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CHRONIC HAND ECZEMA:

All Hands on Deck

Speakers:

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Overall Summary

Chronic Hand Eczema is defined as hand eczema that occurs **for more than 3 months or relapses twice or more often** per year.[2] The pathogenesis can be highly complex which makes diagnosis difficult. [1]

CHE is characterized by **debilitating itch and pain** with a high psychological, functional, and occupational burden.[1]

There is an **unmet need for short- and long-term disease management** that targets all the subtypes of CHE and provides reliable treatment to mitigate signs and symptoms. [1-3]

CHE, Chronic Hand Eczema.

1. Dubin C, et al. *Ther Clin Risk Manag* 2020;16:1319–1332. Erratum in: *Ther Clin Risk Manag* 2021;17:233; 2. Thyssen JP, et al. *Contact Dermatitis* 2022;86:357–378; 3. Grant L, et al. *Adv Ther* 2020;37:692–706;

CHE is described as a heterogenous, long-lasting, fluctuating inflammatory skin disease, with key symptoms of pain and itch[1-5]

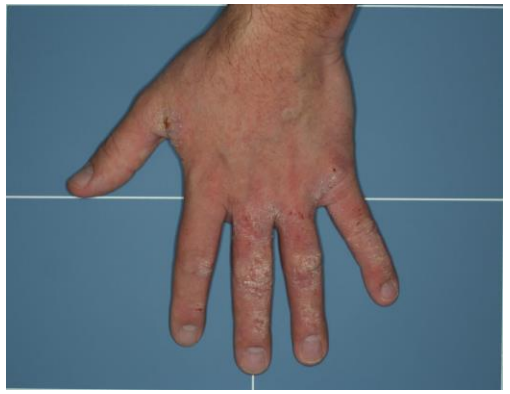
Key clinical signs and symptoms[5]

- Pain and Itch
- Bleeding and swelling of the hands
- Dryness, thickened skin, cracking

Inflammatory signs and symptoms (**itch, pain, erythema, swelling, burning**) are most common during a flare-up, whilst **dry skin, hyperkeratosis and cracking** can persist between flares[5]

Fluctuations in CHE[5]

Symptoms fluctuate in severity over time, with periods of symptom exacerbation described as flare-ups[5]



CHE: chronic hand eczema; SD: standard deviation.

1. Lynde C, Guenther L, Diepgen TL, et al. *J Cutan Med Surg* 2010;14(6):267-84. 2. Menné T, Johansen JD, Sommerlund M, et al. *Contact Dermatitis* 2011;65(1):3-12. 3. Lee GR, Maarouf M, Hendricks AK, et al. *Dermatol Ther* 2019;32(3):e12840. 4. Thyssen JP, Schuttelaar MLA, Alfonso JH, et al. *Contact Dermatitis* 2022; 86(5): 357-378. 5. Grant L, Seiding Larsen L, Burrows K, et al. *Adv Ther* 2020;37(2):692-706.

Impact and Burden of Chronic Hand Eczema

High socioeconomic burden[1–4]

There can be a high cost of sick leave, loss in productivity, and loss of employment[4]

Impact on patients' ability to work[4,5]

Jobs involving wet work or frequent exposure to irritants/allergens are a risk factor for HE[6,7]

Impact on patients' ability to perform domestic tasks[4,8]

Prolonged exposure to skin irritants, such as detergents, and taking care of children increase the risk of HE[4,8]

Can severely impact daily activities and impair quality of life[9,10]

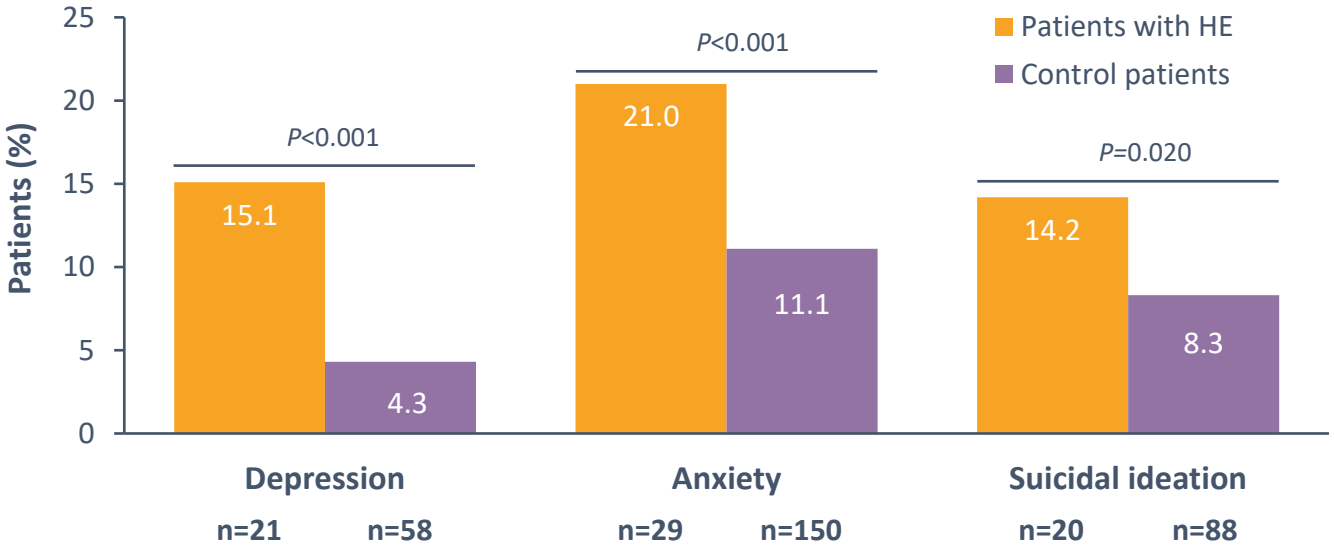
HRQoL impairment for patients with severe HE is similar or greater to QoL impairment in other serious chronic diseases[9,10]

HE, hand eczema; HRQoL, health-related quality of life.

1. 1. Christoffers WA, *et al. Cochrane Database Syst Rev*. 2019;4:CD004055; 2. Politiek K, *et al*. *Contact Dermatitis.* 2016;75:67–76; 3. Augustin M, *et al*. *Br J Dermatol.* 2011;165:845–51; 4. Cortesi PA, *et al*. *Contact Dermatitis.* 2014;70:158–68; 5. Diepgen TL, *et al*. *J Dtsch Dermatol Ges.* 2015;13:e1–22; 6. Apfelbacher C, et al. *Acta Derm Venereol* 2014;94:163–7; 7. Thyssen J, et al. *Contact Dermatitis* 2022;86:357–3; 8. Dubin C, et al. *Ther Clin Risk Manag* 2020;16:1319–1332. Erratum in: *Ther Clin Risk Manag* 2021;17:233; 9. Lynde C, et al. J Cutan Med Surg 2010;14:267–284. Erratum in J Cutan Med Surg 2011;15:360; 10.Fowler J. Cutis 2008;82(4 Suppl):3)

Impact and Burden of Hand Eczema

Psychologic comorbidities in patients with HE (n=143)



*A cross-sectional, multicenter study involving 3,635 dermatologic outpatients, including 143 patients with HE in 13 European countries[4]

Figure adapted from Dalgard, et al. 2015.

CHE has a large **negative** impact on **quality of life** and can severely impact the **ability to perform daily activities** with a **high social, psychological, and occupational burden.**[1,2,3,7]

HE, hand eczema; HRQoL, health-related quality of life.

1. Apfelbacher CJ, *et al. Acta Derm Venereol.* 2014;94:163–167; 2. Kouris A, *et al. Contact Dermatitis.* 2015;72:367–370; 3. Grant L, *et al. Adv Ther.* 2020;37:692–706; **4.** Lynde C, *et al. J Cutan Med Surg.* 2010;14:267–284; **5.** Fowler J. *Cutis.* 2008;82(4 Suppl):3; **6.** Christoffers WA, *et al. Cochrane Database Syst Rev*. 2019;4:CD004055; **7.** Dalgard FJ, *et al. J Inv Dermatol.* 2015;135:984–91; **8.** Politiek K, *et al. Contact Dermatitis.* 2016;75:67–76; **9.** Augustin M, *et al. Br J Dermatol.* 2011;165:845–51;
10. Cortesi PA, *et al. Contact Dermatitis.* 2014;70:158–68.

Patients with CHE may present with a combination of signs[1]

Erythema[1]

Scaling[1]

Lichenification[1]

Edema[1]

Hyperkeratosis[1]

Vesicles[1]

Fissures[1]

Nail dystrophy[2,3]

CHE, chronic hand eczema.

1. Thyssen JP, *et al*. *Contact Dermatitis.* 2022;86:357–78; **2.** Yu M, *et al*. *J Dermatol.* 2013;40:406–7; **3.** Milanesi N, *et al*. *Clin Exp Dermatol.* 2015;40:533-6.

Hand Eczema Subtypes and Etiologies (2022)

Characterization based on the 2022 European guidelines[1]

Irritant contact dermatitis
HE with documented irritant exposure; no relevant contact allergy; an exclusion diagnosis

Atopic HE
HE in a patient with a medical history of atopic eczema

Allergic contact dermatitis
HE caused by relevant[a] contact allergens; identified by patch testing

Protein contact dermatitis/ contact urticaria
HE in patients exposed to proteins[b]; identified with a positive prick test

Hyperkeratotic eczema
Eczema with hyperkeratosis in the palms. More common in men; potential association with tobacco smoking

Acute, recurrent vesicular HE
Recurrent HE with vesicular eruptions. May be seen on the basis of different etiologies

Nummular HE
Eczema characterized by coin-shaped lesions, especially on the back of the hands. Often associated with allergic contact dermatitis

Pulpitis
Eczema located on the fingertips. Often caused by irritation of the skin but might be related to AD or allergic contact dermatitis

Etiologic subtypes | **Clinical subtypes**

- There can also be **mixed forms** of the subtypes where more than one etiologic factor and clinical subtype are present
- The clinical picture may change over time[1]
- The underlying pathophysiology is shared across subtypes[2,3]

[a]"Relevant" means that there is a current exposure of the hands to the allergen; [b]Food, latex, and other biologic materials.
AD, atopic dermatitis; HE, hand eczema.
1. Thyssen J, *et al. Contact Dermatitis.* 2022;86:357–78; **2.** Lee GR, *et al. Dermatol Ther.* 2019;32:e12840; **3.** Tauber M, *et al. J Eur Acad Dermatol Venereol.* 2020;34:1529–35.

Patients with CHE may Present with Multiple Subtypes, each with a distinct Immune Signature[1,2]

Th2/Th22 profile

~34%[a] of CHE Cases

Atopic Hand Eczema

Irritant Contact Dermatitis

Allergic Contact Dermatitis

Cases of CHE can have multiple subtypes

Th1/Th17 profile

~45%[a] of CHE Cases

~22%[a] of CHE Cases

Th1/Th17 profile *(metals)*
Th2/Th22 profile *(rubber and fragrance)*

<5%[4] of CHE Cases

Protein Contact Dermatitis[3]

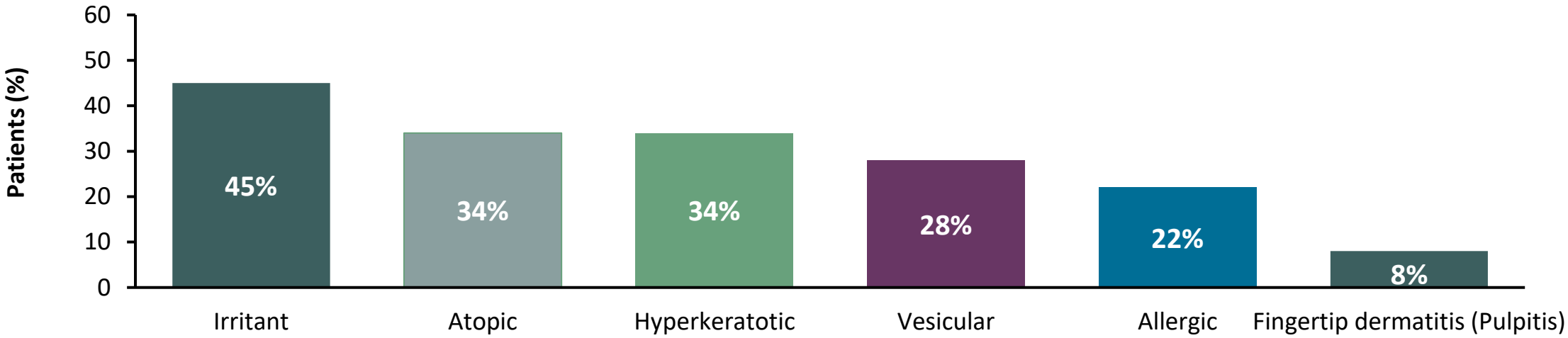
Type 1 Hypersensitivity to e.g., food or animal proteins.

[a]Percentages are from a prospective registry study published in 2014 involving 1163 patients with CHE across 95 centers in Germany.

AD, Atopic Dermatitis; **CHE**, Chronic Hand Eczema; **Th**, T-helper.

1. Apfelbacher C, et al. *Acta Derm Venereol*. 2014;94:163–7; 2. Dubin C, et al. *Ther Clin Risk Manag* 2020;16:1319–1332. Erratum in: *Ther Clin Risk Manag* 2021;17:233;
3. Diepgen T, et al. *J Dtsch Dermatol Ges*. 2009;7(Suppl. 3):S1–16 4. Thyssen JP,et al.Contact Dermatitis 2022;86:357–378;

Most common subtypes of chronic hand eczema



In a CARPE registry study that classified patients with CHE (N=1163) based on their predominant subtype[a], approximately 50% of patients were placed in more than one diagnostic category

[a]Includes a mix of clinical and etiological subtypes.
CARPE, Chronisches Handekzem-Register zum Patienten-Langzeitmanagement (chronic hand eczema registry on long-term patient management); CHE, chronic hand eczema.
Apfelbacher C, *et al. Acta Derm Venereol.* 2014;94:163–7.

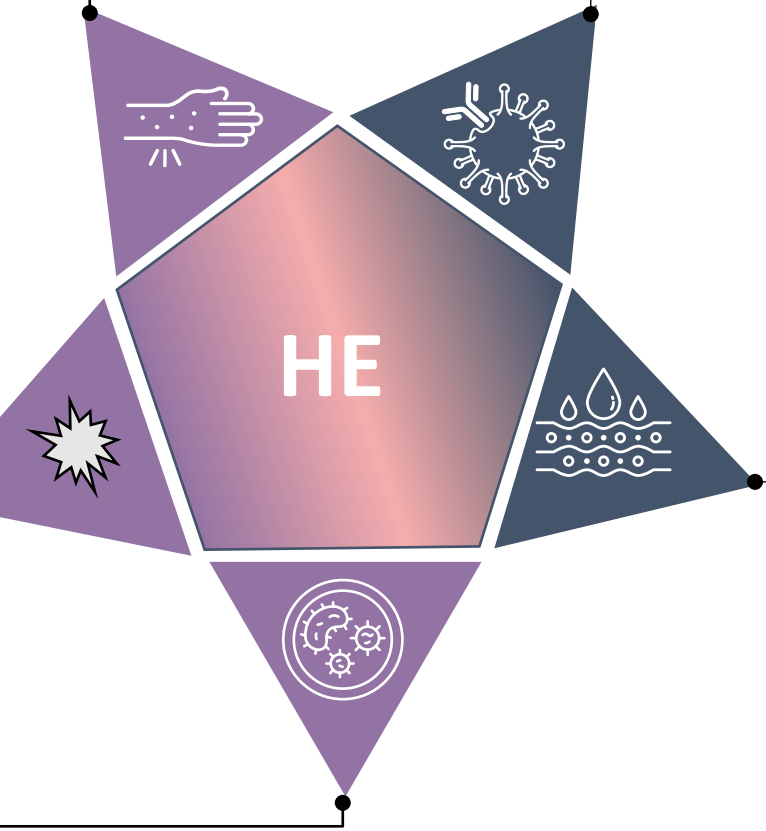
Hand eczema pathogenesis is multifactorial

Exogenous factors

Irritants[1]

Allergens[1]

Pathogens[1]



Inflammation of the skin[1,2]

Skin barrier defects[1]

Endogenous factors

HE, hand eczema.

1. Lee GR, *et al. Dermatol Ther.* 2019;32:e12840; 2. Dubin C, et al. *Ther Clin Risk Manag* 2020;16:1319–1332. Erratum in: *Ther Clin Risk Manag* 2021;17:233.

Cycle of Triggers

The triggers and relative importance of different disease factors differ by CHE subtype, but common mechanisms exist[1,2]

In atopic CHE, there is dysfunction of the skin microbiome and *S. aureus* colonization[1]

Impaired skin barrier

Exposure to irritants, allergens, toxins, pathogens[1]

Exogenous factors may trigger episodes for irritant and allergic CHE[3]

Immune dysregulation is common to all types of CHE[1]

Immune cell activation producing inflammation[1]

Morphologic skin changes, clinical features, symptoms

Differs depending on morphologic and etiological class of CHE[3]

Patients with AD are more susceptible to CHE - **endogenous** genetic factors may contribute, but appear to be less important than skin barrier defects[2]

CHE, Chronic Hand Eczema; **AD,** Atopic Dermatitis.

1. Lee GR, et al. *Dermatol Ther* 2019;32:e12840. 2. Tauber M, et al. *J Eur Acad Dermatol Venereol* 2020;34:1529–1535; 3. Diepgen TL, et al. *J Dtsch Dermatol Ges* 2015;13:e1–22.

Work-up of Chronic Hand Eczema

EU and Canadian guidelines[1,2] There are currently **no standardized guidelines in the United States** for diagnosing and treating CHE	
History taking[1,2]	• Personal and family history of atopy, allergies, and eczema • Exposure profile outcomes • Duration and course • Past treatment outcomes • Factors that improve or aggravate condition • Current work, hobby, and home profiling
Physical examination[2]	• Distribution • Morphology • Severity
Diagnostic skin patch and prick testing[1,2]	• Skin patch testing is the gold standard for diagnosing allergic contact dermatitis, a subtype of CHE • Skin-prick tests and specific IgE assays can be used to diagnose protein contact dermatitis, another CHE subtype
Cutaneous biopsies[1]	• May be useful for differential diagnosis
Microbial testing[1,2]	• Diagnose secondary infection • Exclude scabies or herpes simplex viral infection

Ig, immunoglobulin.

1. Thyssen J, *et al. Contact Dermatitis.* 2022;86:357–78; 2. Lynde C, et al. *J Cutan Med Surg* 2010;14:267–284. Erratum in *J Cutan Med Surg* 2011;15:360.

Differentiating Chronic Hand Eczema from Atopic Dermatitis

AD-CHE	Non-AD CHE
Typically dorsal predilection of hand eczema	Typically predominant palmar or interdigital presentation of eczema
Few present with pompholyx, pulpitis, vesicular hand eczema, chronic and fissured hand eczema	Contains the morphological subtypes including pompholyx, vesicular hand eczema, chronic and fissured hand eczema, pulpitis
AD will typically be found on other body parts	Up to 1/3 may have concomitant foot eczema and some have nummular eczema, and some may have a history of AD.
Often associated with asthma and rhinitis	Often associated with occupational or domestic exposure to skin irritants (e.g. hand wash, rubber glove use) or contact allergens (cosmetics, metals, glues and other).
Associated with positive skin prick test, elevated specific IgE to aeroallergens and/or elevated total IgE	Exposure analysis may reveal skin irritant exposure
Filaggrin gene mutations may be identified	Patch testing may reveal contact allergy. Skin prick-prick test may reveal protein allergy
Strong Th2 inflammatory signature	Mixed Th1/Th2/Th17inflammatory signature. Multiple immune pathways involved.
Intrinsic CHE	Extrinsic CHE

CHE and AD Differentiation

- CHE is a complex disease with overlap in the pathophysiology with AD, particularly atopic HE.[1] **CHE is limited to the hands and wrist** whereas **AD can affect different parts of the body.**[1,2]
- The **JAK-STAT pathway plays a key role** in both conditions, and both AD and CHE are characterized by inflammation and skin barrier dysfunction.[3,4]
- Both AD and atopic HE typically present with a Th2 immune profile that play a key role in the pathogenesis of both conditions.[5,6]
- **Some CHE subtypes are immunologically distinct from AD**.[7] Therapies targeting the type 2 immune response may not be effective in all CHE subtypes[5]

HE, Hand Eczema; **CHE**, Chronic Hand Eczema.

1. Thyssen JP, et al. *J Eur Acad Dermatol Venereol*. 2020;34:e429–30; 2. Eichenfield LF, et al. *J Am Acad Dermatol* 2014;70:338–351; 3. Worm M, et al. *Br J Dermatol* 2022;187:42–51; 4. Huang IH, et al. *Front Immunol* 2022;13:1068260; 5. Dubin C, et al. *Ther Clin Risk Manag* 2020;16:1319–1332. Erratum in: *Ther Clin Risk Manag* 2021;17:233. 6. Napolitano M, et al. *Front Med (Lausanne)* 2023;10:1165098; 7. Rosenberg FM, et al. *Contact Dermatitis* 2024;90:23–31.

No treatments are FDA-approved for moderate-to-severe CHE

Current treatment options:

- Have **limitations** and can be a **challenge** for patients and HCPs[1].
- There are currently **no FDA-approved** therapies available for CHE[1,2].

TCS are typically used first-line, however:

- **CHE can persist despite TCS treatment** and a proportion of patients relapse[1,6]
- **Corticosteroid phobia** can result in poor adherence[1]
- Long term use of TCS can lead to unwanted **adverse events including skin atrophy**, rebound flares and worsening of chronic hand eczema signs or symptoms[1,4].

Other options:

- TCIs provide a steroid-sparing option, but their clinical use may be limited to the atopic subtype[1,3]
- Most patients (76.4%) reported that they would **prefer a steroid free topical therapy if available[4]**

1. Thyssen JP, *et al. Contact Dermatitis.* 2022;86:357–78. 2. Toctino Summary of Product Characteristics. Available at: Toctino 10mg soft capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) [Accessed August 2024]; 3. Ho JSS, Molin S. J Cutan Med Surg. 2023;27(5):493-503; 4. Egeberg A, et al. JAAD Int. 2023 Dec 3;14:77-83; 5. Dubin C, et al. *Ther Clin Risk Manag* 2020;16:1319–1332. Erratum in: *Ther Clin Risk Manag* 2021;17:233; 6. Nygaard U et al. Dermatology 2017;233(5) 333-343.

Unmet Medical Need

There is a high unmet need for a treatment that is:

- **Efficacious**[1]
- **Well-tolerated**[1]
- **Non-steroidal topical**[1]
- Developed specifically for **CHE** to address the heterogeneity of the disease and provide **long-term** disease control **across CHE subtypes**[1,2]

CHE, chronic hand eczema; TCS, topical corticosteroid.

1. Dubin C, et al. *Ther Clin Risk Manag* 2020;16:1319–1332. Erratum in: *Ther Clin Risk Manag* 2021;17:233; 2. Lee GR, et al. *Dermatol Ther* 2019;32:e12840.

Current Topical Therapy Challenges

- A proportion of patients with moderate-to-severe CHE relapse after short-term treatment with TCS[2]
- TCS may not effectively treat patients with irritant contact dermatitis subtype[3-5]
- TCS are not recommended for long-term use due to the risk of skin atrophy[1]
- TCIs provide a steroid-sparing option, but their clinical use may be limited to atopic subtype[1,6]
- Current systemic options have important safety considerations, such as required monitoring and teratogenicity[1]

CHE, chronic hand eczema; JAKi, Janus kinase inhibitor; PUVA, psoralen and ultraviolet A therapy; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; UVB, ultraviolet B. **1.** Thyssen JP, *et al*. *Contact Dermatitis.* 2022;86:357–78; **2.** Veien NK, *et al*. *Br J Dermatol.* 1999;140:882–886; **3.** Levin C, *et al*. *Skin Res Technol.* 2001;7:214–218; **4.** van der Valk PG, Maibach HI. *J Am Acad Dermatol.* 1989;21:519–522; **5.** Egeberg A, et al. *JAAD Int*. 2023 Dec 3;14:77-83; **6.** Guenther L, *et al*. *J Cutan Med Surg.* 2019;23(4_suppl):27S-34S; **7.** Ho JSS, Molin S. *J Cutan Med Surg*. 2023;27(5):493-503.

Additional Treatment Options

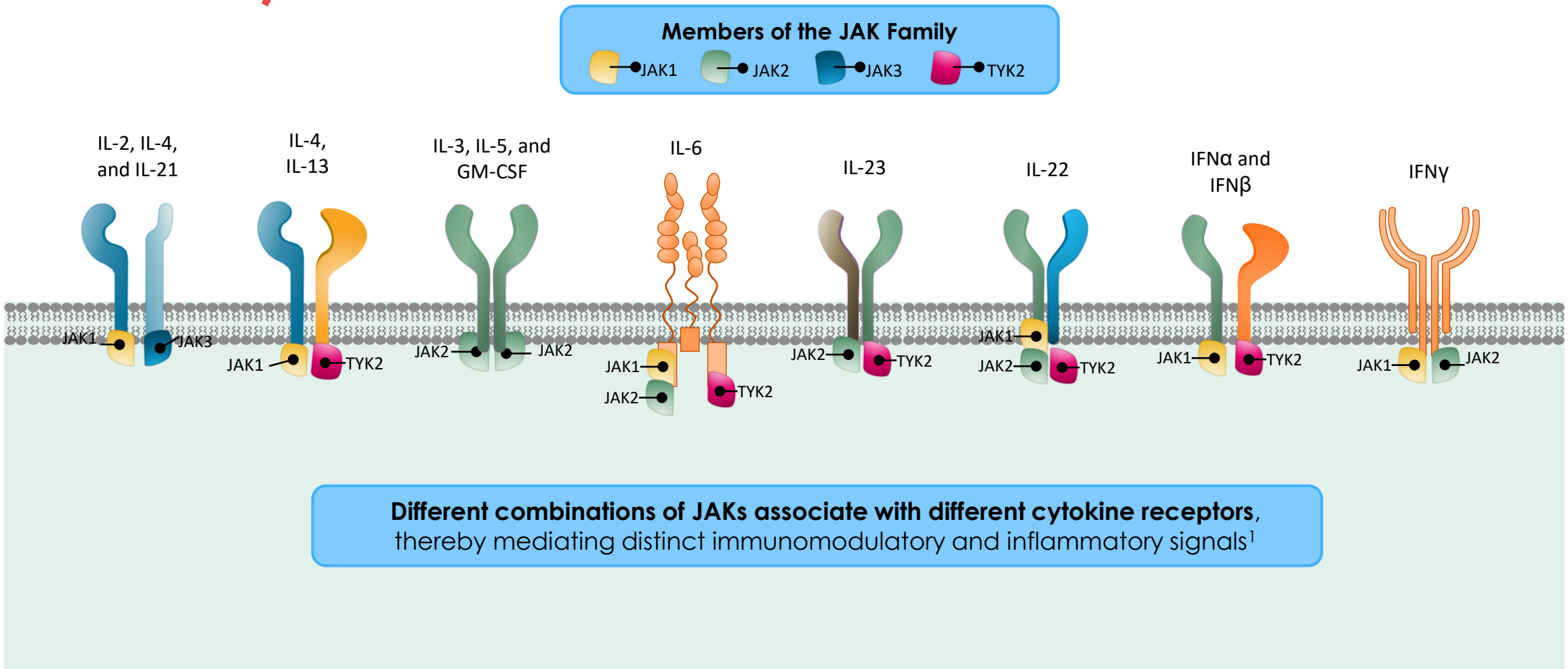
- Short-term oral corticosteroids are recommended only in acute and severe inflammation as part of a treatment plan
- An oral retinoid is the only treatment currently approved and recommended to treat patients with severe CHE who do not respond to very potent TCS.
- Phototherapy is recommended for adult patients with CHE who are refractory to TCS
  - Long-term use should be avoided due to the increased risk of skin malignancy

Off-Label Treatment Options:

- Immunosuppressive agents can be used for CHE patients who are refractory or contraindicated to first- and second-line therapy
- Oral retinoid may be considered for hyperkeratotic CHE

Thyssen JP, et al. *Contact Dermatitis.* 2022;86:357–378.

Cytokine Receptors and JAK Association



Different combinations of JAKs associate with different cytokine receptors, thereby mediating distinct immunomodulatory and inflammatory signals[1]

GM-CSF, granulocyte–macrophage colony-stimulating factor; IL, interleukin; IFN, interferon; JAK, Janus kinase; TYK, tyrosine kinase.
Adapted from Schwartz DM et al. Nat Rev Drug Discov. 2017;16:843–62.

1. Schwartz DM et al. Nat Rev Drug Discov. 2017;16:843–62. 2. Lee GR, et al. *Dermatol Ther* 2019;e12840:1–12; 3. Tanimoto A, et al. *Inflamm Res* 2015;64:41–51;

Clinical Data

Topical novel pan-Janus kinase (JAK) inhibitor in adults with severe CHE

- Treatment showed a superior reduction in Hand Eczema Severity Index (HECSI) score from baseline to week 12.[1]
- Demonstrated superiority in Investigator's Global Assessment (IGA)-CHE treatment success, Dermatology Life Quality Index (DLQI), and a lower number of treatment-emergent adverse events, compared with alitretinoin.[1]
- Significant improvements seen in all assessed CHE signs and symptoms, compared to the vehicle group.[2]
- Long-term safety profile remained consistent with previous results and patients maintained similar levels of symptom relief and treatment success over an additional 36-week treatment regimen.[3]

1. LEO Pharma Press Release. BusinessWire. January 24, 2024. https://www.businesswire.com/news/home/20240123989016/en/LEO-Pharma-Announces-Positive-Phase-3-Head-to-head-Data-Results-from-DELTA-FORCE-Trial-Comparing-Delgocitinib-Cream-With-Alitretinoin-Capsules-in-Adults-With-Severe-Chronic-Hand-Eczema-CHE.
2. Bauer A, et al. *Contact Dermatitis*. 2023 Jul;89(1):46-53.
3. LEO Pharma Press Release.. BusinessWire. October 30, 2023. https://www.businesswire.com/news/home/20231030388942/en/LEO-Pharma-Announces-Positive-Outcome-of-DELTA-3-Open-Label-Extension-Trial-of-Delgocitinib-Cream-in-the-Treatment-of-Adults-With-Moderate-to-Severe-Chronic-Hand-Eczema-CHE.

How can we optimize disease management?

- What key characteristics do you look for to differentiate AD and CHE in the clinical setting?
- How do you make a differential diagnosis?
- What are best practices for treating CHE?
- What impact will emerging therapies have on clinical practice?

Thank you!