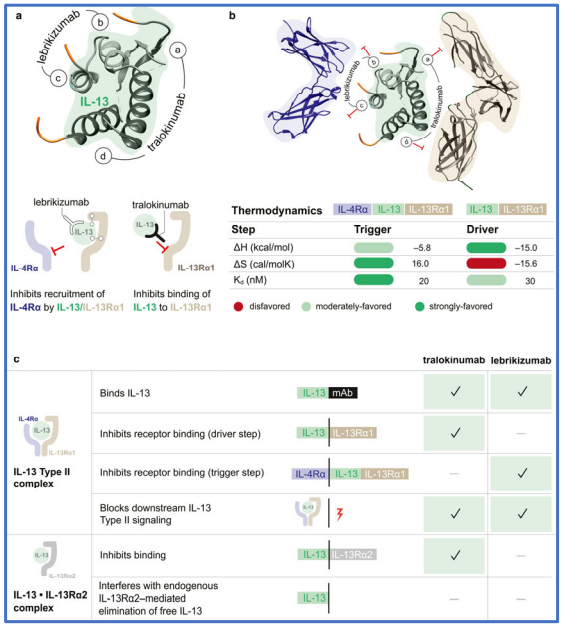
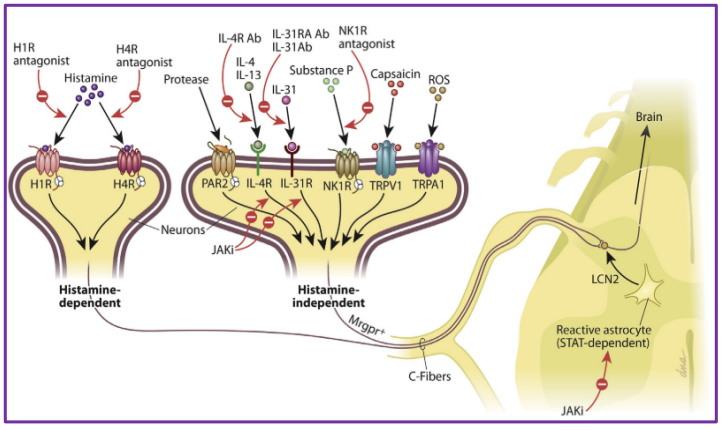
Inhibition of IL-13 signaling by tralokinumab and lebrikizumab



Bunick CG. Biologic Therapies Targeting Type 2 Signaling in Atopic Dermatitis: A Comparative Review of Structural and Thermodynamic Differences in Mechanism of Action. J Invest Dermatol 2025; Aug 6 on-line

23

Nemolizumab & AD: It's all about the itch



J Allergy Clin Immunol 2017;140;633

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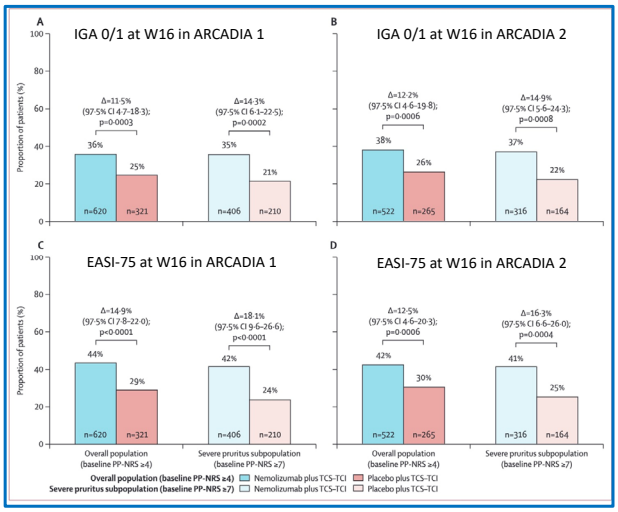
Coprimary endpoints in ARCADIA 1 and 2: overall populations and subpopulations with severe pruritus at baseline



Lancet 2024;404:445

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*No screening or monitoring labs

Monoclonal antibodies approved for AD*

Drug/target	Indication	Age	Dosing	Comments
Dupilumab (Dupixent)/IL-4rec alpha 2017 (initial date of FDA approval for AD)	Moderate-to-severe AD not adequately controlled with topical Rx therapies or when those therapies are not advisable	≥ 6m	≥18y - 600 mg (300 mg x 2), 300 mg Q2W 6-17 y - ≥ 60 kg - 600 mg x 1, 300 mg Q2W 30 kg - < 60 kg- 400 mg x 1, 200 mg Q2W 15 kg - < 30 kg - 600 mg x1, 300 mg Q4W 6 mo-5 y - 15 kg - < 30 kg - 300 mg Q4W (no loading dose) 5 kg - < 15 kg - 200 mg Q4W (no loading dose)	Syringe or pen for age ≥2y Also approved for asthma, EOE, CRSwNP, CSU, COPD, PN, BP
Tralokinumab (Adbry)/IL-13 2021	Moderate-to-severe AD not adequately controlled with topical Rx therapies or when those therapies are not advisable	≥12y	≥18y - 600 mg (4 x 150 syringe or 2 x 300-mg autoinjector x 1), 300 mg Q2W (2 x 150 mg syringe or 1 x 300 autoinjector) 12-17y - 300 mg (2 x 150 syringe x 1), 150 mg Q2W	If clear/almost clear, 300 mg Q4W in adults <220 lbs
Lebrikizumab (Ebglyss)/IL-13 2024	Moderate-to-severe AD not adequately controlled with topical Rx therapies or when those therapies are not advisable	≥12y (weigh ≥40 kg)	500 mg (250 mg x 2) subq (syringe or pen) at W0 and W2, then 250 mg Q2W	Maintenance 250 mg Q4W at ≥W16, when adequate clinical response is achieved
Nemolizumab (Nemluvio)/IL-31RA 2024	Moderate-to-severe AD in combination with TCS and/or TCIs when disease not controlled by topical Rx therapies	≥12y	60 mg (30 mg x 2) subq injector pen, followed by 30 mg Q4W	Maintenance 30 mg Q8W after 16W if clear/almost clear; Also for adult PN

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RETURN TO AGENDA

Comparative efficacy of biologics for atopic dermatitis in adults

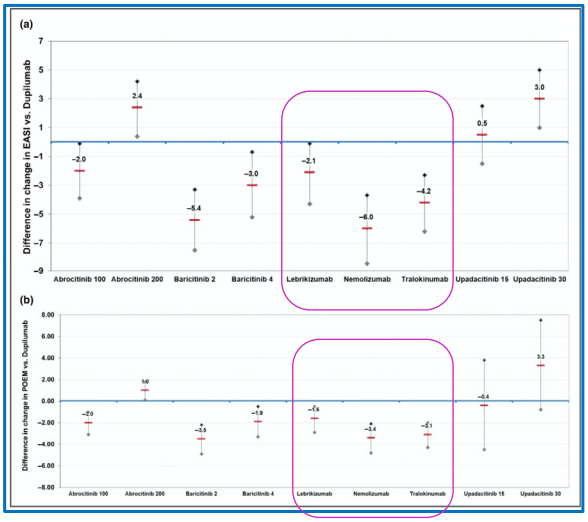
Systemic treatment	Efficacy*
	*Mean difference in change in EASI (95% CrI) vs placebo in network meta-analysis [1,2]
Dupilumab	MD, −10.5 (95% CrI, −11.9 to −9.2) [1]
Tralokinumab	MD, −6.2 (95% CrI, −7.8 to −4.7) [1]
Lebrikizumab	MD, −8.5 (95% CrI, −10.4 to −6.5) [1]
Nemolizumab	MD, −4.4 (95% CrI, −6.5 to −2.4) [2]

[1]JAMA Dermatol 2024;160:936
[2]Br J Dermatol 2025;193:548

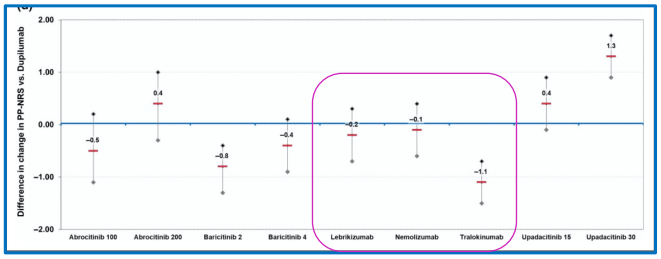
A difference in EASI score of 3.3, which is half the minimal clinically important difference at the individual patient level, is considered clinically important at the trial group level, indicating that these medications are associated with clinically meaningful improvement relative to placebo

Drucker AM. JAMA 2025; on line Aug 20

27



Living network meta-analysis to compare nemolizumab against other available targeted systemic treatments for atopic dermatitis*



Drucker AM, et al. Br J Dermatol 2025; Aug 18 on-line

*adults (some adolescents) treated between 8-16 wks

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In progress!

Back to the JTFPP AD guidelines...commitment to timely updates

- represent an evolution in trustworthy allergy guidelines distinguished from other guidelines through systematic reviews of the evidence with multidisciplinary panelist engagement, adherence to a rigorous guideline development process, robust use of GRADE that fulfils requirements to report its proper use, core involvement of patient and caregiver voice from start to finish, focus on equity, diversity and inclusiveness, clear translation of evidence to clinically actionable and contextual recommendations and novel approaches to facilitate knowledge translation
- emphasize in addition to standards of trustworthiness, the third principle of evidence-based medicine: that evidence alone is never enough; that patient values and preferences must be carefully considered when determining optimal treatments for patients and populations
  - Supplement provides 1-2 page patient-friendly handouts to facilitate education, discussion, and shared decision-making

Ann Allergy Asthma Immunol 2024;132:274

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Atopic Dermatitis Yardstick Update

Update to the Update in the works...

- AD Yardstick published in 2018
- 2023 Update addresses:
  - Biologics: dupilumab, tralokinumab
  - JAK inhibitors: ruxolitinib, abrocitinib, upadacitinib
- **Incorporates Expert Commentary from group of allergist-immunologists and dermatologists**
  - **Clinical pearls for real world management**
    - Managing ocular symptoms or facial redness with dupilumab
    - Vaccines in patients on biologic therapy
    - Appropriate screening labs and interval monitoring of patients on sJAKi's

Boguniewicz M, Fonacier L, et al. Ann Allergy Asthma Immunol 2023; 130:811

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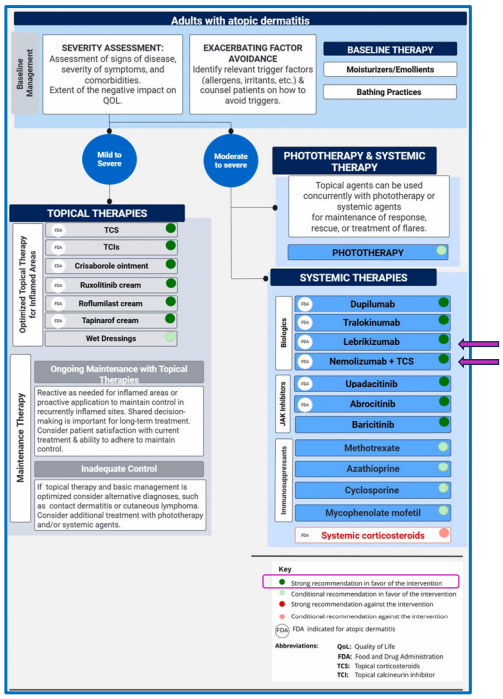
RETURN TO AGENDA

Focused update: Guidelines of care for the management of atopic dermatitis in adults



J Am Acad Dermatol 2025; June 17 Online ahead of print

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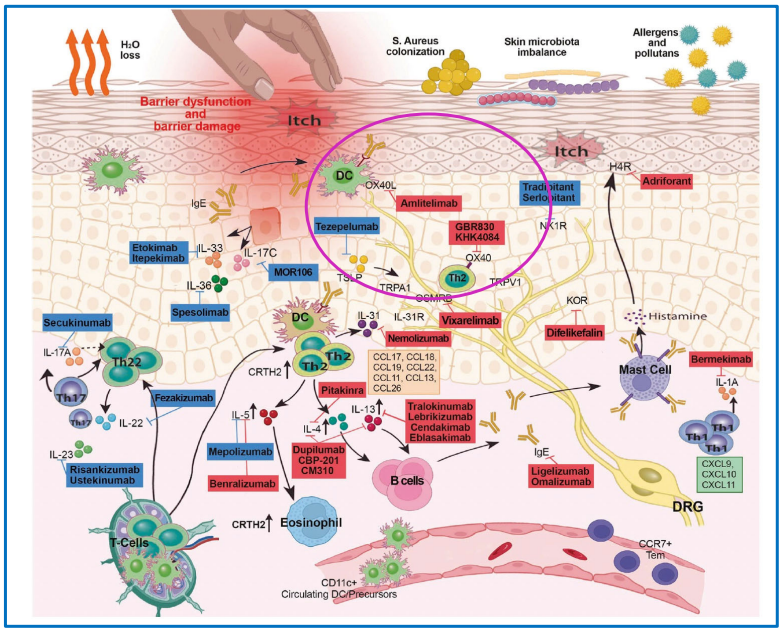
Systemic therapies for AD

Red box = Under investigation or with positive results

Blue box = Failed to reach 1° endpoint in clinical trials



Cell Mol Immunol 2023;20:448

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Tezepelumab, an anti-thymic stromal lymphopoietin monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: A randomized phase 2a clinical trial

- V plus
- nd 5-D
- for all

J Am Acad Dermatol 2019;80:1013

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Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments: A randomized, double-blind, phase 2a trial

- Intravenous fezakinumab monotherapy Q 2 wks for 10 wks with follow-up assessments until 20 wks
- At 12 wks, mean declines in SCORAD for entire study population were 13.8 ± 2.7 in fezakinumab arm and 8.0 ± 3.1 in placebo arm (P = .134)
- In severe AD subset (baseline SCORAD ≥50), SCORAD decline significantly stronger in fezakinumab treated patients than placebo treated patients at 12 wks (21.6 ± 3.8 vs 9.6 ± 4.2, P = .029) and 20 wks (27.4 ± 3.9 vs 11.5 ± 5.1, P = .010)

J Am Acad Dermatol 2018;78:872

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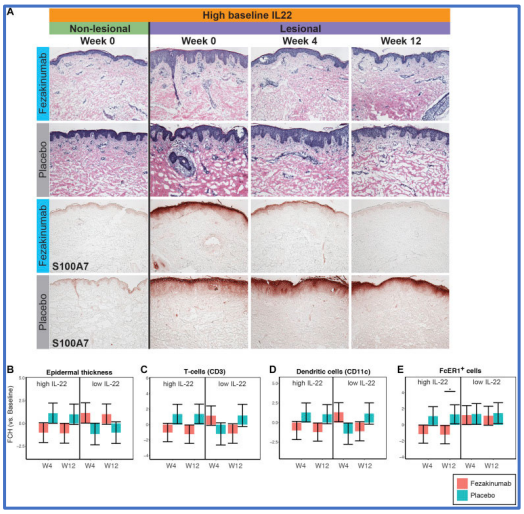
Baseline IL-22 expression in patients with atopic dermatitis stratifies tissue responses to fezakinumab

- Greater reversal of the AD genomic profile was seen with fezakinumab versus placebo, namely 25.3% versus 10.5% at 4 weeks ($P = 1.7 \times 10^{-5}$) and 65.5% versus 13.9% at 12 weeks ($P = 9.5 \times 10^{-19}$), respectively
- Much stronger mean transcriptomic improvements were seen with fezakinumab in the IL-22-high drug-treated group (82.8% and 139.4% at 4 and 12 weeks, respectively) than in the respective IL-22-high placebo-treated group (39.6% and 56.3% at 4 and 12 weeks) or the IL-22-low groups



J Allergy Clin Immunol 2019;143:142

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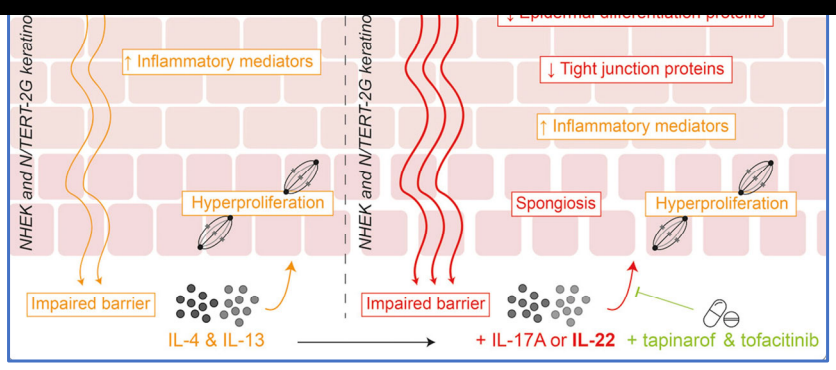
Dissecting key contributions of Th2 and Th17 cytokines in atopic dermatitis pathophysiology

Presence of TH2 + IL-22 most closely resembled AD hallmarks including spongiosis, more severe keratinocyte differentiation defects, and epidermal barrier dysfunction



J Allergy Clin Immunol 2025;156:690

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Emerging biologic therapies for AD...

- Systemic
  - Lebrikizumab (anti-IL-13) – APPROVED 09/13/24
  - Nemolizumab (anti-IL-31 RA) - APPROVED 12/13/24
  - Rocatinlimab (anti-OX40)
  - Amlitelimab (anti-OX40L)

- **>1600 clinical trials for atopic dermatitis registered with ClinicalTrials.gov**
  - **534 phase 3 trials (10/25)**

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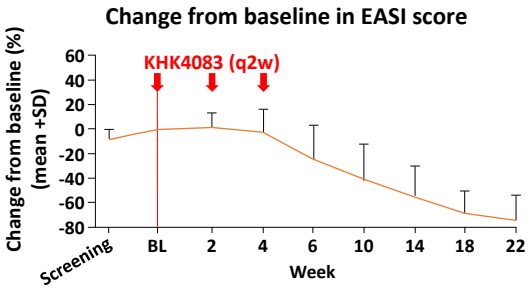
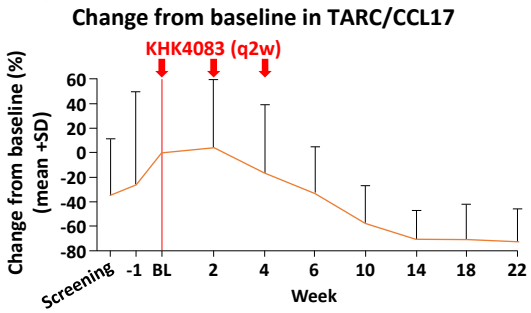
Phase 1 study of intravenous KHK4083 (anti-OX40 mAb) in moderate-to-severe AD

Baseline characteristics	Safety analysis set (n=22)	Clinical symptom analysis set (n=20)
Age, years	33.6 ±11.4	33.7 ±11.4
Sex, male	18 (81.8)	18 (90.0)
BMI, kg/m²	23.96 ±4.59	23.74 ±4.76
Rajka & Langeland AD severity		
Moderate	8 (36.4)	8 (40.0)
Severe	14 (63.6)	12 (60.0)
TARC, pg/ml	6260 ±6118	–
EASI	33.98 ±9.68	33.11 ±9.72
IGA	3.8 ±0.6	3.8 ±0.6
%BSA	57.4 ±16.4	56.4 ±16.9
DLQI	8.9 ±5.2	8.7 ±5.0
Pruritus NRS	7.0 ±2.1	6.8 ±2.2
POEM	15.3 ±6.9	14.9 ±7.2

Data are mean ±SD or n (%) unless otherwise denoted

- **22 patients received 3 doses of KHK4083**
- **No concomitant treatments were allowed**





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Nakagawa H, et al. EADV 2018, P0252.

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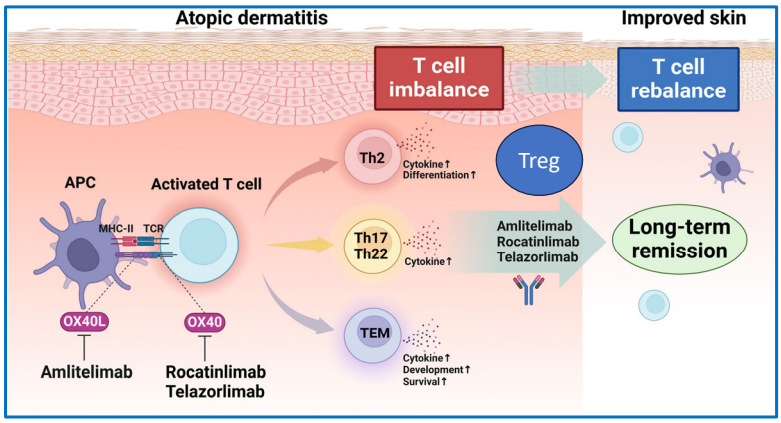
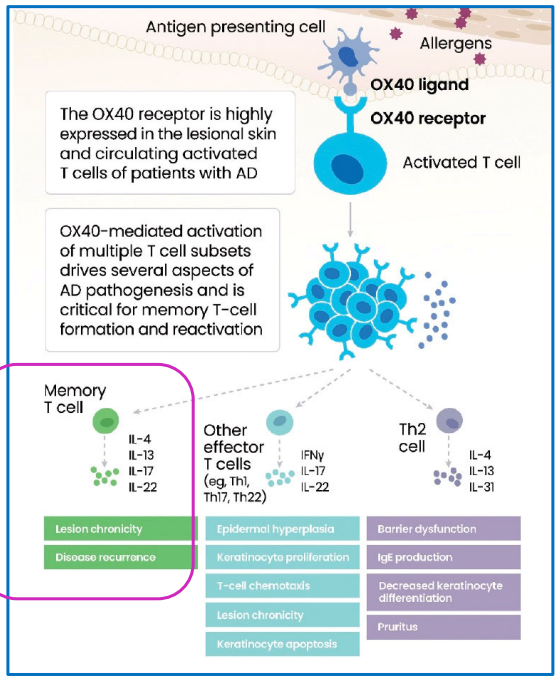
Mechanism of OX40-OX40L pathway in AD and therapeutic targets



J Allergy Clin Immunol 2025;155:1211

39

OX40 mediated activation of multiple T cell subsets



Immunotherapy 2025;17:83

40

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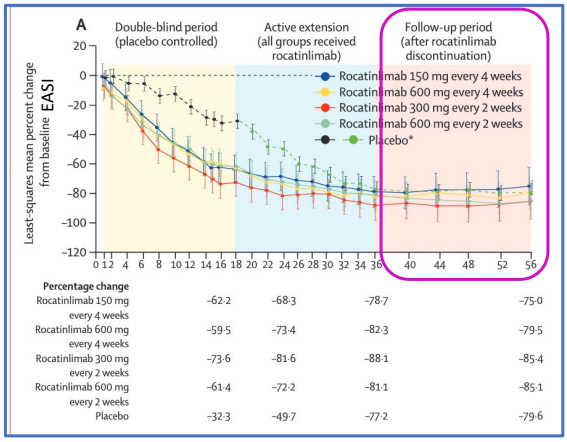
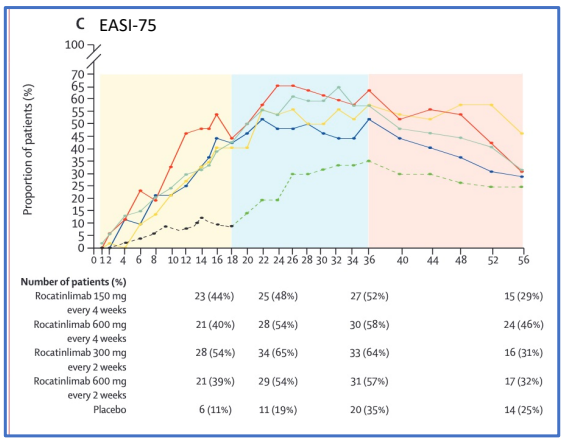
An anti-OX40 antibody to treat moderate-to-severe atopic dermatitis: a multicentre, double-blind, placebo-controlled phase 2b study

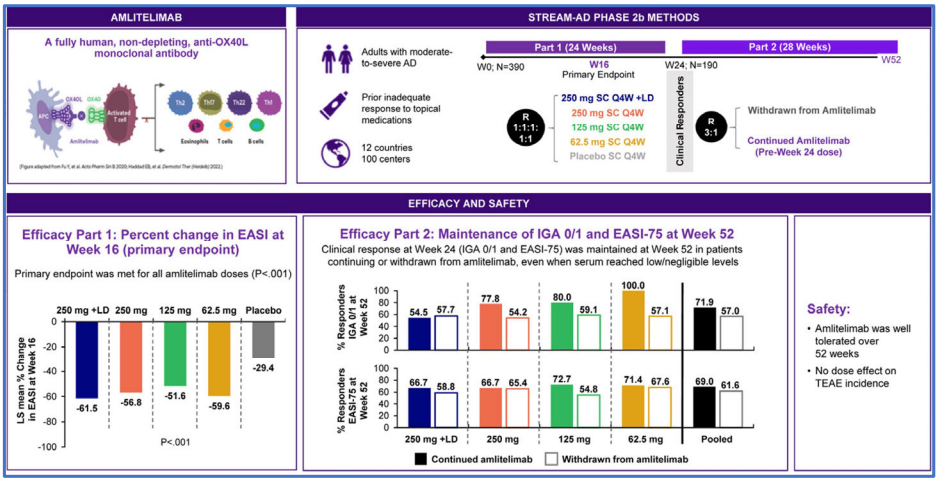




Lancet 2023;401:204

41

Phase 2b randomized clinical trial of amlitelimab, an anti-OX40 ligand antibody, in patients with moderate-to-severe atopic dermatitis



J Allergy Clin Immunol 2025;155:1264

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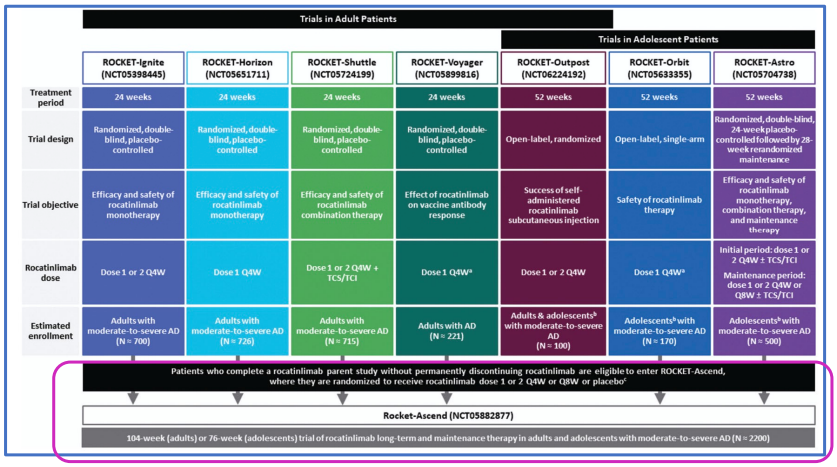
ROCKET: a phase 3 program evaluating the efficacy and safety of rocatinlimab in moderate-to-severe atopic dermatitis



Immunotherapy 2025;17:83

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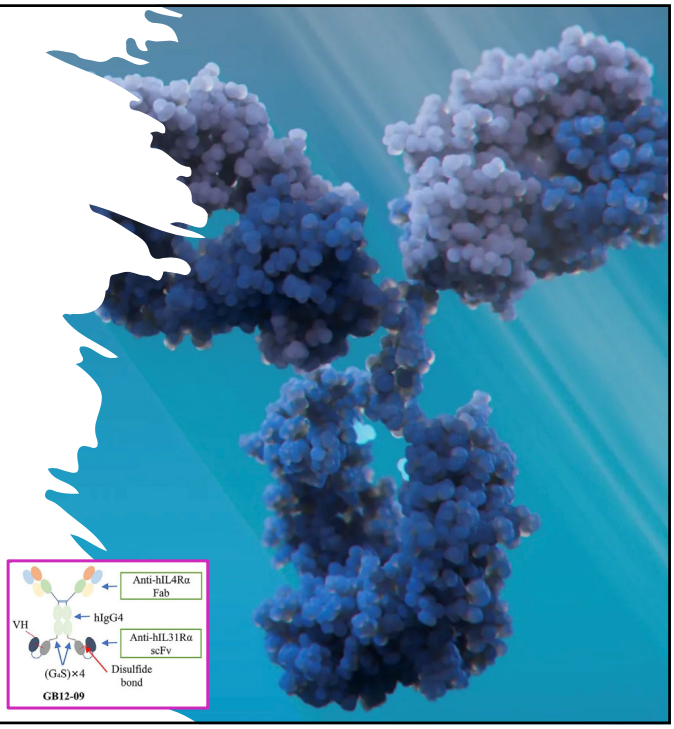
Novel approaches to mAb therapy for atopic dermatitis

- mAbs with extended activity
  - e.g. Anti-OX40 half-life extended mAb utilizing "YTE modification" (a change involving 3 amino acids) within the mAb's Fc region leading to enhanced binding affinity for the neonatal Fc receptor (FcRn), thus protecting the mAb from degradation (Astria Therapeutics)
- mAbs with extended activity used in combination
  - e.g. targeting IL-13 & OX40L (Apogee Therapeutics)
- Bispecific mAbs
  - e.g. targeting IL-4Rα & IL-31Rα (GB12-09, Antibody Therapeutics 2024;7:77)



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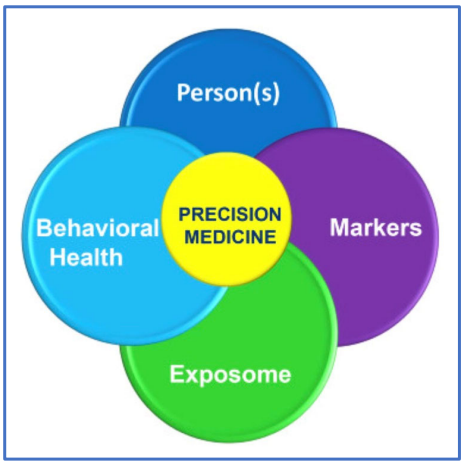
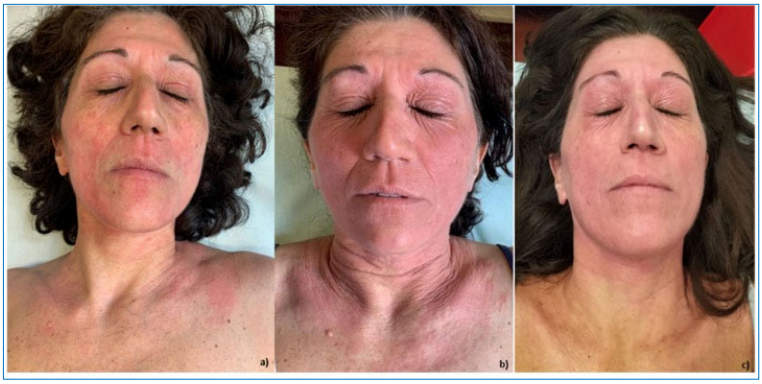
Moving from “one size fits all” to a precision medicine approach



health.ucdavis.edu

45

Efficacy of tralokinumab after failure with upadacitinib and dupilumab in a patient affected by atopic dermatitis



- (a) At end of dupilumab therapy: extensive erythematous involvement of the face and neck
- (b) At end of upadacitinib therapy: erythema and lichenification of the face, neck, and neckline
- (c) First follow-up after initiation of tralokinumab: initial reduction in the extent of erythematous lesions and reduction in lichenification at the face

J Dermatol Treat 2023;34:2153578

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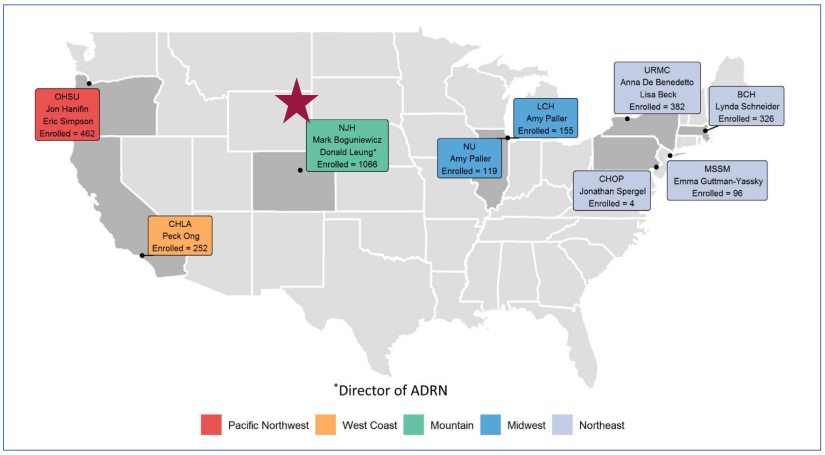
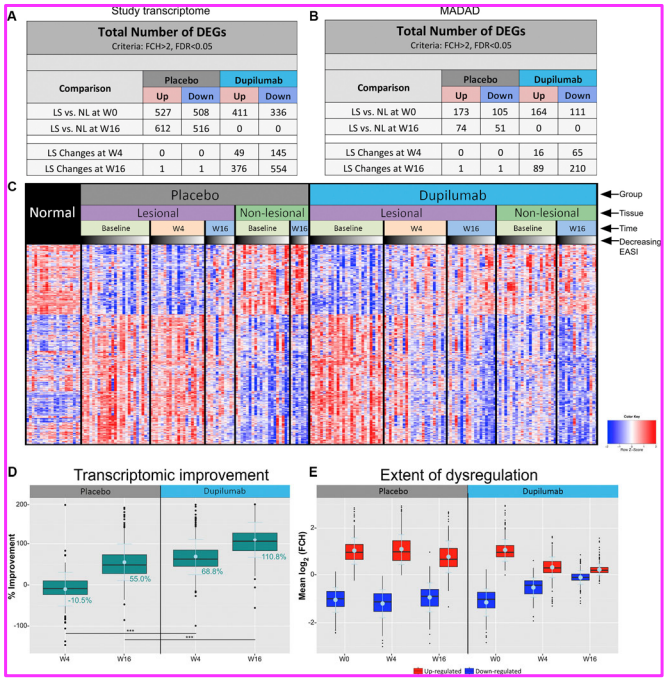
NIAID Atopic Dermatitis Research Network



J Allergy Clin Immunol Pract 2023;11:2504

47

Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis



J Allergy Clin Immunol 2019;143:155

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A · D · R · N
Atopic Dermatitis Research Network

NIAID

LEADS: Longitudinal Endotyping of Atopic Dermatitis Through Transcriptomic Skin Analysis

Primary Objective

To determine if the type 2-high non-lesional skin (skin tape) endotype is associated with current mild versus moderate-to-severe AD disease

Secondary Objectives

1. To determine how gene expression in the skin (skin tape) differs between non-AD participants and those with current mild or moderate-to-severe AD disease
2. To determine how gene expression in the skin (skin tape) changes over time among the study outcome groups: (1) steroid responders, (2) dupilumab responders, (3) dupilumab non-responders, (4) non-AD, and (5) long-term dupilumab participants

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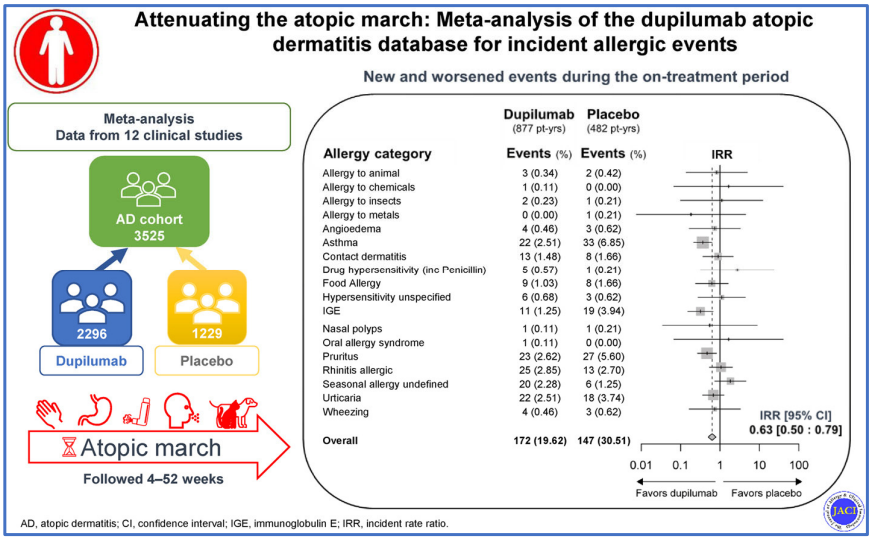
Disease modification in atopic dermatitis



J Allergy Clin Immunol 2023;151:756

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Reduced atopic march risk in pediatric atopic dermatitis patients prescribed dupilumab versus conventional immunomodulatory therapy: A population-based cohort study

- Retrospective cohort study utilized data from the TriNetX US Collaborative Network (2011-2024) of AD patients <18 yrs
- Atopic march progression defined by incident asthma or allergic rhinitis
- 2192 pts in each cohort (Dupilumab vs Conventional)
- 3-year cumulative incidence of atopic march progression lower in the DUPI-cohort vs CONV-cohort (20.09% vs 27.22%; P<.001)
- DUPI cohort demonstrated significant risk reduction in atopic march progression (hazard ratio [HR] 0.68, 95% CI 0.55-0.83), individual asthma (HR 0.60, 0.45-0.81), and individual AR (HR 0.69, 0.54-0.88)
- Younger patients on dupilumab exhibited a greater risk reduction for atopic march progression and individual asthma

J Am Acad Dermatol 2024;91:466

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Deciding which patients with atopic dermatitis to prioritize for biologics and Janus kinase inhibitors

TABLE I. Pros and cons of biologics and Janus kinase inhibitors

Deciding factor	Dupilumab	Tralokinumab	Lebrikizumab	Nemolizumab	Abrocitinib	Baricitinib	Upadacitinib
AD approval by age							
≥15 yo	Y	Y	Y	Y	Y	Y-EU/J	Y
12-14 yo	Y	Y-US/EU	Y	Y	Y	Y-EU/J	Y
6-11 yo	Y	N	N	Y-J	N	Y-EU/J	N
2-5 yo	Y	N	N	N	N	Y-EU/J	N
6 mo to 1 yo	Y	N	N	N	N	N	N
Approval in other indications							
Atopic disorders	***	N	N	PN	N	N	N
Autoimmune disorders	P	ND	ND	ND	P	Y	P
Administration route							
Oral administration	N	N	N	N	Y	Y	Y
Efficacy							
Direct anti-inflammatory	Y	Y	Y	P	Y	Y	Y
Rapid effect on inflammation	**	*	**	–	***	**	***
Rapid efficacy on pruritus	*	*	*	***	***	*	***
High global efficacy	**	*	**	*	**	*	***
Sustained efficacy ≥12 yo	*	*	**	*	N	N	N
Sustained efficacy <12 yo	**	**	**	*	NA	N	NA
Side effects							
↓Bacterial skin infections	**	**	**	ND	ND	ND	ND
Injection reactions	*	*	*	*	NA	NA	NA
Ocular surface disease risk	**	*	*	N	N	N	N
Head and neck erythema	Y	N	N	N	N	N	N
Cutaneous adverse events[31,32]	N	N	N	Y	N	N	N
Risk of acne	N	N	N	N	**	*	**
Risk of Herpes zoster	N	N	N	N	**	*	***
Safety and monitoring							
Safety profile	***	***	***	***	*	**	*
IgE levels	↓↓	↓	↓	→	→	→	↑
Live vaccinations	P	ND	ND	ND	N	N	N
Administration during pregnancy	P	ND	ND	ND	N	N	N
Laboratory monitoring required	N	N	N	N	Y	Y	Y
Boxed warning for class	N	N	N	N	Y	Y	Y

–, none; *, some; **, moderate; ***, high.
AD, Atopic dermatitis; *EU*, Europe; *J*, Japan; *mo*, months; *N*, no; *ND*, no data available; *P*, possibly/there is growing real-world evidence of safety or of efficacy with studies in progress or planned; *PN*, prurigo nodularis, which can be associated with AD and is neuroimmune; *Y*, yes; *yo*, year old.

J Allergy Clin Immunol Pract 2025;13(Aug):1901

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Podium to Practice Takeaways

1. Identification of key immune abnormalities in atopic dermatitis along with technological advances have led to development of targeted therapy that has proven to be both safe and effective.

2. For patients with moderate-to-severe atopic dermatitis not responding to topical therapy or when such therapies are not advisable, one biologic (dupilumab) is approved down to 6 months of age and 3 (tralokinumab, lebrikizumab and nemolizumab) are currently approved down to 12 years of age; none of the currently approved mAbs for atopic dermatitis requires lab monitoring, though AEs have been reported infrequently.

3. Emerging biologic therapies target novel immune pathways such as OX40-OX40L and may result in disease modification while advances in precision medicine may help match patients with optimal therapy.

RETURN TO AGENDA

Navigating JAK Inhibitors: Timing and Strategies for use in Atopic Dermatitis

Clinton Dunn MD FACAAI

1

Objectives

- Understand the mechanism of JAK inhibition and role in Atopic Dermatitis
- Understand the efficacy of the current topical and oral JAK inhibitors
- Discuss the Black Box Warning for the JAK inhibitors
- Apply the use JAK inhibitors to appropriate populations and the ongoing monitoring that is needed
- Understand the future of personalized medicine for AD using biomarkers for severity and pheno/endotyping

2

RETURN TO AGENDA

Who is the right patient for the JAK inhibitors?

How do these work?
How are they administered?
What is the approval age?
What else can they treat?
Are these safe?
What do I need to worry about or monitor?
Where is our field going to help us make a tailored therapeutic approach?

3

Definitions/Abbreviations

- JAKi/JAKinh: Janus Kinase (JAK) Inhibitor, ends in -tinib
- STAT: Signal Transducer and Activator of Transcription
- Small Molecule: Low molecular weight agent that is typically oral or topical
- EASI: Eczema Area and Severity Index, range from 0-72
  - EASI50/75/90- reduction in baseline EASI score to the number attached
- SCORAD: Scoring Atopic Dermatitis, range from 0-103
- VIgA: Validated Investigator Global Assessment

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AD Systemic Therapeutic Timeline

2017:
Dupilumab

2021:
Tralokinumab

2022:
Abrocitinib and
Upadacitinib

2024:
Lebrikizumab
and
Nemolizumab

*Baricitinib currently not FDA approved for AD but approved in EU/Japan for AD

5

AD Overview

- Predominantly T_H2 skewed disease state
  - T_H22: important for chronic AD with epidermal thickening/ hyperplasia
  - T_H1 and T_H17 are involved in nonclassical phenotypes with neutrophilic inflammation and psoriasiform phenotypes

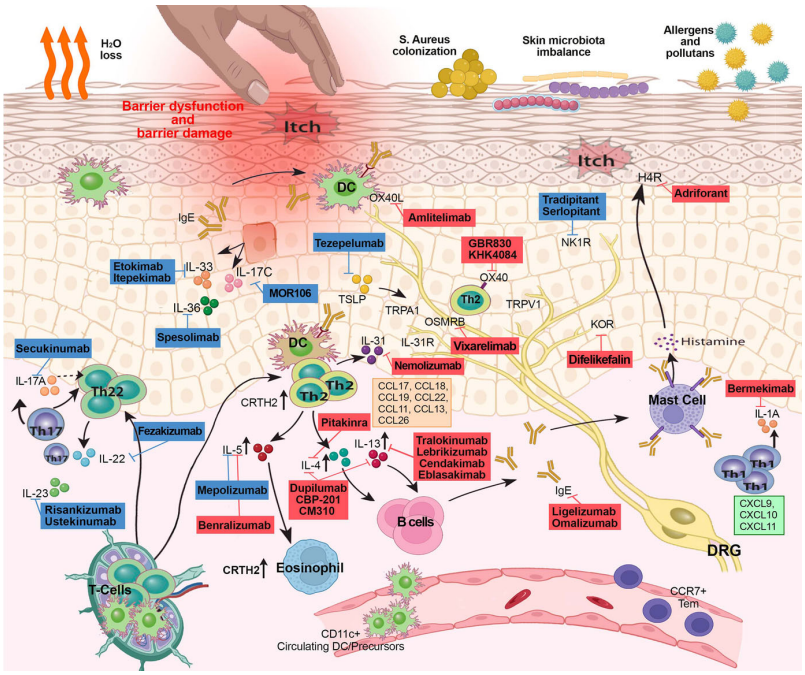

Figure 1: Facheris, P et al,. Cell Mol Immunol. 2023.

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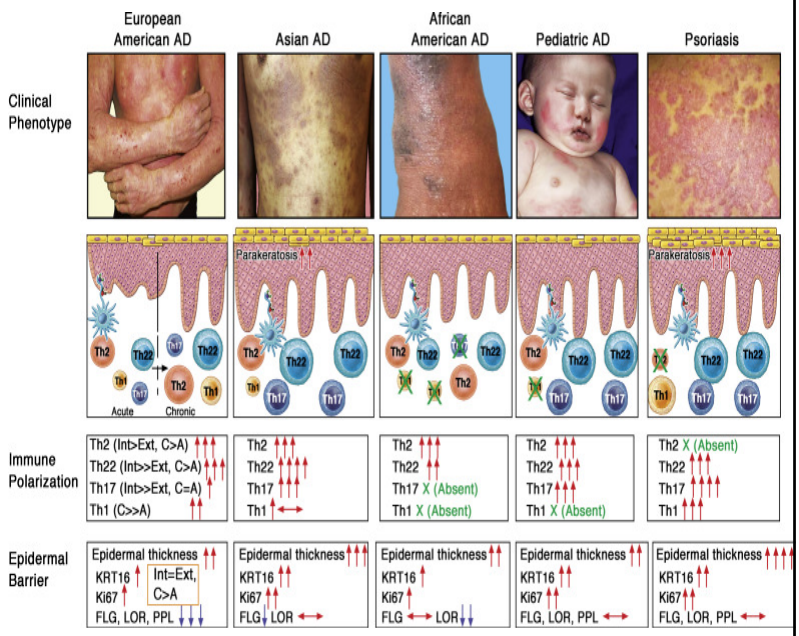
Subtypes of Atopic Dermatitis

- Heterogeneous presentations, morphology, distribution and severity
- Various subtypes have overlapping but different dominant signaling pathways
- Opportunities for personalized medical therapies



82. Czarnowicki T, et al. J Allergy Clin Immunol. 2019

7

JAK involvement in signaling

- 4 Major JAK isoforms that combine as homodimers or heterodimers
- Pharmacotherapy: Efficacy is based on the selectivity of the JAK targeted.
- Side effects are determined by alternate uses of these same JAK or JAK non-selectivity
  - At higher doses, JAKinh do interact with other JAK, leading to off target effects

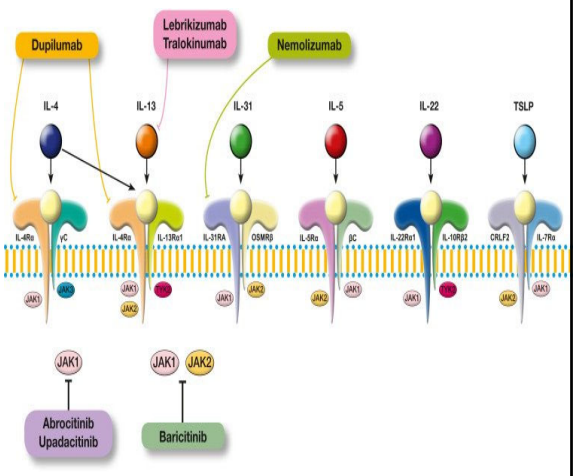


Figure 1 from Kamata M et al. JACI in pract. 2024

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Topical JAK Inhibitors

9

Topical JAK inhibitors

- Delgocitinib 2% cream- Topical Pan JAK inhibitor
  - Approved for 18 years and older for moderate to severe chronic hand eczema (CHE) failing topical steroids
  - Was not studied alongside TCS use [3,4]
- Ruxolitinib 1.5% Cream- Topical JAK1/2 inhibitor
  - Approved for 2 years and older with mild/moderate AD
    - Topical Preparation also for daily use in nonsegmental vitiligo <10% BSA
    - Oral preparation for Myelofibrosis, Polycythemia
  - Efficacy comparable to mid potency TCS specifically triamcinolone 0.1% cream[5]

3. Bissonnette R. et al. Lancet 2024
4. Gooderham M, et al. J American Academy of Dermatology. 2025
5. Kim BS, et al. J Allergy Clin Immunol. 2020.

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Topical JAK inhibitors

- Pros[3-8]
  - Steroid sparing
  - Quick onset of relief
  - Superior treatment of pruritus compared to TCS
- Cons[3-8]
  - Not studied alongside use of other agents
  - Not superior to TCS or TCI
  - Class Specific Warning including risk for cancer, major cardiovascular events, thromboembolic, infections
  - Limitations on use due to risk of systemic absorption
    - Limited BSA <20% for Ruxolitinib and hands only for Delgocitinib
    - No more than 60g per 4 weeks

3. Bissonnette R, et al. Lancet 2024
4. Gooderham M, et al. J American Academy of Dermatology. 2025
5. Kim BS, et al. J Allergy Clin Immunol. 2020.
6.Papp K, et al. J Am Acad Dermatol. 2021.
7. Papp K, et al. J Am Acad Dermatol. 2023
8. Ytterberg SR, et al. New England Journal of Medicine. 2022.

JTF Atopic Dermatitis Practice Parameter for topical JAKi

9. Chu DK, et al. Annals of Allergy, Asthma & Immunology. 2023.

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Oral JAK inhibitors

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Oral JAK inhibitors

Medication	JAK Selectivity	Approved Age	Doses Available	Starting Dose	Titration/Special Notes	Other Approved Indications
Abrocitinib	JAK1 selective	≥12 years (AD)	50 mg, 100 mg, 200 mg orally once daily	100 mg once daily *Start at 50 mg in moderate renal impairment (GFR<60mL/min)	Titrate to 200 mg if incomplete response after 12 weeks. Caution with CYP2C19 inhibitors (e.g., azoles, PPIs, SSRIs, antivirals).	Atopic Dermatitis only
Upadacitinib	JAK1 selective	≥12 years (AD)	15 mg, 30 mg, 45mg (IBD) orally once daily	15 mg once daily	May increase to 30 mg if ≥40 kg and <65 years old with inadequate response.	Psoriatic Arthritis, Ulcerative Colitis, Crohn's Disease, Rheumatoid Arthritis, Ankylosing Spondylitis, Non-radiographic Axial Spondyloarthritis
Baricitinib	JAK1/2	≥2 years*** (Europe/Japan for AD)	1 mg, 2 mg, 4 mg orally once daily	Varies by age/indication	Not FDA-approved for AD	Rheumatoid Arthritis, Alopecia Areata

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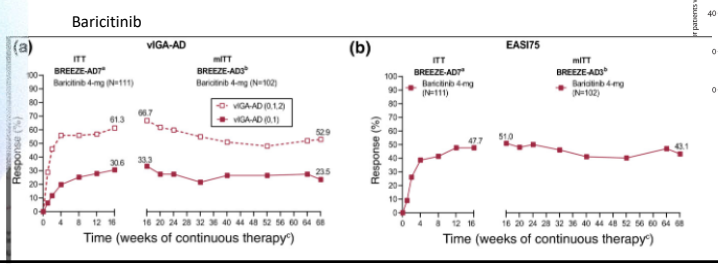
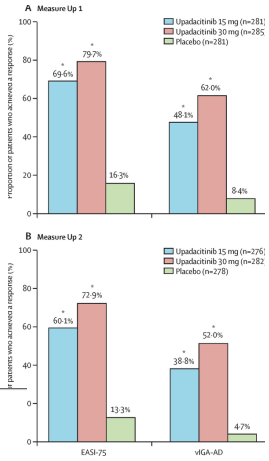
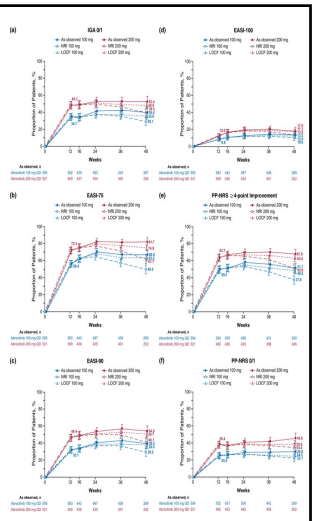
Oral JAK inhibitors Efficacy

- Dose Related Improvement in EASI/vIgA and itch scores
  - Itch reduction and improvement within 2 weeks
- Sustained efficacy in the long-term extensions
  - No sustained benefit if discontinued







Top right: 10. Reich K, et al. J Eur Acad Dermatol Venereol 2023
Middle: 11. Guttman-Yassky E, et al. Lancet. 2021
Far Left: 12. Silverberg JI, et al. J Eur Acad Dermatol Venereol. 2023

15

How do these compare to the biologics?

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RETURN TO AGENDA

Head-to-Head

- 2 head-to-head 16 week studies with single JAKinh vs dupilumab in adults using 300mg q2week and varying doses
- Abrocitinib[13]
  - Shorter time to effect for the oral JAK
  - Dupilumab reached the same efficacy
- Upadacitinib[14]
  - 30 mg Upadacitinib with effect sooner and higher EASI 90/100 and Pruritus score

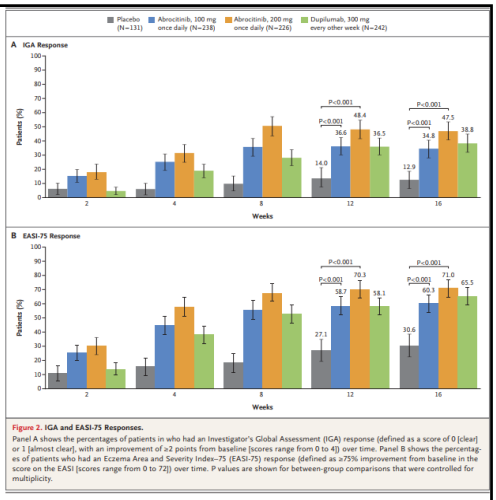
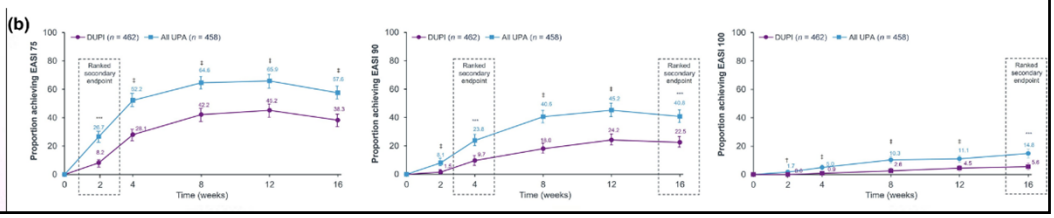


Figure 2. IGA and EASI-75 Responses.
Panel A shows the percentages of patients in who had an Investigator's Global Assessment (IGA) response (defined as a score of 0 [clear] or 1 [almost clear], with an improvement of ≥2 points from baseline [scores range from 0 to 4]) over time. Panel B shows the percentages of patients who had an Eczema Area and Severity Index–75 (EASI-75) response (defined as ≥75% improvement from baseline in the score on the EASI [scores range from 0 to 72]) over time. P values are shown for between-group comparisons that were controlled for multiplicity.

Top: 13. Bieber T, et al. N Engl J Med. 2021
Bottom: 14. Silverberg et al Br J Dermatol 2024



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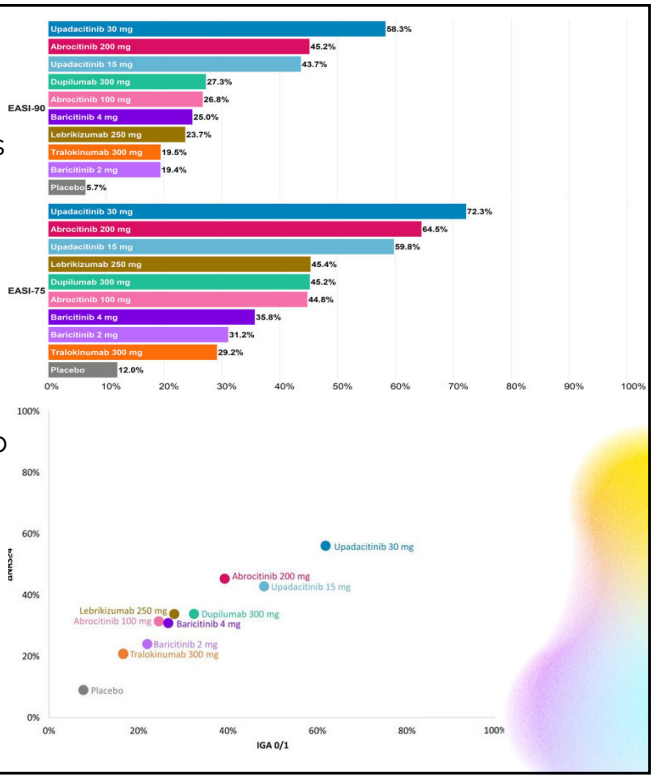
Which is best?

- Cochrane Review in 2020[15] found dupilumab as the most effective systemic therapy for AD
- Network Meta-analysis in 2022 and 2023[16,17]
  - Highest Efficacy based on EASI/vIgA/Itch
    - Upadacitinib 30mg
    - Then Abrocitinib 200mg, and Upadacitinib 15mg
    - Then Dupilumab 300mg, Abrocitinib 100mg, Lebrikizumab 250mg, Tralokinumab 300mg, ***Baricitinib 4mg/2mg
  - Highest Safety
    - Dupilumab
    - Then Tralokinumab, Lebrikizumab
    - Then Baricitnib, Upadacitinib, Abrocitinib



15. Sawangjit R, et al. Cochrane Database of Systematic Reviews 2020
16. Chu AWL, et al. J Allergy Clin Immunol. 2023
17. Silverberg JI, et al. Dermatol Ther (Heidelb). 2023 (Figures 2 and 3)

18

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The Dreaded Black Box Warning

FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions

18. US Food and Drug Administration 2021

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RETURN TO AGENDA

Why is the Black Box Warning there? Lessons learned from tofacitinib

- Based on long term literature from Tofacitinib (pan JAK inhibitor) compared to anti-TNF in patients with Rheumatoid Arthritis specifically older than 50 years and additional cardiovascular risk factors[8]
  - Higher rates of:
    - Major cardiovascular events (3.4% vs 2.5%)-did not meet non-inferiority criteria
    - Cancer (4.2% vs 2.9%)-did not meet non-inferiority criteria
    - Venous thromboembolism (2.3% to 0.7%)
    - Serious infections (11.6% vs 8.2%)
    - Herpes zoster (12.2% vs 4.0%)

8. Ytterberg SR, et al. New England Journal of Medicine. 2022

21

Is this generalizable to our AD patients?

MACE, VTE

- 2 Population based retrospective studies noted that adults with AD do have higher incidence of MACE, VTE which may correlate with AD severity and age [19,20]
  - MACE over 65
  - VTE over 45

Malignancy

- Patients with AD were at higher risk for non-melanoma skin cancer correlating with severity and age
  - Over 65 and severe AD were at increased risk of non-cutaneous T cell lymphoma

19. Chen TL, et al. JAMA Dermatol. 2023.
20. Hedderson MM, et al. PLoS One. 2022
21. Wan J, et al. Br J Dermatol. 2023
22. Hedderson MM, et al. BMJ Open. 2023

22

RETURN TO AGENDA

What about the currently available JAK inhibitors?

23

Class Warning Adverse Events of concern

- Topical Ruxolitinib long term studies: Myocardial infarction, Cerebral Vascular Accident, Thrombotic events but none directly linked to the medication[7]
- Delgocitinib in their trial[5]
- Abrocitinib: none reported in the trials[10]
  - Study Population was intentionally young, healthy without risk factors
- Baricitinib had 1 VTE in the long term extension[23]
- Upadacitinib: MACE, VTE and cancers have been reported[24,25]

5. Gooderham M, et al. J American Academy of Dermatology. 2025
7. Papp K, et al. J Am Acad Dermatol. 2023
10. Reich K, et al. A J Eur Acad Dermatol Venereol 2023
23. Silverberg JI, et al. J Eur Acad Dermatol Venereol. 2023
24. Guttman-Yassky E, et al. J Allergy Clin Immunol. 2023
25. Silverberg JI, et al. J Allergy Clin Immunol. 2022

24

RETURN TO AGENDA

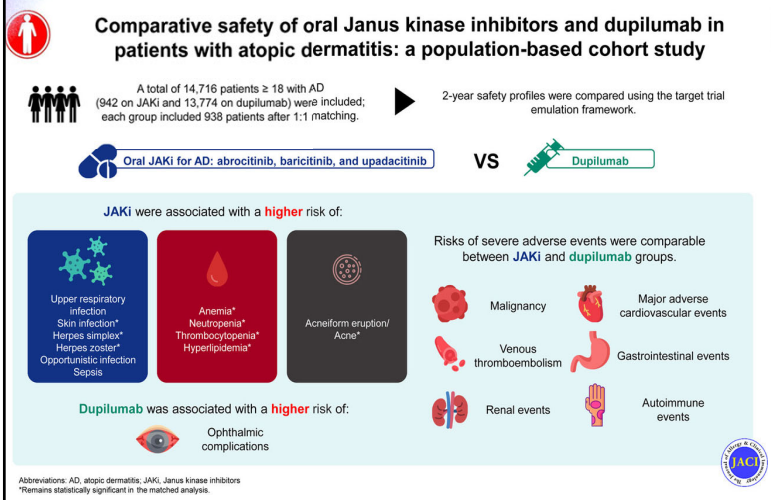
Oral JAK inhibitor Most common Adverse effects

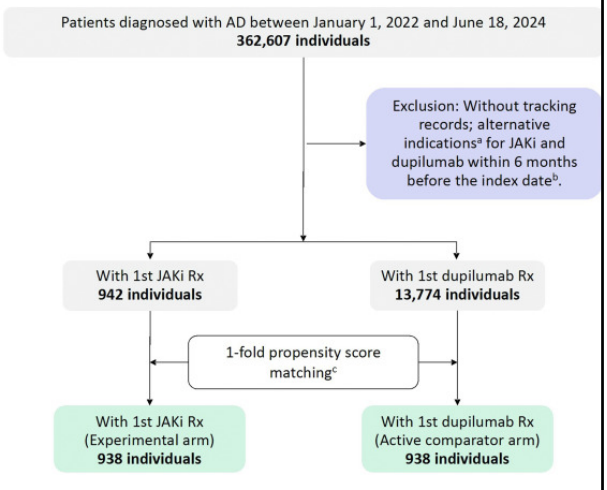
- Abrocitinib[10]
  - Most common: Nasopharyngitis, nausea, headache, acne, cytopenias
    - Nausea and acne were higher at the 200mg dose
  - Most common Severe: Increased risk of infections, herpes zoster
- Upadacitinib[24-26]
  - Most common: Acne, Nasopharyngitis/URTI, nausea, headache, transient Creatinine Phosphokinase elevation
  - Most common serious event: Herpes infections, serious infections
  - Serious Adverse effects in AD taking into consideration they had patients with a history of MACE and VTE and cardiovascular risk factors in the studies
    - 3 MACE (two at 15mg, one at 30mg), 2 VTE (one at each dose), 9 cancers nonmelanoma skin cancers
      - 1 death in a 67 yo male from MI after COVID19 infection and comorbid DM, obesity, HTN and hypercholesterolemia
  - Rates in pooled safety analysis: MACE/VTE (<0.1events/100patient years), Malignancy exclude NMSC (0.2 and 0.4E/100PY for 15/30mg), Herpes zoster (3.0and 5.7E/100PY for 15/30mg)

12. Reich K, et al.J Eur Acad Dermatol Venereol 2023
24. Guttman-Yassky E, et al. J Allergy Clin Immunol. 20
25. Silverberg JI, et al. J Allergy Clin Immunol. 2022.
26. Burmester GR, et al. RMD Open. 2023.

25

Comparing systemic agents: Safety





26. Tsai SY, et al. J Allergy Clin Immunol. 2024

26

RETURN TO AGENDA

Who is the right patient for the JAK inhibitors versus biologics?

How do these work?
How are they administered?
What is the approval age?
What else can they treat?
Are these safe?
What do I need to worry about or monitor?
Where is our field going to help us make a tailored therapeutic approach?

27

It is not injection versus pill

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RETURN TO AGENDA

Prior to initiation

- TB screen
- Hepatitis B and C testing
- CBC with differential attention to the Hgb, Platelet, ANC, ALC
  - Avoid if:
    - ALC <500cells/mm^3
    - ANC <1000cells/mm^3
    - Hgb <8g/dL
    - platelet count <150,000/mm^3
- CMP for hepatic enzymes and renal function
  - Abrocitinib 50mg dose if GFR <60mL/min
- Pregnancy test

28. Boguniewicz M, et al. Ann Allergy Asthma Immunol. 2023

29

Ongoing monitoring needed for the JAK inhibitors

- Laboratory monitoring: 4-12 weeks after initiation and every 12 weeks
  - CBC w/Differential, creatinine kinase after 4-12 weeks or increased dose or symptomatic
  - Lipid panel after 4 weeks (abrocitinib), 12 weeks (upadacitinib)

28. Boguniewicz M, et al. Ann Allergy Asthma Immunol. 2023

30

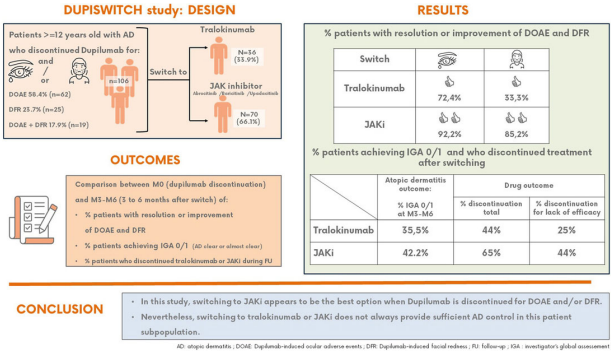
RETURN TO AGENDA

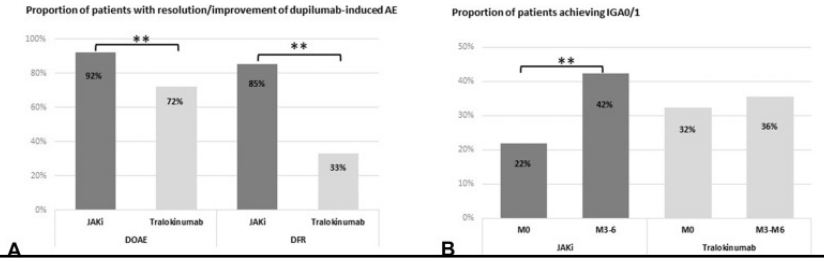
What if they have had an adverse effect on another agent?

31

Switching from Dupilumab

- Option for those with Dupilumab induced Ocular Disease or Facial Erythema
  - Not specifically mentioned but the psoriasoform presentations





29. Beyrouti A et al. J Allerg Clinical Immunology: In Practice. 2024

32

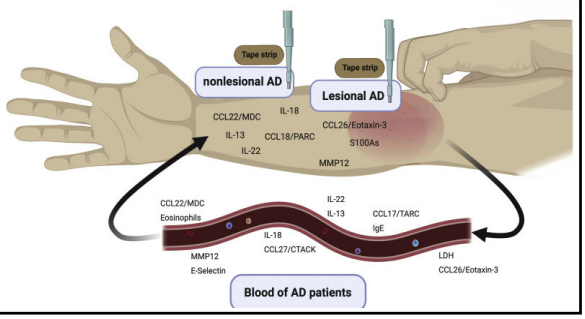
RETURN TO AGENDA

IS THERE SOME WAY TO DETERMINE WHAT WOULD BE THE RIGHT AGENT?

33

Future Promises: Biomarkers

- Needs to be able to predict severity and therapeutic response
- Hurdles: Correlating serum and skin biopsies
  - Availability of minimally invasive options including tape stripping
- Strongly promising biomarkers
  - Metalloproteinase 12 (MMP12) general inflammatory mediator
  - T_H2 related: eosinophil count, IL13, CCL17/TARC, CCL18/PARC, CCL22/MDC
  - T_H22 related: IL22
  - T_H17 related: IL19
  - Skin only S100A7 & S100A12 (TH17/22)

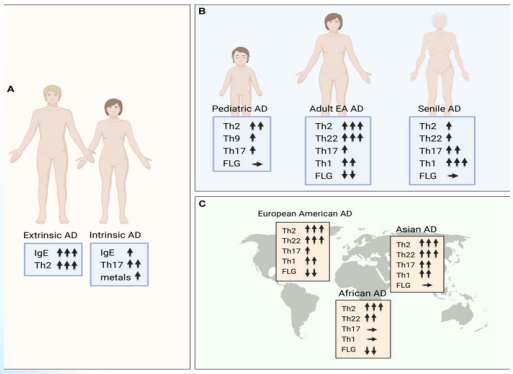


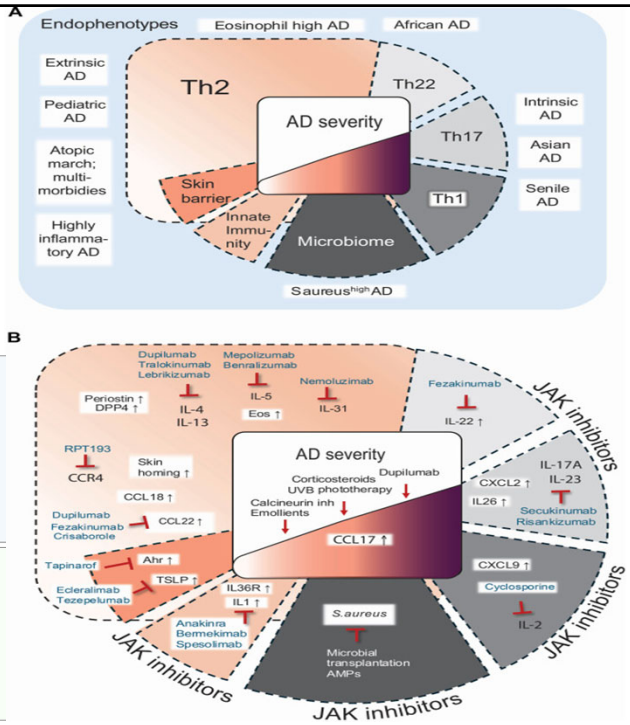
30. Renert-Yuval Y et al. Journal of Allergy and Clinical Immunology. 2021

34

RETURN TO AGENDA

Endotypes of Atopic Dermatitis Driving Decisions on Therapy





31. Fyhrquist N, Yang Y, Karisola P, Alenius H. J Allergy Clin Immunol. 202

35

Which is the right patient?

- What is the age of the patient?
  - Younger than 12 versus older than 65
- What have they tried before?
- What is the patient's preference:
  - Oral versus injection?
  - Time to effect?
  - Most bothersome symptom?
- Comorbidities?
  - Are we trying to modify other diseases?
- What is the frequency of their symptoms?
  - Could seasonal treatment be an option?
- Do they have specific infection concerns?
  - Herpes Simplex/Zoster history? Can they be vaccinated prior to initiation?
- What is the cost/insurance coverage?

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RETURN TO AGENDA

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11.Guttman-Yassky E, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials [published correction appears in Lancet. 2021 Jun 5;397(10290):2150]. Lancet. 2021;397(10290):2151-2168
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Podium to Practice

- The JAK inhibitors add another option for severe AD especially for pruritus
- If used appropriately, JAK inhibitors can be safe and effective medications and work fast
- It is not just choosing a pill versus an injection but risk stratification and shared decisions
- The JAK inhibitors are options for those who have failed or had adverse effects on biologic therapy
- Personalized medicine will help us chose the best option for our patients

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RETURN TO AGENDA

PATCH TESTING 101

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ENT & Allergy Associates – New York, NY

Associate Clinical Professor,
Icahn School of Medicine at Mount Sinai

1

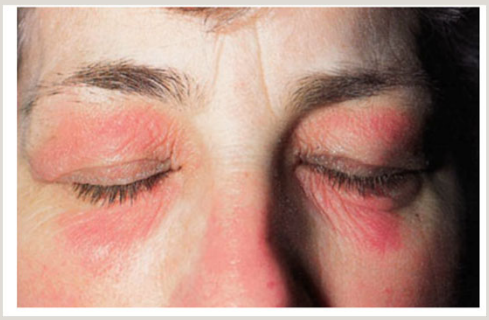
PATCH TESTING

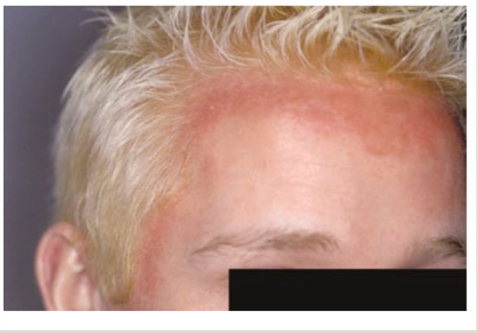
- Gold standard for diagnosis of contact dermatitis
- Allergic = Type IV Gell & Coombs
- Irritant dermatitis

2

RETURN TO AGENDA

SUSPECTED CONTACT DERMATITIS
CONSIDER PATTERN, DISTRIBUTION, SYMMETRY





Johansen JD et al, ed. Contact Dermatitis Sixth Edition. 2021

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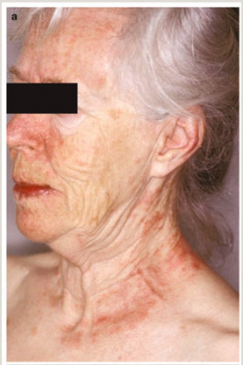
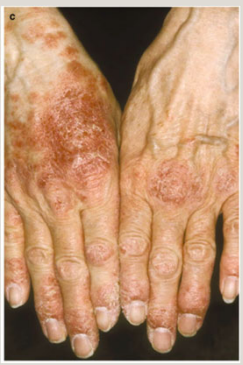
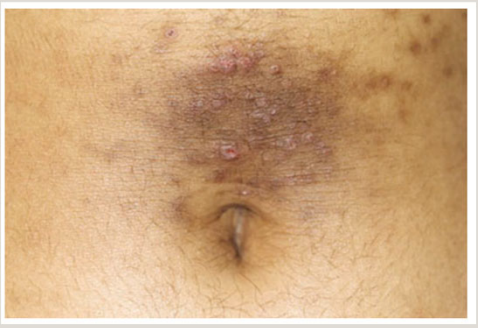
SUSPECTED CONTACT DERMATITIS
CONSIDER PATTERN, DISTRIBUTION, SYMMETRY







Johansen JD et al, ed. Contact Dermatitis Sixth Edition. 2021

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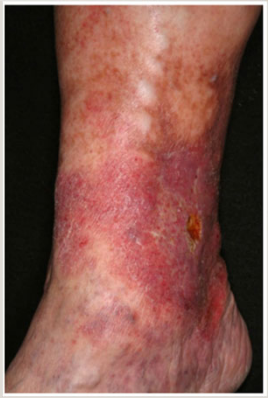
CONSIDER CONTACT DERMATITIS

- Any extensive pruritic dermatitis
  - ACD may also be secondary:
    - Inflamed skin more susceptible to sensitization
    - AD patients use more topical products
- Unexpected worsening or abrupt onset of eczema
- Stasis ulcer
- Persistent rash without clear pattern
- Hx alone will identify only less than 50% of ACD



5

PREPARE THE PATIENT

- Explain what the test is, and how it is different: delayed reaction = delayed test
- Clear skin for testing; back is standard, alternative sites possible
- Cannot get the back wet … the whole time
- No exercise
- Back must not be tan
- Men should clipper hair on back day prior
- No creams/lotions
- Dark clothes (we mark on removal day)

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RETURN TO AGENDA

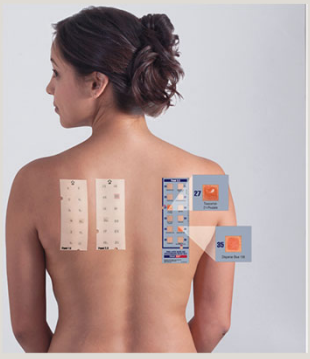
MEDICATIONS TO BE AVOIDED

- Potent TCS/TCI – 5-7 days
- Oral steroid, ideally 2 weeks
- Other immunosuppressants (cyclosporine, MFM)
- If needed, can PT on prednisone <20mg/day or cyclosporine/MFM may offer meaningful results
- Dupilumab – variable impact
- JAK inhibitors may be more likely to suppress
- Antihistamines not a problem; may help

7

T.R.U.E. TEST
THIN LAYER **R**APID USE **E**PICUTANEOUS **T**EST

- The only FDA approved test, 6+
- 35 preloaded allergens (+1 negative control)
- 25% of patients reacted to an allergen not in T.R.U.E.[1]



[1]Warshaw EM, Belsito DV, Taylor JS, Sasseville D, Dekoven JG, Zirwas MJ, et al. North American Contact Dermatitis Group Patch Test Results: 2009 to 2010. Dermatitis 2013;24:50-9 (III).

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RETURN TO AGENDA

T.R.U.E. TEST ALLERGENS

T.R.U.E. TEST Allergen Information

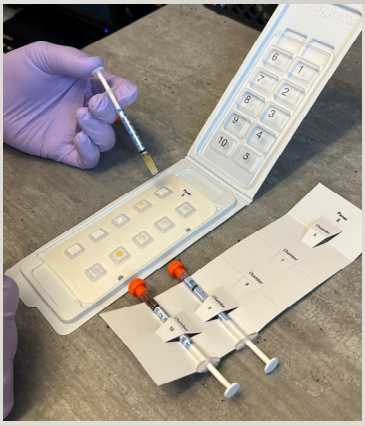
Each T.R.U.E. TEST patch test unit contains Panel 1.3, 2.3 and 3.3, and includes 35 common allergens and a negative control.

Panel 1.3	Panel 2.3	Panel 3.3
Nickel Sulfate	p-tert-Butylphenol Formaldehyde Resin	Diazolidinyl Urea
Wool Alcohols	Epoxy Resin	Quinoline Mix
Neomycin Sulfate	Carba Mix	Tixocortol-21-Pivalate
Potassium Dichromate	Black Rubber Mix	Gold Sodium Thiosulfate
Caine Mix	CI+ Me- Isothiazolinone (MCI/MI)	Imidazolidinyl Urea
Fragrance Mix	Quaternium-15	Budesonide
Colophony	Methyldibromo Glutaronitrile	Hydrocortizone-17-Butyrate
Paraben Mix	p-Phenylenediamine	Mercaptobenzothiazole
Negative Control	Formaldehyde	Bacitracin
Balsam of Peru	Mercapto Mix	Parthenolide
Ethylenediamine Dihydrochloride	Thimerosal	Disperse Blue 106
Cobalt Dichloride	Thiuram Mix	Bronopol

9

MORE COMPREHENSIVE TESTING

- Load allergens onto chambers
- NACDG (65-70)
- ACDS (80)
- Allergens mixed with petrolatum (or aqueous)
- Aqueous or volatile allergens (acrylates, fragrances) to be applied immediately at testing
- Expanded panels based on history



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RETURN TO AGENDA

MOST COMMON ALLERGENS MISSED BY T.R.U.E.

- fragrance mix II
- iodopropynyl butylcarbamate
- carmine
- propylene glycol
- propolis
- dimethylaminopropylamine
- hydroxyethylmethacrylate
- oleamidopropyl dimethylamine
- shellac
- decyl glucoside
- cocamidopropyl betaine (CAPB), majantol
- DMDM hydantoin
- glutaral

Fonacier L. A Practical Guide to Patch Testing. J ALLERGY CLIN IMMUNOL PRACT 2015;3(5)669-75.

11

FRAGRANCES

- Balsam of peru
- Fragrance Mix I
  - amyl cinnamal, cinnamal, cinnamyl alcohol, eugenol, geraniol, hydroxycitronellal, isoeugenol, and oakmoss absolute
- Fragrance Mix 2
  - Coumarin, Lyral, Citronellol, Farnesol, Citral, a-Hexylcinnamicaldehyde

Will detect 73% of patients sensitized to fragrance[1]

Wenk KS, Ehrlich A. Fragrance series testing in eyelid dermatitis. Dermatitis 2012;23:22-6.

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RETURN TO AGENDA

PRESERVATIVES

TABLE IV. Cosmetic preservatives[1]

Formaldehyde releaser	Nonformaldehyde releaser
Formaldehyde	Iodopropynylbutylcarbamate
Quarternium 15	Methychloroisothiazolinone/ methylisothiazolinone (MCI/MI)
Diazolidinyl urea	Parabens
Imidazolidinyl urea	Methyldibromoglutaronitrile
Bromonitropropane	Chloroxylenol
DMDM hydantoin	Benzalkorium chloride
	Thimerosal
	Phenoxyethanol

Bernstein D. Contact Dermatitis for the Practicing Allergist. J Allergy Clin Immunol Pract 2015;3:652-8

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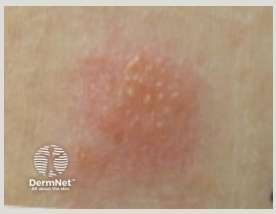
METALS FOR STANDARD USE

- Nickel
  - The most common contact sensitizer
  - Direct contact, transference, systemic CD
- Cobalt
  - Jewlery, ceramics, make up/blue
  - Systemic CD (B12)
- Chromates
  - Leather manufacturing, footware, cement
- Gold
  - Jewelry
  - Often not clinically relevant; may leave persistent reaction



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RETURN TO AGENDA

MEDICATIONS

- Topical corticosteroids
- Anesthetics/caine mix
- Bacitracin/neomycin/polymyxin B
- Chlorhexidine/povidone

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OTHER ALLERGENS

- Other allergens found in personal care prods: surfactants, foaming agents, skin conditioners, etc
  Lanolin, propylene glycol – need to check topical meds
- Glues & adhesives: acrylates, colophony
- Rubber allergens: thiuram mix, mercapto mix, carba mix, black rubber
- Dyes for clothing and hair
- Sunscreens

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RETURN TO AGENDA

TABLE III. Geographical location of cutaneous eruptions with sources and causative allergens[1]

Geographical location	Sources of sensitizers	Causative allergens
Face	Cosmetics, plant sources, topical medicines, ectopic transfer resulting in eyelid and periorbital dermatitis (nickel, nail enamel)	Botanical ingredients, airborne pollen (Compositae), fragrances, Balsam of Peru, neomycin, methyl methacrylate (artificial nails), tosylamide/ formaldehyde (nail polish)
Lip inflammation (cheilitis)	Lip and oral hygiene products (eg, lip balm and toothpaste)	
Scalp and neck	Cosmetics, hair products, and jewelry	*Hair products:* Paraphenylenediamine, glycerol thioglycolate (permanent wave products); cocoamidopropyl betaine (shampoo surfactant) *Cosmetics:* Fragrances, Balsam of Peru, and Quarternium-15
Hands	Cosmetics, rubber gloves	Quarternium-15 (a preservative), Balsam of Peru, nickel, fragrance mix, topical antibiotics (eg, neomycin), rubber chemicals (thiurams, carbamates, mercaptobenzothiazole)
Axilla	Deodorants, clothing dyes	Fragrance chemicals: hydroxyisohexyl-3-cyclohexene, cinnamic aldehyde; disperse blue dyes
Anogenital	Topical medications, diaper products	Topical corticosteroids, fragrances, neomycin; methylisothiazolinone preservative in baby wipes
Feet or soles	Shoe materials or chemicals including adhesives, chromates, and rubber chemicals	Dialkyl thioureas, carbamates, thiurams, chromates
Legs	Topical preparations often to treat leg ulcers	Fragrances, Balsam of Peru, antibiotics, topical corticosteroids, and lanolin
Sun-exposed areas	Photoallergens in sunscreens	Para-aminobenzoic acid (PABA)

Bernstein D. Contact Dermatitis for the Practicing Allergist. J Allergy Clin Immunol Pract 2015;3:652-8

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TESTING PATIENTS' PRODUCTS

- Leave-on products only: make up, moisturizer
- Clothing, gloves, shoe materials
- Rinse off products (shampoo, conditioner) must be diluted
- Do not test noxious substances!

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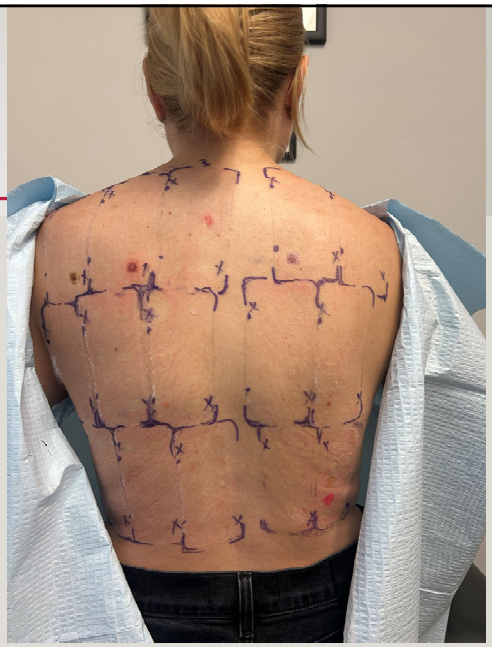
RETURN TO AGENDA

READING THE PATCH TEST

- Apply day 1
- Remove & 1st read day 3
- 2nd read day 4 – 7
- Delayed read for TCS, metals, some topical abx
- Wait 20 – 30 min after removal to read



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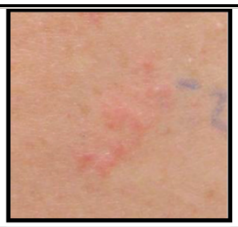
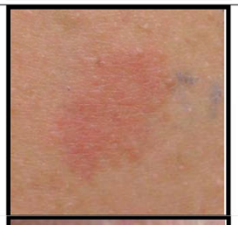
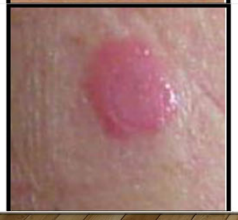
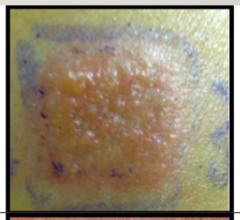
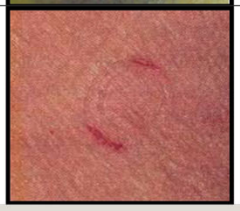
(?+)		Doubtful reaction with faint erythema only
(1+)		Weak positive reaction with non-vesicular erythema, infiltration, possibly papules
(2+)		Strong positive reaction with vesicular erythema, infiltration, and papules
(3+)		Extreme positive reaction with intense erythema and infiltration, coalescing vesicles, bullous reaction
(IR)		Irritant reaction

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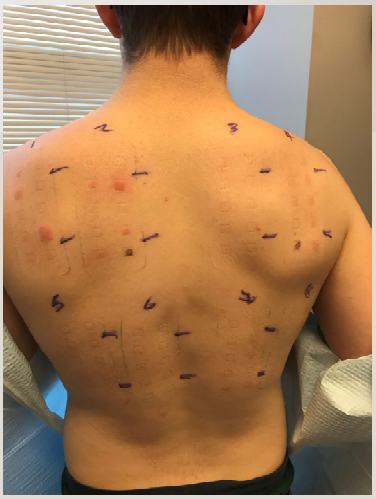
RETURN TO AGENDA

COUNSELING YOUR PATIENT

- Review the full results
- Written info sheets
- Databases
  - Contact Allergy Management Program (CAMP) – requires ACDS membership www.contactderm.org
  - Contact Allergen Replacement Database (CARD) – no membership www.allergyfreeskin.com
- Avoidance for weeks leads to results



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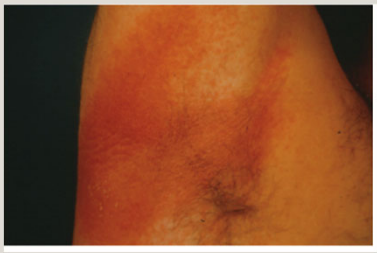
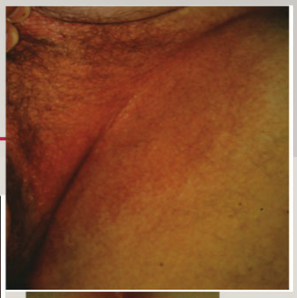
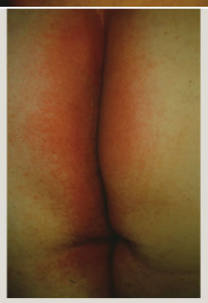
SYSTEMIC CONTACT DERMATITIS

- Metals (mercury, nickel, gold, cobalt)
- Medications (aminoglycosides, corticosteroids, aminophylline)
- Plants (compositae, balsam of peru)
- Baboon syndrome/SDRIFE Systemic Drug Related Intertriginous & Flexural Eruptions







Hauserman P. et al. Baboon syndrome resulting from systemic drugs: is there strife between SDRIFE and allergic contact dermatitis syndrome?. Contact Dermatitis 2014 : 51, 297-310.

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RETURN TO AGENDA

PODIUM TO PRACTICE - TAKEAWAYS

- Patch testing is the gold standard to identify contact allergens in suspected contact dermatitis OR chronic/refractory pruritic dermatoses
- This is a lengthy, cumbersome test – so prepare your patients and staff properly to get the best results
- Make sure to use a thorough panel of relevant allergens and consider the possibility of systemic contact dermatitis

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RETURN TO AGENDA

Diagnosing Drug-Induced Rashes in Clinical Practice Should We Be Patch Testing

Contact Dermatitis and Drug Allergy
American College of Allergy, Asthma & Immunology (ACAAI)

Ana Maria Copaescu MD PhD FRCP FAAAAI
Physician-Scientist Immunology and Allergy
The Research Institute of the McGill University Health Centre
McGill University Health Centre (MUHC) | Canada

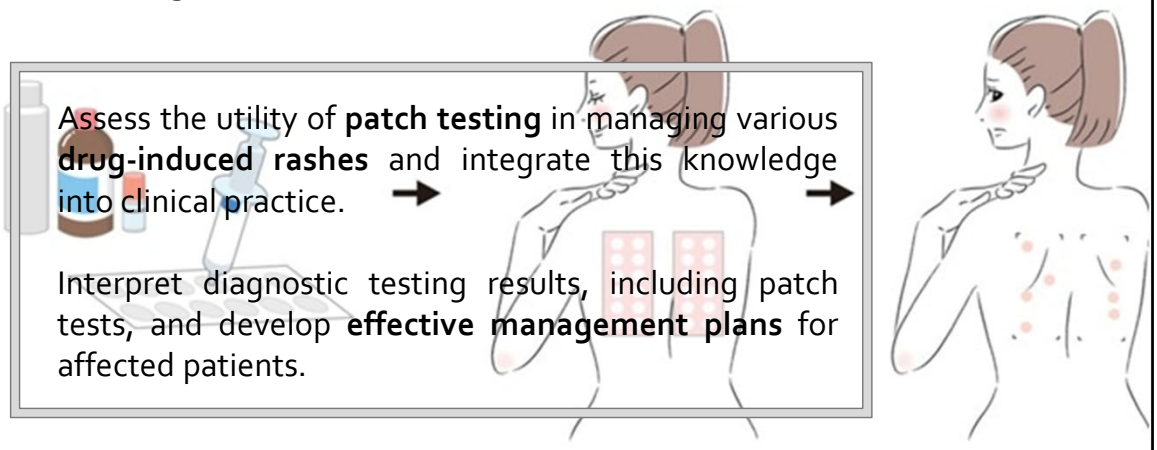
Centre for Antibiotic Allergy and Research
Austin Health | Australia

1

Session Objectives

Assess the utility of **patch testing** in managing various **drug-induced rashes** and integrate this knowledge into clinical practice.

Interpret diagnostic testing results, including patch tests, and develop **effective management plans** for affected patients.



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RETURN TO AGENDA

PLAN


Drug-Induced Rashes


Patch Testing


Case Example


Future research

3

PLAN


Drug-Induced Rashes


Patch Testing


Case Example


Future research

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RETURN TO AGENDA

Drug hypersensitivity reactions

Low-risk allergies

High-risk allergies

Isolated benign skin conditions

Severe cutaneous adverse reactions (SCAR)

In vivo skin testing and drug challenges

Patch Testing

Research *ex vivo* tools

Copaescu, A. et al. 2023. J Allergy Clin Immunol

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Adverse drug reactions

10% **World** Population

2-3% **Hospitalized** Patients

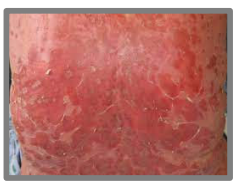
1/ 1,000 SCAR

Copaescu, A. et al. 2022. Front Med | AlGassim, M. et al. 2025.JACI IP

Morbidity/Mortality

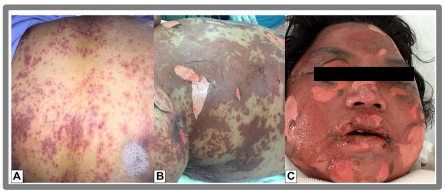
Hospital costs

Limited treatment choices



Complicates treatment infectious diseases

Affects immunocompromised/ vulnerable populations



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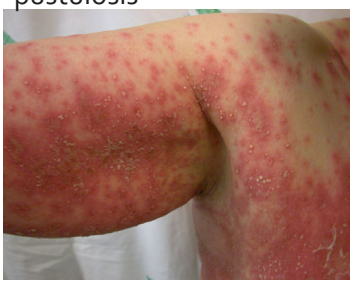
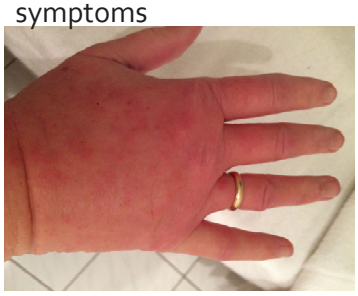
AGEP: Acute generalized exanthematous pustulosis	**DRESS**: Drug rash with eosinophilia and systemic symptoms	**SJS/TEN**: Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis
		
1-5 cases/million	2-4 cases/10,000	2-7 cases/million
2-4% mortality	10% mortality	30% mortality (severe)
Antibiotics Antimycotics	Antibiotics Anticonvulsants Allopurinol	Antibiotics Anticonvulsants Allopurinol

Copaescu, A. et al. 2022. Front Med

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PLAN

 Drug-Induced Rashes

 Patch Testing

 Case Example

 Future research

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RETURN TO AGENDA

In vivo for SCAR

Practice Parameters

Khan, D. et al. 2022. J Allergy Clin Immunol

- **6 weeks to 6 months** post skin healing
- 6 months following DRESS reactions
- 4 weeks after systemic steroids
- **"May be useful as adjunctive test…." [Very low evidence]**

International Consensus Document

Phillips, EJ. et al. 2019. J Allergy Clin Immunol

- **6 months** following DRESS (patch)
- 4 weeks after systemic steroids

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Diagnostic tests

Test Utility

- Prevalence disease
- Broad spectrum evaluation
- Test accuracy
- Cost
- User dependant

Influenced by the **Prevalence** of the Disease

Positive Predictive Value
Proportion of Positive Test that have the disease

Negative Predictive Value
Proportion of Negative Test that do NOT have the disease

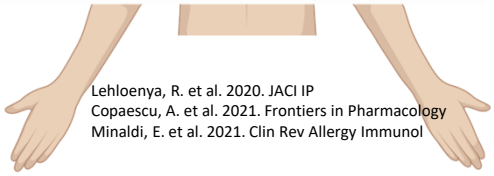
Patch testing

> 4 - 6 weeks (6 months)

- Drugs (various concentrations)
- Applied directly on skin – upper back
- Occlusion for 48 hours
- Negative control

Ready to use

- Chemotechnique (Sweden)
- SmartPractice (Canada)



Lehloenya, R. et al. 2020. JACI IP
Copaescu, A. et al. 2021. Frontiers in Pharmacology
Minaldi, E. et al. 2021. Clin Rev Allergy Immunol

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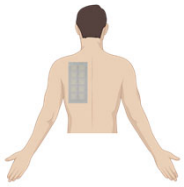
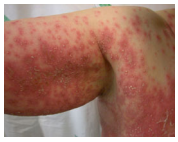
Skin Testing

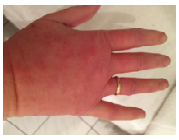


- Patch Testing
  - Low drug concentration on an adhesive patch – Almost all drugs
  - Oral form – Max 30% dilution in petrolatum - *What is the % of the active ingredient?*

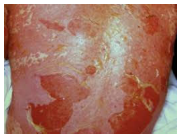


Sensitivity/ Positivity: 50-58%
Rare relapse cases

Step 1 for Severe drug reactions
Role in SJS/TEN?



Sensitivity/ Positivity: 60% (drug-dependent)
Rare relapse cases (HIV-infected)



Sensitivity/ Positivity: 25%
Limited utility

Barbaud, A., et al. 2024. JACI IP

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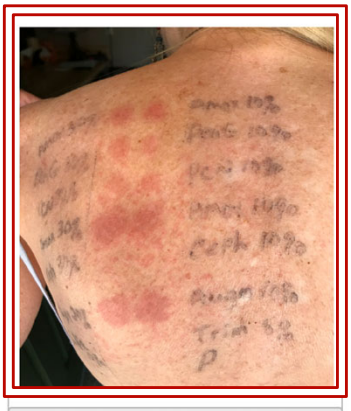
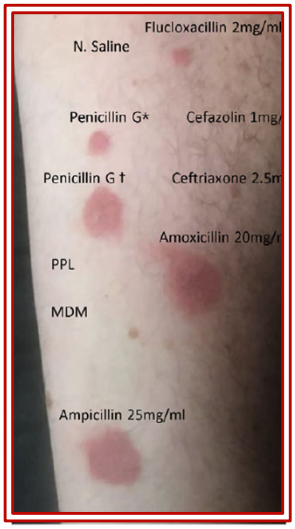
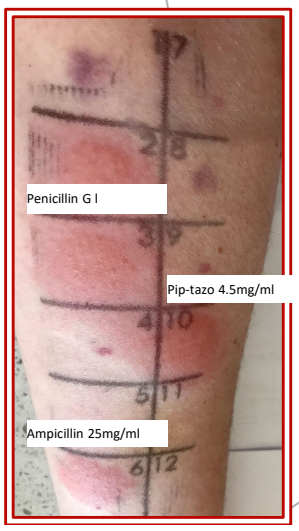


D: "Penicillin" ring positive PT

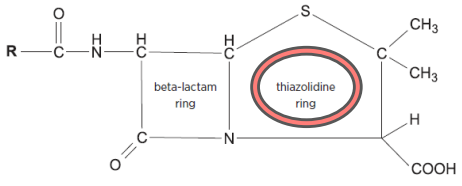
Barbaud, A., et al. 2024. JACI IP



Trubiano, J. *et al*. 2020. JACI IP



Thiazolidone ring



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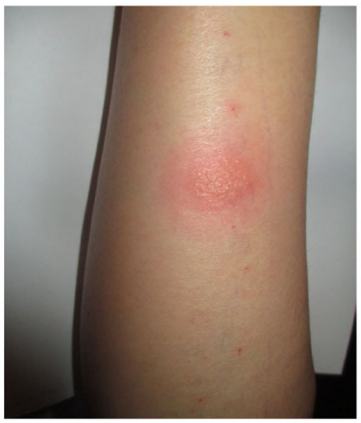
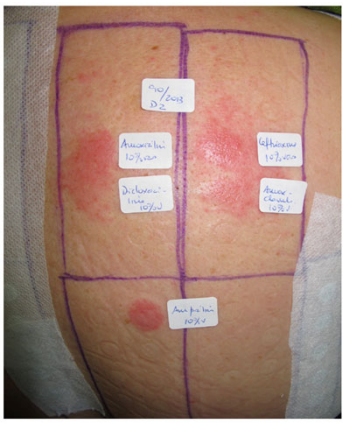


E: Cefepime positive PT



F: B-lactam ring positive PT

Barbaud, A., et al. 2024. JACI IP

Beta-lactams Patch Testing

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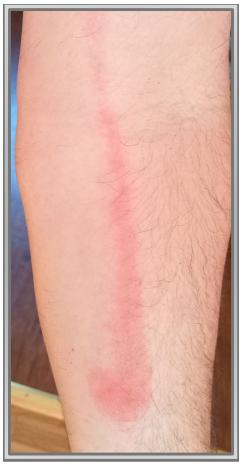
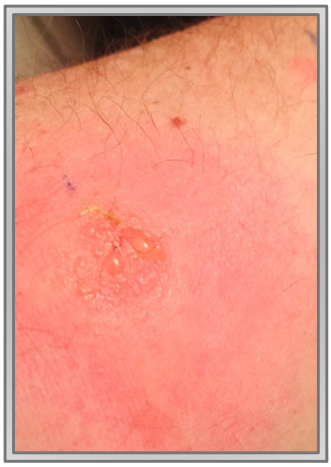
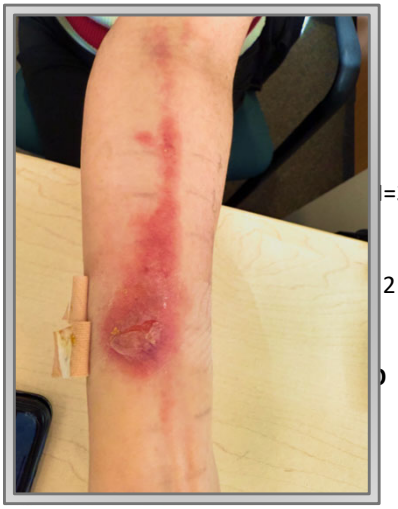
Why PT before IDT

Phenotype – risk stratification
Reported local reaction to topical
Antibiotic amoxicillin powder







Alotaibi, I., et al. 2025. J Allergy Clin Immunol Pract

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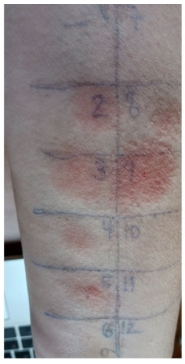
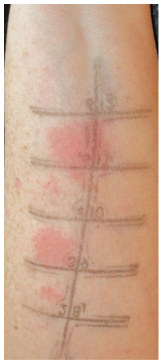
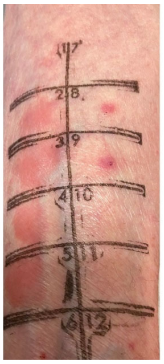
IDT - Iodinated contrast media



Iohexol 1/10 (#2) and 1/1 (#3) Iodixanol 1/10 (#4) and 1/1 (#5) Iopamidol 1/10 (#8) and 1/1 (#9)

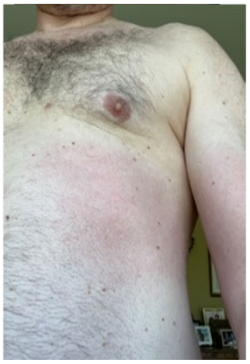


Iohexol 1/10 (#2) and 1/1 (#3) Iodixanol 1/1 (#5)

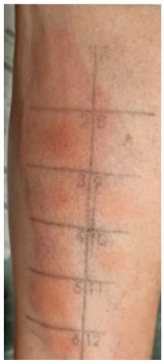


Iohexol 1/10 (#2) and 1/1 (#3), Iodixanol 1/10 (#4) and 1/1 (#5), Iopamidol 1/10 (#8) and 1/1 (#9)

Non-severe systemic reaction after IDT
Prednisone 25 mg PO X 3 d



Iohexol 1/10 (#2) and 1/1 (#8) Iodixanol 1/10 (#3) and 1/1 (#9) Iopromide 1/10 (#4) and 1/1 (#10) Ioversol 1/10 (#5) and 1/1 (#11).



Iohexol 1/10 (#2) and 1/1 (#3) Iodixanol 1/10 (#5) and 1/1 (#6) Iobitridol 1/10 (#9) and 1/1 (#10)

Copaescu, A., et al. 2025. Allergy, Asthma & Clinical Immunology

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Why PT before IDT?

SAFER FIRST STEP

Patch testing is non-invasive and minimizes risk [severe delayed reactions]

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RETURN TO AGENDA

Why IDT first?

OPTIMIZE CLINICAL RESOURCES

Streamline workflows and reduce unnecessary testing

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Dermatology - Allergy Patch Testing Clinic

Centre universitaire de santé McGill
Institut de recherche

McGill University Health Centre
Research Institute

Specialized evaluation of delayed reactions

Standardized testing protocols
[validated concentrations and application techniques]

Collaborative care model
[dermatology and allergy expertise - optimize diagnosis, patient education, and management plans]

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RETURN TO AGENDA

In vivo diagnostics

42% Sensitivity (N=31)
(2015-2017)
Trubiano, J. et al. 2019. JACI IP

49% Sensitivity (N=68)
(2017-2020)
Copaescu, A. et al. 2021. JACI IP

58% sMPE Sensitivity (N=24)
(2015-2018)
Trubiano, J. et al. 2019. JACI IP

IDT

42-46%	46-97%	33-100%
SJS/TEN	AGEP	DRESS

PT

<30%	58%	25-100%

Copaescu, A. et al. 2023. J Allergy Clin Immunol
Copaescu, A. et al. 2022. Frontiers Med
Phillips, EJ. et al. 2019. J Allergy Clin Immunol

OC

Data primarily in HIV/TB setting; alternative data is for challenged class related not implicated drug

Porter, M. et al. 2022. J Investigative Dermatology
Lehloenya, R. et al. 2011. Int J Tuberc Lung Dis

"Salvage" protocol in event of mild-to-moderate life-threatening reactions successful

Lehloenya, R. et al. 2022. JACI In Pract

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In vivo Investigational Tools

Clinical Phenotype	Delayed IDT testing	Patch Testing	Oral challenge
MPE	✓	✓	✓
AGEP	✓	✓	✗
DRESS	✓	✓	✗
SJS/TEN	✗	✓	✗

Copaescu, A., et al. 2023. J Allergy Clin Immunol
Copaescu, A., et al. 2022. Front Pharmacol
Copaescu, A., et al. 2022. Front Med

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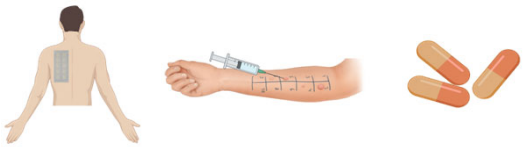
In vivo testing

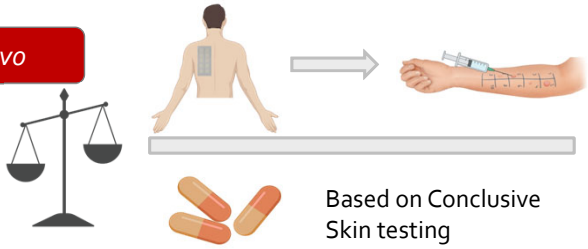


Multiple Culprit Drugs
(Drug Timeline – Causality Score)

→ Avoidance ?

Re-Introduction Alternative Drugs
Cross-reactivity with Culprit Drugs
Re-challenge with Culprit Drugs

In vivo



Based on Conclusive
Skin testing

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PLAN


Drug-Induced Rashes


Patch Testing


Case Example


Future research

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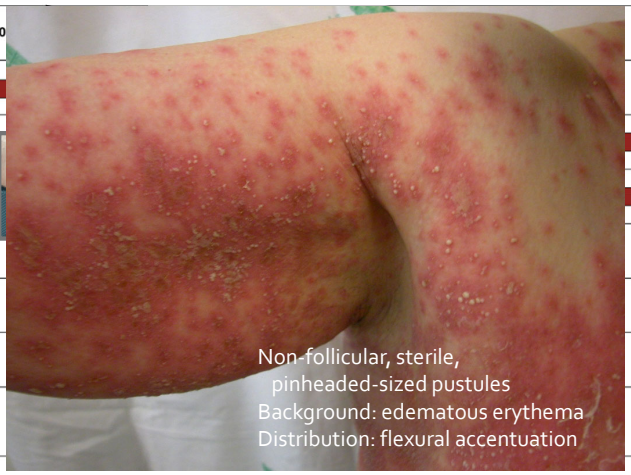
57 year old

PMH

Drug Allergy – Penicillin
(isolated rash age 6
avoidance Beta-lactams)

22 June ED: Acute Abdominal pain
CT scan: non-complicated diverticulosis
Tx: Amoxicillin- Clavulanate for 10 days

	22.06	23.0		30.06	1.07
Amoxicillin/ Clavulanic Acid					
Metronidazole					
Ciprofloxacin					
Omnipaque					
Skin Eruption					
Temperature					
Labs	ANC 3.03 ALT 11 Creat 86			ANC 7.8 ALT 14 Creat 94 CRP 78	ANC 8.2 ALT 20 Creat 90 CRP 26



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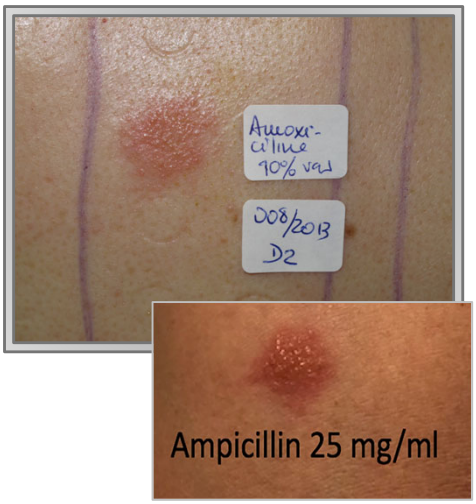
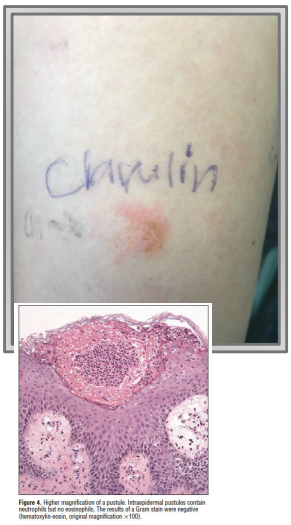
AGEP
AGEP Score 8

Possible identified culprits on History
- **Amoxicillin – Clavulanate**
- **Radio-contrast media – Omnipaque**
- Metronidazole and Ciprofloxacin

(the skin eruption had started; notion of increased skin reaction?)

Patch Test
48 H





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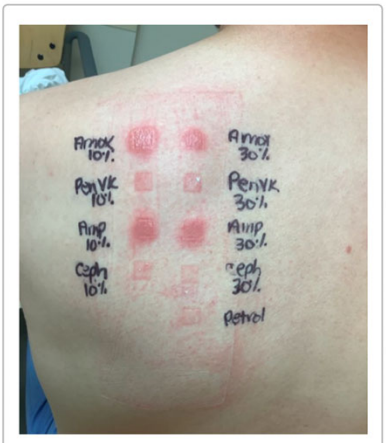
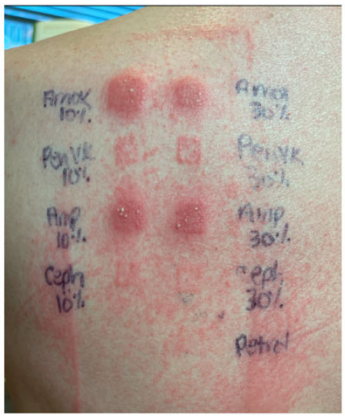
Patch Testing



A: Ampicillin positive PT (48h)



B: Ampicillin positive PT (72h)

Barbaud, A., et al. 2024. JACI IP

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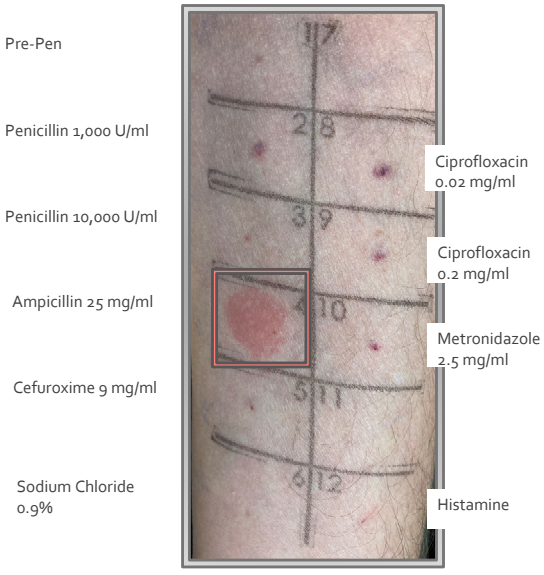
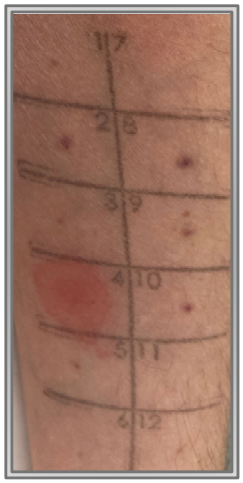
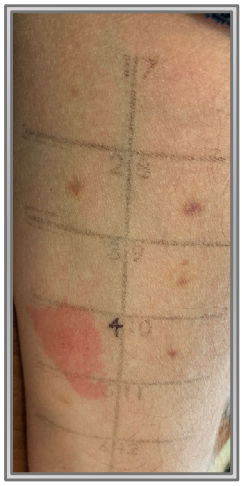
IDT with delayed reading
24 H

IDT
48 H

IDT
72 H







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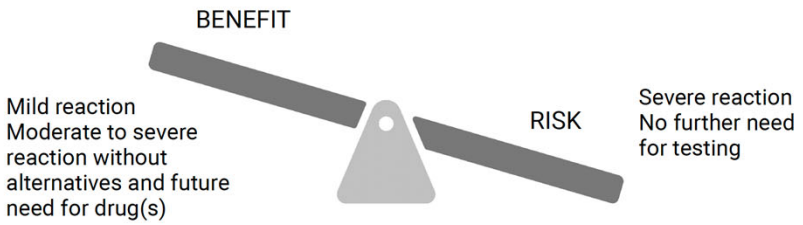
COMPOSITE CAUSALITY SCORE FOR EACH DRUG



Barbaud, A., et al. 2024. JACI IP
Lehloenya, R. et al. 2020. J Allergy Clin Immunol Pract

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PLAN


Drug-Induced Rashes


Patch Testing


Case Example


Future research

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Integrating Drug Hypersensitivity Tools

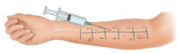
T-cell mediated

Clinical Phenotyping
Allergy Evaluation
Tissue (skin)
Blister Fluid
HLA

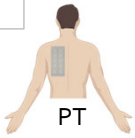
In vivo

Ex vivo

Data Management
Lab Management
REDCap



Delayed IDT



PT

Education
Networking
Collaborations

Lymphocyte transformation test (LTT)
Enzyme linked ImmunoSpot (ELISpot)
Genetic screening

Barbaud, A., et al. 2024. JACI IP
Copaescu, A., et al. 2023. J Allergy Clin Immunol

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Takeaways - *Podium to Practice*

1. Use patch testing selectively for severe delayed-type reactions where culprit identification is unclear (no IV formulation available)

2. Follow validated concentrations and application methods to improve reproducibility and diagnostic accuracy.

3. Combine skin testing results with detailed history, timing, and morphology to guide safe re-exposure or alternative therapy.

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Thank you

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Contact Dermatitis and Drug Allergy Delayed Hypersensitivity to Metals and Other Implants

Luz Fonacier MD, FACAAI, FAAAAI
Professor of Medicine, NYU Long Island School of Medicine
Section Head of Allergy
Program Director, Allergy and Immunology
NYU Langone Hospital, Long Island

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Objectives

- Recognize delayed hypersensitivity reactions to metals and other implantable devices
- Interpret diagnostic testing results including Patch Tests
- Develop effective management plans for affected patients

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Biomedical Devices

- Cutaneous and systemic delayed-type hypersensitivity reactions to metal implants are documented
- Culprits:
  - Orthopedic implants
  - Dental implants
  - Intravascular and cardiac stents
  - Pacemakers
  - Implanted gynecologic devices
- **Direct causal relationship** between metal sensitivity and these reactions remains to be elicited
- **Role of Patch Testing** in diagnosis or prevention is still undefined

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Metal Composition of Implants

IMPLANT	COMPOSITION
Orthopedic	Stainless steel*, Chromium-cobalt alloy, Vitallium, Titanium, Zirconium (Oxinium)
Dental	Mercury amalgam (tin, silver, zinc, copper), Gold , Chromium, Stainless steel, Palladium, Titanium, Cobalt, Nickel
Endovascular Devices	Stainless steel, Nitinol**
Pacemakers	Titanium
Gynecologic Implants	Copper, Nitinol

*Stainless steel is comprised of: 10-24% Ni, 18% Cr, 65% Fe
**Nitinol: 55% titanium, 45% nickel
*Vitallium: chromium/cobalt alloy
CoCrMo Alloy: < 2% Ni, ~64% Co, 28% Cr, 5% Mo
Ti Alloy: 90% Ti, 6% Al, 4% V
Zr Alloy: 95% Zr, 5% Nb

Juliana L. Basko-Plluska, Jacob P. Thyssen, and Peter C. Schalock . Cutaneous and Systemic Hypersensitivity Reactions to Metallic Implants. Dermatitis, Vol 22, No 2 (March/April), 2011: pp 65–79
Sicilia A, Cuesta S, Coma G, Arregui I, Guisasola C, Ruiz E, et al. Titanium allergy in dental implant patients: a clinical study on 1500 consecutive patients. Clin Oral Implants Res. 2008;19(8):823–835

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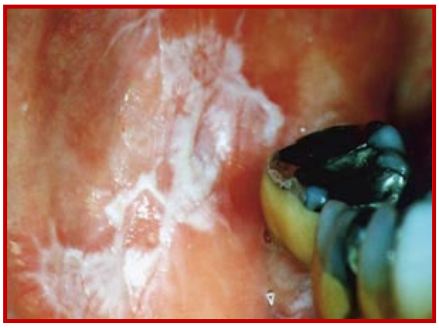
Manifestations of Metal Sensitivity in the Mouth

Oral lichenoid reaction (most common)

- associated with amalgams and gold



http://www.intechopen.com/

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Mercury amalgam: Amalgam Tattoos

- Less used restorative material in dentistry
- release large quantities of mercury ions (most frequent potential allergens that induce a cell-mediated DTH reaction)
- asymptomatic patches of particles of amalgam (blue, black, or gray) implanted into oral soft tissues during dental procedures

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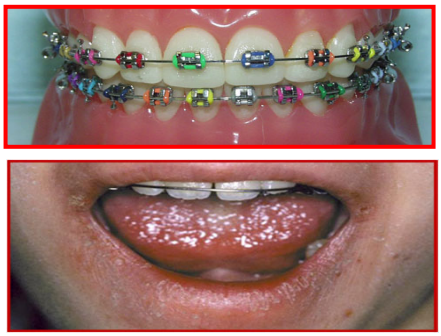
Orthodontic Devices



- Flexible titanium-nickel arch wires
  - release more nickel than stainless steel
- Potential allergen groups
  - Nickel: most common contact allergen to orthodontics
  - Ni–palladium &/or Ti alloys
  - CoCrMo alloys
  - Epoxy & epoxy-acrylate preparations
  - Anesthetics & flavorings
  - Rubber bands
- In vitro studies of stainless steel braces in artificial saliva show that metal ions are leached into saliva over time
- Case reports of systemic dermatitis from dental appliances support conclusion that there is likely absorption of nickel from this nickel leaching

Schalock1, et al Hypersensitivity reactions to metallic implants – diagnostic algorithm and suggested patch test series for clinical use. *Contact Dermatitis, 66, 4–19*

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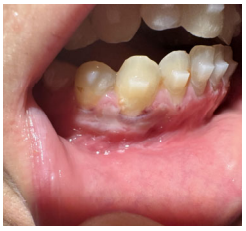
Orthodontic Devices with little or no metal



- **Clear aligners:** Invisalign use a series of clear, removable trays made of plastic or thermoplastic resin to gradually shift teeth.
- **Ceramic braces:** brackets made of a translucent or tooth-colored ceramic material that blends in with teeth for a less noticeable appearance.
  - Note that while the brackets are not metal, the arch wire is still metal.
- **Removable retainers:** made entirely of clear plastic
- **Plastic molar bands:** newer options with little to no metal components

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Oral Tolerance

- Oral tolerance to nickel demonstrated in animal models
- Finnish adolescents and the effect of age, gender, onset, duration and specific orthodontic treatment, and age of ear piercing on the incidence of nickel sensitization*
  - **Ear piercing prior** to orthodontic treatment: 35% of the girls were nickel allergic
  - **Orthodontic treatment prior** to ear piercing : NONE were nickel allergic

* Kerosup et al. Nickel allergy in adolescents in relation to orthodontic treatment and piercing of ears. American Journal of Orthodontics and dentofacial Orthopedics . February 1996, Vol 100 Pages 148–154

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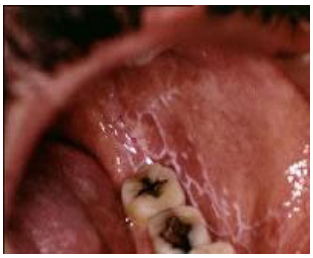
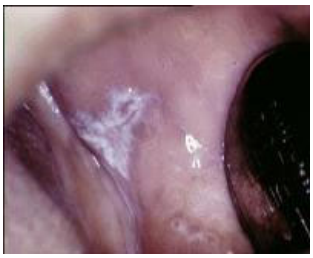
Allergic Contact Dermatitis From Dental Implants

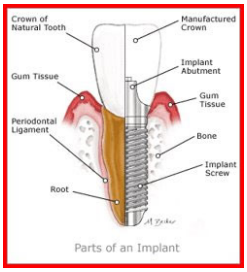
- Low rates of intraoral nickel-induced allergic reactions
- Lichenoid reaction or oral lichen planus-like lesions
- Most frequent manifestation: reticular, atrophic, erosive, or plaque like
  – Usually abut the eliciting implant



Reticular



Plaque-like



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Burning mouth syndrome &
"burning lips syndrome" (subtype of BMS)

- Reported in association with strong allergy to cobalt, nickel, mercury, gold & N,N-dimethylp-toluidine (DPT) in bone cement
- Study of 26 "burning mouth" patients*
  - 34.6% to nickel (vs. 20% general European population)
  - 19% to chromium (vs 5.4%)
  - 11.5% to gold (vs 6%)
  - 11.5% to cobalt (vs. 6.5%)
  - 7.7% to mercury (vs 2.9%)
  - 11.5% had (-) PT to any of the metals tested
- In some cases, removal of the mercury amalgam filling or dental gold cause resolution of symptoms

*Forte G et al. *Metal allergens of growing significance: epidemiology, immunotoxicology, strategies for testing and prevention. Inflammation and Allergy,*2008, 7: 1-18

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Generalized Dermatitis as Manifestation of Oral Metal Sensitivity (Case Reports)

- Foussereau & Langier: generalized dermatitis in the setting of a chromium-nickel denture (1966)
  - PT strongly (+) to nickel & chromium
  - Eruption resolved completely after denture removal
- Hubler & Hubler: generalized eczema following denture plate of chromium-cobalt alloy
  - Eruption cleared after removal of dental plate
  - Eruption reappeared within 24 hours of denture plate reinsertion
- Pigatto et al: generalized eczematous dermatitis after titanium dental implants and (later) a dental prosthesis containing chromium-cobalt alloy
  - PT (+) to dental amalgam, nickel sulfate, palladium chloride

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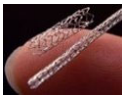
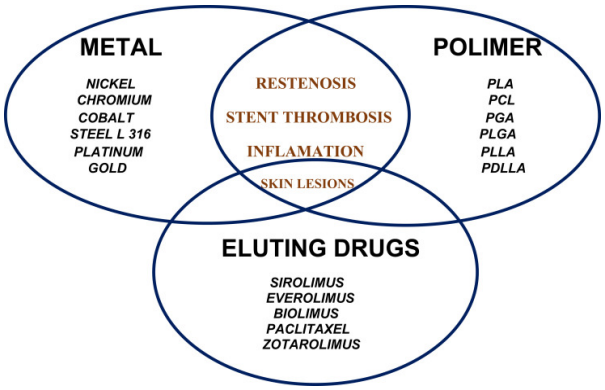
Coronary Stents





- Bare Metal Stents

-Stainless steel L316: Ni 14%, Cr 16%, Mo 2%, Mn 2%

-Cobalt alloys:

  - L605 cobalt chromium : Ni 10%, Cr 20%, Co 50%, Mn1.5%
  - MP35N : Ni 35%, Cr 20%, Co 35%, Mo 10%, Mn < 1%

-Gold alloy- No longer used

- Coated drug eluting stents: to minimize inflammation and reduce re-stenosis
  - First Generation DES
  - Second Generation DES: developed with biodegradable polymers (degrade in 6–24 mos), decrease in late and very late stent-thrombosis and also hypersensitivity reactions.

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Studies or Case Reports About Stents' Side Effects

Instent Restenosis		
Köster et al[26] (2000)	100% restenosis (patch-positive) vs 65% restenosis (patch-negative)	p=0.03
Iijima et al[27] (2005)	Patch test – significant predictor of restenosis	p = 0.02
Aliagaoglu et al[39] (2012)	23% restenosis (patch-positive) vs 0% restenosis (patch-negative)	p = 0.006
Svedman et al[28,40,41] (2005-6, 2009)	Restenosis rate higher in gold stents	
Saito et al[42] (2009)	Restenosis group: 39% patch-positive vs 11% patch-negative	p = 0.02
Norgaz et al[47] (2005)	No difference in spite of restenosis	
Thyssen et al[48] (2011)	Similar rate of restenosis	
Slodovnik et al[49] (2018)	No restenosis difference between patch-positive and patch-negative	p = 0.921
Romero-Bruffau et al[50] (2012)	No difference of main endpoints (metal allergy vs no metal allergy)	
Stent Thrombosis		
Konishi et al[71] (2015)	Reccurent stent thrombosis in patient with metal allergy	
Nebeker[52] (2006)	Eosinophilic infiltrates in patients with stent thrombosis (post-mortem study)	
Stone[38] (2004)	Stent thrombosis due to stent allergy	
Kounis Syndrome (acute coronary syndrome caused by allergic reaction or strong immune reaction		
Tzanis[76] (2017)	Early stent thrombosis after allergic reaction	
Tripolino[77] (2019)	Acute stent thrombosis after allergic reaction to contrast media	
Michas[78] (2017)	Stent thrombosis after mushroom allergy	
Skin Reactions		
RADAR[29] (2003)	17 from 262 patients: rash, itching, hives, fever, anaphylaxis	
Guntani et al[44] (2020)	Generalized pruritus after iliac metallic stent	

Chioncel V, Andrei CL, Brezeanu R, Sinescu C, Avram A, Tatu AL. Some Perspectives on Hypersensitivity to Coronary Stents. *Int J Gen Med*. 2021;14:4327-4336 https://doi.org/10.2147/IJGM.S326679

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Perspective

- **Routine testing is not advised:** There is no official guideline recommending routine patch testing for metal allergy prior to coronary stenting.
- **History is key:** For patients with clear history of adverse skin reactions to metals (e.g., jewelry or belt buckles), a patch test may be appropriate to identify the specific allergen.
- **Stent metals:** Stents commonly contain metals such as nickel, chromium, cobalt, molybdenum.
  - However, some newer stents have low-nickel or platinum-chromium content.
- **Conflicting evidence:** Studies on association between metal allergy & complications like in-stent restenosis have had conflicting results. Some studies have suggested a link, while others have found no association.
- **Skin vs. arterial reactions:** Unclear if a skin reaction (allergic contact dermatitis) reliably predicts a reaction within the coronary artery.
- **Urgency of intervention:** The need for the coronary intervention often outweighs the need for patch testing. In emergent situations, the procedure should proceed without delay.
- **Alternative devices:** If a patient with a known metal allergy requires a stent and a pre-procedural test is not possible, cardiologist may opt for a device with a metal platform that is less likely to cause a reaction (e.g., oxidized zirconium or titanium-containing devices). Some modern stents also use biodegradable polymers to reduce the risk of reaction to the coating

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Pacemakers/Defibrillators

- Majority of reactions are infections
- Allergic complications rare:
  - Titanium: most common alloy used to make pacemakers
  - Manifestations:
    - dermatitis localized above implant
    - impaired wound healing
    - generalized or remote dermatitis (uncommon)
  - Options:
    - polytetrafluoroethylene (PTFE) is considered inert and very rarely causes allergic reactions
    - Leadless pacemaker

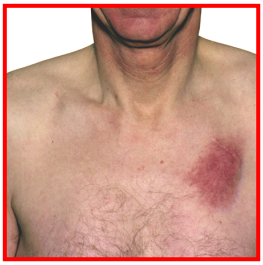

Table 2. Allergens in pacemakers/defibrillators

Confirmed allergens in pacemaker/defibrillator devices	Unconfirmed allergens in pacemaker/defibrillator devices
Wire/electrodes	
Silicone (polydimethylsiloxane)	Molybdenum
Nickel	Silver
Cobalt	Iridium
Chromium	Platinum
Palladium	Tantalum
Leads	
Polyurethane	Polytetrafluoroethylene
Silicone	—
Parylene (polychloroparaxylene)	—
Shell	
Titanium	Vanadium
Aluminium	—
Other	
Rubber accelerator (thiuram)	—
Epoxy resin	—
Epoxy hardener (triethylenetetramine)	—
Mercury	—

Schalock et al Hypersensitivity reactions to metallic implants – diagnostic algorithm and suggested patch test series for clinical use. *Contact Dermatitis*, 66, 4–19
HonariG, et al. Hypersensitivity reactions associated with endovascular devices. *Contact Dermatitis* 2008: 59: 7–22
Hallab N J, Jacobs J J. Biologic effects of implant debris. *Bull NYU Hosp Jt Dis* 2009: 67: 182–188
Oprea M L, Schnöring H, Sachweh J S, Ott H, Biertz J, Vazquez-Jimenez J F. Allergy to pacemaker silicone compounds: recognition and surgical management. *Ann Thorac Surg 2009*: 87: 1275–1277

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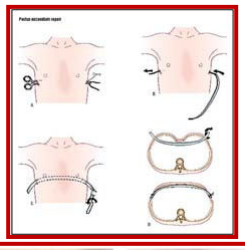
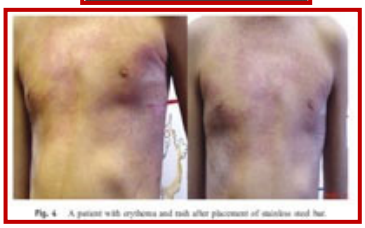
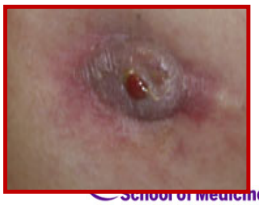
Nuss Bar Allergy: Dermatitis and Granuloma formation

- 10% of the general population have metal allergy
- Allergic reaction to Nuss bar is reported ~ 2.7%
  - caused by metals used (nickel & chrome)
- It has been suggested that PT be used in all patients prior to the Nuss procedure to potentially avoiding reoperations*
- Use of the manufacturer-provided metal disc testing alone is generally not recommended due to high irritant, false negative and false positive reactions
- Although the risk of an allergic reaction to titanium is smaller it still exists, the titanium substitute is not routinely used due to its higher cost and lesser plasticity which has a negative impact on matching a stabilizing bar during the surgery.







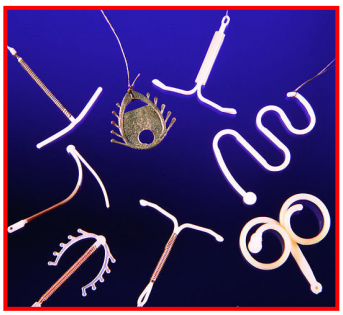
Shah B, Cohee A, Deyerle A, et al. High rates of metal allergy amongst Nuss procedure patients dictate broader pre-operative testing. J Ped Surg. 2014;49:451–4. doi: 10.1016/j.jpedsurg.2013.07.014.
Rushing GD et al : *J pediatr Surg, 2007*

17

Gynecological devices

- Mostly from contraceptive devices
  - contain copper
- EssureR: permanent contraceptive deviceimplanted in the fallopian tubes
  - made of Nitinol (55% Ti/45% Ni) outer coils and an SAE 316L stainless steel inner coil
  - all prospective users should be patch-tested with nickel prior to placement
- Contraindication to placement
  - Copper allergy in Copper IUCDs (Paragard)*
  - Ni allergy in Nitinol

  (Essure:www.accessdata.fda.gov/cdrh_docs/pdf2/P020014c.pdf)
- Reports of systemic allergic dermatitis resolving with IUCD removal



*Paragard. Product description. Available at: http://www.paragard.com/hcp/aboutparagard/product-description
** Essure. Instructions for use. Available at:http://www.essuremd.com/portals/essuremd/PDFs/TopDownloads/L3002% 2009_09_09%20smaller.pdf .
Bibas N, et al. Nickel-induced systemic contact dermatitis and intratubal implants: the baboon syndrome revisited. *Dermatitis : contact, atopic, occupational, drug : official journal of the American Contact Dermatitis Society, North American Contact Dermatitis Group.* Jan-Feb 2013;24(1):35-36.
Al-Safi Z, et al. Nickel hypersensitivity associated with an intratubal microinsert system. *Obstet Gynecol.* Feb 2011;117(2 Pt 2):461-462.

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RETURN TO AGENDA

Joint Replacements: Scope of the Problem

- US: >1 million joint replacements/year
- Main recipients
  - 65-84 y/o – largest Medicare expenditure
  - 45-64 y/o, significant increase since 2000
- Joint replacements are cost effective
- Estimates: 4 million/year by 2030
  - Aging of US population
  - Requests to maintain mobility

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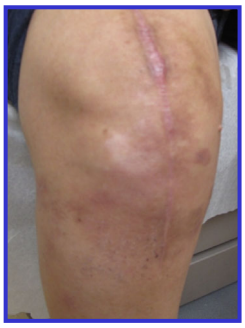
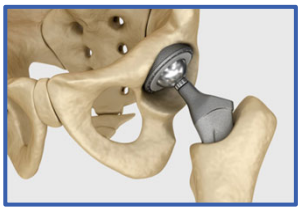
Sensitivity to Biomedical Devices

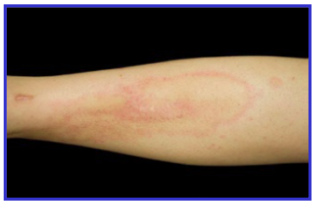
Reported manifestation of implant allergy

1. Dermatitis usually above joint itself, diffuse rash possible
2. Implant failure

Contentious issue







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Which subgroups have increased risk of complications with metal implants?

- Unknown… Sensitization to metals increased 6.5% following arthroplasty*

Hip arthroplasty:
- sensitization to nickel, cobalt or chromium
  - 25% in well-functioning implants (>2x general population)**
  - 60% in failed or failing prosthesis (6x general population)**

Total knee arthroplasty:
- metal sensitization rate
  - 20% in pts w/ no implant
  - 48.1% in pts w/ stable implant
  - 59.6% in unstable implant group***

- Available evidence indicates a correlation between metallic orthopaedic implants, development of metal hypersensitivity and implant loosening

Does loosening cause hypersensitivity or…….
……. does hypersensitivity cause loosening?

* E. Frigerio, P. D. Pigatto, G. Guzzi, and G. Altomare, "Metal sensitivity in patients with orthopaedic implants: a prospective study," Contact Dermatitis, vol. 64, no. 5, pp. 273–279, 2011.
** N. Hallab, "Metal sensitivity in patients with orthopedic implants," Journal of Clinical Rheumatology, vol. 7, no. 4, pp. 215–218, 2001.
*** D. Granchi, E. Cenni, D. Tigani, G. Trisolino, N. Baldini, and A. Giunti, "Sensitivity to implant materials in patients with total knee arthroplasties," Biomaterials, vol. 29, no. 10, pp. 1494–1500, 2008.

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Allergic Causes of Joint Failure

Metals
- Nickel
- Cobalt
- Chromium
- Titanium (rare)

Bone Cement
- Liquid component:
  - Methyl methacrylate
  - n,n-dimethyl-p-toluidine
  - hydroquinone
- Powder:
  - poly methyl acrylates
  - benzoyl peroxide
- 2-HEMA (hydroxyethyl methacrylate)
- Gentamycin is the most common antibiotic added
  -Tobramycin, Clindamycin & Erythromycin also used

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Acrylates

- **3 main Groups**
  - Acrylates (mono & di)
    - Most allergenic
    - Screened with ethyl acrylates
  - Methacrylates
    - Screened with methacrylate and Hydroxyethylmethacrylate (HEMA)
  - Cyanoacrylates
    - 3 ethyl cyanoacrylate (superglue)
    - Octyl cyanoacrylate (dermabond)
    - Butylcyanoacrylate

- **Where are they found?**
  - **Cosmetics:** artificial nails, nail polishes, hair sprays, fragrances, dentifrices, insecticides
  - **Medical:** orthopedics bone cement, EKG leads, diabetic insulin pumps, glucose sensors, dental bonds and fillings, prostheses, heart valves, adhesives, splints
  - **Industrial:** Adhesives, paints, sealers and stoppers, grout

Acrylates penetrate gloves!

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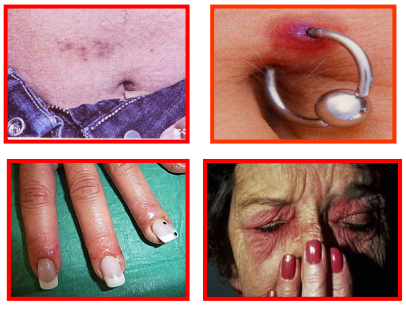
Preoperative Patch Testing:

Testing is indicated in patients with
- History of **metal** reactivity (jewelry, jean snaps, watch bands, belt buckles, necklace etc.)
- **Methacrylate's**: reactions to gel nails, skin glue (Derma bond), Gorilla Glue
- Topical **antibiotics** (Bacitracin, Neosporin, Polymixin)



- ≈70% of patients with pre-operative history of metal reactivity are sensitized to a metal:
  - Nickel
  - Cobalt (30% of Ni allergic are sensitive to Co)
  - Chromium
- Bone cement allergy is rare in this group

Some studies show patients with high suspicion of metal allergy
- who had pre-operative PT that guided implant selection
- have improved outcomes

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Issues to address with a positive Pre-implantation patch test

1. **Which implant/device will give the best outcome (functionality/durability)**
   - **Role of patient's surgeon**
2. **Does a positive PT to metal found in the 'best' device warrant using an inferior device?**
   - **Role of allergist/ dermatologist**
     - **Identify metal/s with positive PT**
     - **Give guidance on safe materials for implantation (i.e. negative reactions with metal screening series)**

Retrospective case–control study prior to total hip replacement
• (+) PT to **metals** & history of metal hypersensitivity had significantly shorter life spans of their implants
• (+) PT to **bone cement** components, none had stable implant at a 10-year endpoint

Schalock PC et al Patch Testing for Evaluation of Hypersensitivity to Implanted Metal Devices: A Perspective From the American Contact Dermatitis Society. Dermatitis, Vol 27 ¡ No 5 ¡ September/October, 2016
Thomas P, Summer B, Sander CA, et al. Intolerance of osteosynthesis material: evidence of dichromate contact allergy with concomitant oligoclonal T-cell infiltrate and TH1-type cytokine expression in the peri-implantar issue. Allergy 2000;55:969Y972

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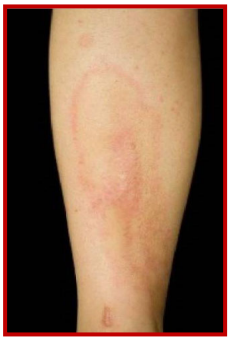
Post Implantation PT:

Patients with no symptoms after implantation do not require PT

- Joint Failure: joint loosening, pain
- Dermatitis (above site of implant)
  - beginning weeks to months after implantation
  - resistant to medical therapy
  - localized reactions of skin overlying the implant site
  - generalized eczematous eruptions have been reported in both static and dynamic implants



Thyssen JP et al. Pragmatic approach to the clinical work-up of patients with putative allergic disease to metallic orthopaedic implants before and after surgery. Br J Dermatol. 2011;164(3):473–8.

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Joint Failure: Post Implantation Patch Test

- ~ 10% of patients with joint replacements will fail (pain, swelling, itching/burning, and/or ↓ range of motion)
- More common Causes
  - Infection
  - Biomechanical issues
  - Metallosis – a toxic/necrotic reaction to metal wear particles
- Contributing factors:
  - Obesity
  - Cigarette smoking
  - Osteoporosis

- ~ 50% of patients referred after infection/mechanical causes are ruled out, are sensitized to some component of their joint replacement:
  - ~ 25% to a relevant metal
  - ~ 21% to bone cement

There is increasing evidence to support PT as the next step in evaluating patients as the cause of joint failure when other causes have been ruled out.

Thyssen JP et al. Pragmatic approach to the clinical work-up of patients with putative allergic disease to metallic orthopaedic implants before and after surgery. Br J Dermatol. 2011;164(3):473–8.
Schalock PC et al Patch Testing for Evaluation of Hypersensitivity to Implanted Metal Devices: A Perspective From the American Contact Dermatitis Society. Dermatitis, Vol 27 ¡ No 5 ¡ September/October, 2016

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What to do with a Post implantation Positive Patch Test to Biomedical Device Components

What Information do we need?

- **Identify components used in surgery (operative report)**
- **"Sticker sheet" lists product name, manufacturer, part number, issue batch, date**
- **Indications for surgery**
  - **Traumatic injuries may damage joint structure & lead to mechanical difficulties**
  - **Previous joint infection increase risk of subsequent one**
- **Was bone cement used**
- **How was incision closed**
  - **Vicryl (absorbable)**
  - **Monocryl (absorbable)**
  - **Silk**
  - **Staples**
    - **Stainless steel or titanium**
  - **Dermabond**
- **Other surgical replacements tolerated**

Fonacier L, Bernstein D, Pacheco K, Holness DL, et al. Contact Dermatitis: A Practice Parameter Update – 2015. JACI In Practice. Vol 3, No 3 May/June 2015. S1-39
Schalock PC et al Patch Testing for Evaluation of Hypersensitivity to Implanted Metal Devices: A Perspective From the American Contact Dermatitis Society. Dermatitis, Vol 27 ¡ No 5 ¡ September/October, 2016
Pacheco KA, Thyssen JP. Contact Dermatitis From Biomedical Devices, Implants, and Metals-Trouble From Within. J Allergy Clin Immunol Pract. 2024 Sep;12(9):2280-2295. doi: 10.1016/j.jaip.2024.07.016. Epub 2024 Jul 25. PMID: 39067854.

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What to do with a Positive Patch Test to Biomedical Device Components

What do we write in our consults?

- Sensitization to metals were significantly higher in patients with failed than with well-functioning or without an implant.
- A positive metal test does not prove causality of symptoms.
- Other causes of implant failure (infection and biomechanical issues) must be been ruled out.
- There is not enough evidence at this time to make overreaching recommendations for symptomatic patients with (+) PT to metals or bone cement components.
- **The decision on implant revision following (+) PT results can only be made after a thorough discussion between the patient, the allergist or dermatologist, and the orthopedic surgeon.**

Fonacier L, Bernstein D, Pacheco K, Holness DL, et al. Contact Dermatitis: A Practice Parameter Update – 2015. JACI In Practice. Vol 3, No 3 May/June 2015. S1-39
Schalock PC et al Patch Testing for Evaluation of Hypersensitivity to Implanted Metal Devices: A Perspective From the American Contact Dermatitis Society. Dermatitis, Vol 27 ¡ No 5 ¡ September/October, 2016

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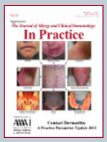
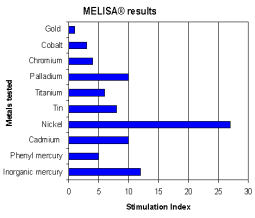
Patch Testing vs Lymphocyte Transformation Test



Practice Parameters:
The clinical relevance of commercially available blood tests to diagnose metal sensitization have not been determined

ACDS:
The LTT is not widely available, not standardized, expensive, subject to variability, may be overly sensitive (false-positive reactions)

- *Measures lymphocyte proliferation* (stimulation index) after 7 days incubation +/- allergen
  - Limited allergens
  - Rapid decay of T cells (rapid transportation)*
- May be useful in questionable cases
  - (-) PT & persistent concerns about metal allergy
  - 54/56 patients with Ti implants, (-) PT & (+) Ti LTT whose systemic symptoms resolved after implant removal



*(MELISA test: Health Diagnostics and Research Institute, South Amboy, NJ)
Muller K E, Valentine-Thon E. Hypersensitivity to titanium: clinical & laboratory evidence. *Neuro Endocrinol Lett* 2006: 27: 311–313

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Patch testing to Biomedical Device:

Who to test:

1. Preoperative patients with strong history of local skin reaction to metal (jewelry, jean snaps) or to acrylic/artificial/silk/gel nails or to skin glue
2. Post operative patients with joint failure in whom other causes (infection or mechanical issues) have been ruled out

Who not to test

1. Worried well patient before surgery "just to make sure"
2. Worried post op patient with no prior history of reactivity before 1 year has elapse from surgery (time for healing)

Exception: rash over implant (probability of implant sensitization is higher)

Pacheco & Thyssen. Contact dermatitis from biomedical device, Implants and metals-Trouble from within. J Allergy Clin Immunol Pract 2024 Vol 12 No 9: 2280-2295

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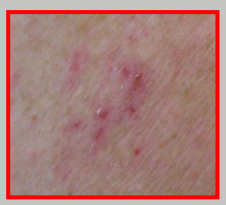
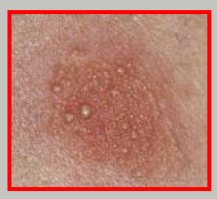
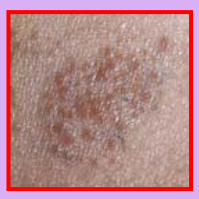
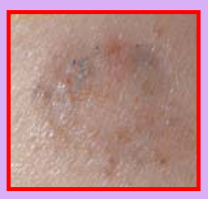
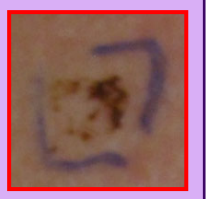
False Positive reactions to Metals

Pustular patch reaction
- Common in atopics
- Nickel, copper , arsenic & mercuric chloride
- Minimal pruritus

Cobalt
- false (+) cobalt "poral" reaction
- punctate erythema, almost petechial
- probably toxic effect of cobalt on acrosyringium of the sweat duct

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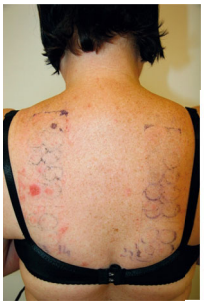
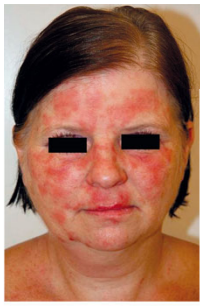
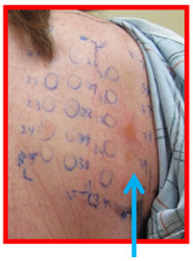
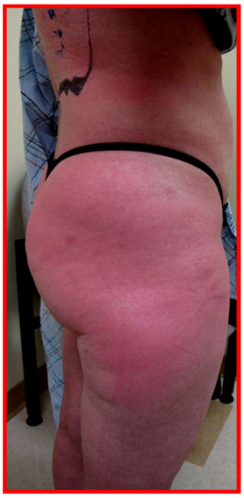
Clues: “Reactivation”

Tangential form of SCD:

- If after patch test, original dermatitis flares → suggests relevancy
  - Especially in cases of drug-related dermatoses (DRESS, morbilliform etc.,)
- If you orally challenge a person and their previously positive patch test reactivates → probably relevant

Obtułowicz, Aleksander, et al. "The flare-up phenomenon: recurrence of distant dermatitis during patch testing." *Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii* 33.1 (2016): 68-69.

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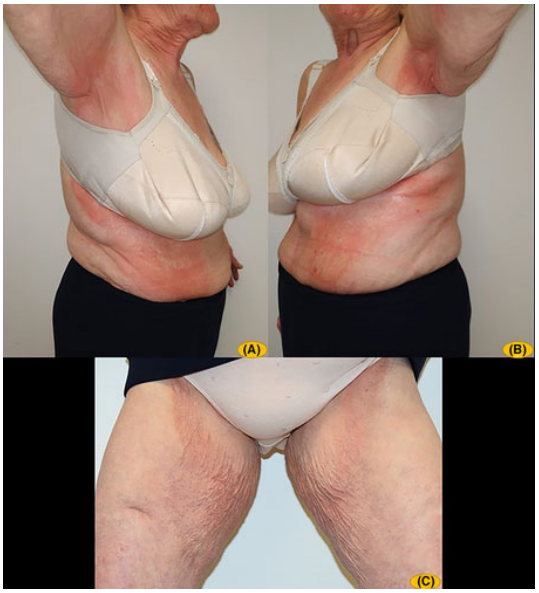
Other metals

Cobalt

- exceeding rare
- typically from vitamin B12 oral supplements (contain cobalt)
- Vitamin B12 intolerance could be underestimated as ~3% of the general population is cobalt sensitized



Pegalajar-García, María Dolores, et al. "Systemic allergic dermatitis to cobalt present in cyanocobalamin supplementation." *Contact Dermatitis* (2023).

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Take away message:
Patch testing to Metals: Problems and Pitfalls

1. Problems and pitfalls to patch testing with metals:
   - Limited commercially available Metals PT preparations, accessibility and availability
   - Dosing, concentration (%petrolatum, aqueous), ideal salt (-chloride, -oxide, -dihydrate etc)
   - Metallic disc from the manufacturer can be considered
     - should not be the only product tested, need metal salts
     - consider false positive and negative results
     - yield tends to be low; in Reed's series* none of the 22 patients tested with metal disc from manufacturer had a positive result.
2. Interpretation of metal patch test : High irritancy: follicular, pustular, poral
3. Patch test to metals need delayed read (7-10 days)
4. Acrylates are volatile and need to load prior to PT
5. It is difficult to establish relevance of a positive patch test to components of biomedical devices

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Baby Boomers

If we live long enough, we will all get there

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