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Eczema herpeticum in atopic dermatitis

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Abstract

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin disease leading to pruritic skin lesions. A subset of AD patients exhibits a disseminated severe HSV infection called eczema herpeticum (EH) which can cause life-threatening complications. This review gives an overview of the clinical picture, and characteristics of the patients as well as the diagnosis and therapy of EH. A special focus lies on the pathophysiological hallmarks identified so far that predispose for EH. This aspect covers genetic aberrations, immunological changes and environmental influences displaying a complex multifactorial situation, which is not completely understood. Type 2 skewing of virus-specific T cells in ADEH⁺ patients has been implicated in immune profile abnormalities, along with impaired functions of dendritic cells and natural killer cells. Furthermore, aberrations in interferon pathway related genes such as *IFNG* and *IFNGR1* have been identified to increase the risk of EH. IL-4, IL-25, and thymic stromal lymphopoietin (TSLP) are overexpressed in EH, whereas antimicrobial peptides like human β -defensins and LL-37 are reduced. Concerning the epidermal barrier, single nucleotide polymorphisms (SNPs) in skin barrier proteins such as filaggrin were identified in ADEH⁺ patients. A dysbalance of the skin microbiome also contributes to EH due to an increase of *Staphylococcus aureus*, which provides a supporting role to the viral infection via secreted toxins such as α -toxin. The risk of EH is reduced in AD patients treated with dupilumab. Further research is needed to identify and specifically target risk factors for EH in AD patients.

Atopic dermatitis (AD) is a chronic inflammatory skin disease, which is characteristically associated with intense pruritus and eczematous lesions(1). Robert Willan, an English dermatologist, was the first to describe the disease in 1808(2).. In most countries over 20% of children are affected at least once during a period of their lives(5-7). Despite the fact that 85% of all cases manifest before the age of five, AD can occur lifelong and the prevalence of AD is still high in adulthood (8-10). Surprisingly, recent data based on two birth cohorts revealed that only 38% of adult AD patients in the UK reported a childhood onset of symptoms(11).

Patients suffering from AD are prone to viral and bacterial infections(7). *Staphylococcus aureus* (*S. aureus*) infections are particularly common in AD patients, leading to superinfection(12).

Viral infections in AD

Regarding viral infections, herpes simplex virus (HSV), molluscum contagiosum virus (MCV), human papillomavirus (HPV), coxsackieviruses, and vaccinia virus (VV) lead to disseminated clinical rashes in patients with AD. The nomenclature of the rash matches the causative virus: eczema herpeticum (EH), eczema molluscatum, eczema verrucatum, eczema coxsackium (EC) and eczema vaccinatum (EV), respectively(13). Whilst disseminated HPV and MCV infections are largely harmless, EH and EV affect around 7-10% of AD patients and can lead to serious life-threatening complications (14,15). AD patients suffer more often from upper respiratory infections, chest cold, and influenza than healthy individuals (16,17). Of note, no increased prevalence of COVID-19 has been reported so far. The treatment with dupilumab, an antibody directed against the α -chain of IL-4 and IL-13 receptors, appears to reduce the risk for EH(18,19). Additionally, no increased risk for COVID-19 infection was seen in AD patients treated with dupilumab(20,21).

HSV and eczema herpeticum

Herpes simplex viruses are strict human pathogenic viruses affecting mainly skin and mucosa. They can be distinguished into HSV-1 and HSV-2(22). HSV-1 primarily affects labial and oral regions whereas HSV-2 most commonly affects the genital area. HSV-1 and 2 persist in sensory

neurons, most notably in cells of the trigeminal ganglion for HSV-1 (23), but also in the ciliary ganglion(24), superior cervical ganglion, thoracic ganglia and the ganglion of the vagus nerve(25,26).

HSV, which can induce recurrent herpes febrilis in healthy subjects, is able to cause a disseminated skin infection in patients with AD (14). This was first described in 1887 by the Hungarian dermatologist Moritz Kaposi with the term “eczema herpetiforme”(27). The initial name “herpetiforme” arose not from the knowledge that the disease is caused by a herpes virus but the greek meaning of “herpein”, meaning “creeping”. EH is also known as “pustulosis acuta varioliformis” based on a publication of the German dermatologist Fritz Juliusberg in 1898(28). Likewise, the term “Kaposi’s varicelliform eruption” was used in this context as well(29). Generalized HSV skin infections have also been reported in several other diseases. In order to group them, they may be subdivided according to whether they occur in diseases with predominant skin malfunctions or those with hematological/immunological aberrations (see table 1). Concerning skin diseases, EH has often been reported in Darier’s disease in addition to AD(30-33).

Case histories have also been published for a variety of other skin diseases such as epidermolysis bullosa simplex (34), pemphigus foliaceus (35), Hailey-Hailey disease (36), pityriasis rubra pilaris(37), irritant contact dermatitis(38), staphylococcal scalded skin syndrome (39), Grover’s disease(40), psoriasis(41), rosacea(42), patients with skin grafts(43), trauma(44), cosmetic procedures such as follicular hair unit extraction(45), and severe burns (46,47). EH has also been described in two patients with ichthyosis vulgaris and a history of AD. Interestingly, in these cases EH appeared in a period when AD was absent, which has led to a controversial discussion on ichthyosis vulgaris as a possible risk factor for EH.(14,48,49). Hematological diseases affecting immune cells with a report of EH cover the spectrum of cutaneous T cell lymphoma(50), Sézary disease(51), Hodgkin’s disease(52), multiple myeloma(53) and Wiskott-Aldrich syndrome(54). EH was reported in an immune suppressed patient treated with everolimus for a metastatic renal cell carcinoma(55) and in a patient with a phenytoin-induced drug rash(56). It should be mentioned that the diagnosis of a history of AD has not been carried out very carefully in some of these works. Regarding AD, the disease contains immunological abnormalities as well as a disturbed skin barrier. Skin damaging factors such as contact sports can contribute to the eruption of EH in AD

patients(57). Laser resurfacing was described as a possible additional trigger of EH in a HIV positive patient(58).

Clinical picture and patients' characteristics

The clinical manifestation of EH is characterized by disseminated non-grouped vesicular eruptions and pustules on erythematous lesions, preferentially affecting the head, neck, chest and arm (see figure 1). These vesicles potentially lead to erosions after 2-7 days(59-61). The skin morphology is often accompanied by general symptoms such as fever, malaise, and headache along with lymphadenopathy(62,63). Furthermore, the clinical picture can be exacerbated by bacterial superinfections, most notably with streptococci and staphylococci(64,65). It was shown that patients suffering from acute EH exhibit lower levels of lymphocytes and higher levels of monocytes(66). EH can be accompanied by herpes encephalitis or hepatitis, which can also occur in immune competent patients (67,68). Additionally, EH is also reported in pregnancy(69).

At least 20% of EH patients report recurrent herpes infections in their medical history. In a smaller group of patients the recurrent HSV infections appear generalized (70). Recently, Seegräber et al. published a retrospective European multicenter study analyzing 224 EH cases that identified a recurrence rate of 26.5% (71). Recurrence was associated with an earlier onset of AD; however, no differences were seen concerning total IgE. Many patients exhibited AD lesions without EH, yet skin absent of AD lesions was never affected by herpetic lesions(71). Wheeler et al. demonstrated that recurrent EH is less severe compared to the first manifestation (72). The mean age of adult EH patients was estimated at 22.5 years (73,74). In 1985 Wutzler et al. provided the information that the majority of EH was due to HSV-1 infection (75), which is often confirmed by the experiences of most clinicians, however, no current data of the distribution between HSV-1 and HSV-2 in EH is available. Patients with AD and EH have a significantly earlier onset of AD(73,74). Increased total IgE levels, asthma frequency and sensitizations to aeroallergens, food and *Malassezia sympodialis* indicate stronger type 2 immune responses (15,76).

A case report published by Lübke et al. documented EH in two AD patients using the topical immunomodulatory substance tacrolimus (77), although this was not evident in studies of tacrolimus using larger cohorts (78). Treatment of AD with corticosteroids was not identified as

a risk factor following a cohort study by Wollenberg et al. This study was also unable to identify any significant seasonal differences in the incidence of EH (74). However, a slight accumulation of cases in winter and spring was observed in other studies (13,73). Accordingly, Rerinx et al. suggested an association between increased AD severity in these seasons and the slightly increased occurrence (79). Furthermore, ADEH⁺ patients seem to exhibit a general susceptibility for pathogens as they manifest cutaneous infections with MCV or *S. aureus* more often than ADEH⁻ patients (15).

Diagnosis and differential diagnosis

EH is often diagnosed clinically, yet established criteria for its diagnosis are not currently available. Diagnosis can be reinforced by the high sensitive detection of HSV-DNA by means of the polymerase chain reaction (PCR) allowing the discrimination of HSV type 1 and 2 (14,80). PCR is, however, unable to differentiate between active virions and virus proteins. Detecting HSV in virus culture can prove active virions, however, this requires 60-130 additional hours compared to PCR (81). The use of indirect immunofluorescence to detect HSV antigens is regularly applied (82). Additionally, methods such as direct detection of HSV by electronic microscopy or Tzanck test are also available, but rarely used (72). The latter represents a practical and quick method that shows giant viral multinucleated cells, but is not frequently performed due to the comprehensive availability of PCR and the lack of specific detection of HSV. Tzanck test cannot differentiate HSV and varicella-zoster virus (VZV) infections of the skin. A histological analysis of a punch biopsy shows signs of an HSV infection as the virus induces a cytopathic effect in the keratinocytes as well as multinuclear giant cells with intranuclear inclusions.

Concerning the diagnosis based on clinical morphology, EH can be confused with EC, a recently described complication of coxsackie infection in AD patients (see Figure 2) (83). EC is most commonly caused by coxsackievirus A6. In 2013 Mathes et al. proclaimed vesicles and erosions in areas of AD as clinical hallmarks for EC. Additionally, coxsackievirus A6 associated eruptions provide several further clinical characteristics: widespread vesiculobullous and erosive eruption, a Gianotti Crosti-like eruption with acrofacial papulovesicles and erosions, a petechial and purpuric rash and delayed cutaneous manifestations as acral desquamation (83). In the case of an unclear clinical picture, diagnostic PCR from skin lesions for both HSV and enteroviruses

isrecommended. Additionally, bacterial superinfections can mimic EH or severe manifestation of AD with intense excoriated papules can imitate erosive non-grouped vesicles.

Lacking clinical diagnostic criteria for EH, hallmarks are listed to guide diagnosis (see table 2):

1. Non-grouped vesicular eruptions
2. Vesicles and erosions focused on predominant AD lesions (cubital and popliteal fossa, head, neck)
3. Fever, malaise
4. EH episode in the patient history

In conclusion, in most cases EH can be diagnosed based on clinical characteristics. In order to assure the diagnosis, a pursuing diagnostic, PCR in particular, is recommended (see figure 3).

Pathophysiology of EH in AD

The pathophysiology of AD involves genetic aberrations, immunological changes and environmental influences amounting to a complex multifactorial disease. Figure 4 shows the different hallmarks of AD predisposing for EH.

Skin barrier

Regarding the structural skin abnormalities, manifold investigations have analyzed loss-of-function mutations of the filaggrin gene (*FLG*) as a major genetic risk factor for AD. This gene encodes a protein which is not only essential for a functional skin barrier, but also for the homeostasis of the epidermis (84). Mutations of this gene lead to a threefold risk of developing AD (85). Interestingly, a *FLG* loss-of-function mutation can be detected in up to 50% of AD patients, yet around 42% of heterozygous carriers do not manifest the disease (84,86,87). Filaggrin is downregulated in AD lesions, even in patients without a *FLG* mutation as type 2 inflammatory mediators, such as IL-4, IL-13, and IL-22 decrease the expression of filaggrin (88). Analysis by Gao et al. of 112 AD patients with a history of EH (ADEH⁺) compared to those without (ADEH⁻) demonstrated that the filaggrin mutation *FLGR501X* raises the risk for EH three times (OR: 3.4, 95% CI: 1.7-6.8) (89). This observation was present in European American patients as well as African Americans. When combined with a 2282del4 mutation the risk for EH is ten times higher

compared to AD patients without these mutations (OR: 10.1, 95% CI: 4.7-22.1). Both R501X and 2282del4 depict two common loss-of-function mutations in the AD population. As acquiring both FLG R501X and 2282del4 was observed to be associated with an increased eczema area severity index (EASI), one might argue that susceptibility relates to disease severity. However, when restricting the analysis on ADEH⁺ patients, the association of the mutations with higher EASI values was absent. Therefore, a severity independent mechanism, likely based on a skin barrier dysfunction leading to a more unrestrained viral spread, may be speculated (89). Regarding filaggrin, Kim et al. analyzed skin biopsies of ADEH⁺, ADEH⁻ and healthy individuals. IL-25 was augmented in ADEH⁺ skin compared to ADEH⁻ and healthy skin biopsies. Furthermore, it has been shown that HSV-1 replication is enhanced as an indirect result of IL-25 inhibiting filaggrin expression (90).

Besides filaggrin, claudins, which take part in the determination of tight junctions' resistance, were identified to be associated with AD. It was shown by gene expression analysis that claudin-1 and -23 are expressed in lower amounts in AD patients compared to healthy individuals (91). De Benedetto et al. identified specific single nucleotide polymorphisms (SNP) in *CLDN1* associated with EH: In European American ADEH⁺ patients rs3774032 (OR = 0.44, 95% CI: 0.22-0.85) and rs3732923 (OR = 1.93, 95% CI: 1.21-3.07) (91) and in African-Americans rs3954259 (OR = 2.16, 95% CI: 1.02-4.59). Silencing of Claudin-1 by siRNA, and a subsequent reduction of >50% of transcripts, mirrored the conditions of AD skin. It was shown that keratinocytes with silenced claudin-1 were more susceptible to infection with HSV-1 in an *in vitro* approach (91).

Pertaining to the skin barrier, several risk factors for the development of EH were identified in AD patients that may enable the identification of patients at risk of EH and allow intervention with specific preventive approaches.

Immune system and the role of AD typical type 2 immune response

The immune response in AD is characterized by T helper (Th) 2 cell-driven inflammation (1). Raychaudhuri et al. were the first to investigate the role of Th2 cytokines in viral defense, showing that IL-4 increases the extent of cytopathic effected cells in HSV infected cell culture and decreases the production of IFN- γ (92). Several studies emphasized the enhanced replication of the virus in the presence of IL-4 and IL-13 and the worsening of HSV infections under the influence of IL-4 in animal models (90,93).

Additionally, it was shown that IL-4 and IL-13 downregulate filaggrin, which may contribute to viral susceptibility as previously described (90). IL-4 and IL-13 act via the signal transducer and activator of transcription (STAT)6, which itself plays a role in the adaptive immune system(94,95). Howell et al. compared 20 ADEH⁺ patients with 55 ADEH⁻ patients demonstrating that *STAT6* SNPs (rs3024975, rs841718, rs167769 and rs703817) were associated with EH ;The haplotypes rs167769 and rs324013 increased the risk for EH three times (OR: 3.33, 95% CI: 1.39–8.55)(96).

Analysis of the epigenome in AD patients with EH identified several sites of the genome with significant differential methylation when compared to healthy controls (97). Interestingly, two differentially methylated CpGs were revealed to be associated with IL-4 and IL-13 in AD patients; ADEH⁺ and ADEH⁻ patients, however, could not be distinguished based on these findings.

T cells are central to cell-mediated adaptive immunity and have been characterized in AD lesions in detail. Type 2 polarization is an important hallmark of the T cell infiltrate in AD lesions. Investigating the T cell mediated anti-viral immune response in AD patients, we recently showed that T cell lines from ADEH⁺ individuals reactive to HSV antigens secrete higher levels of IL-4 as compared to healthy individuals(98). Investigation of antigen activated CD154⁺ subsets in ADEH⁺ patients revealed that increased frequencies of HSV-specific Th2 cells were present. Moreover, these patients were found to have elevated HSV-1-specific cytotoxic (Tc) 2 cells and decreased numbers of Tc1 cells. Additionally, elevated expression of IL-4 by HSV-1-specific T cells was observed upon staining with HSV-1-specific MHC class I tetramers(98).

In addition to Th and Tc cells, the role that regulatory T cells (Tregs) might have in ADEH has also gained interest over the last decade. Tregs are a subset of CD4⁺ T cells characterized by immunosuppressive properties. In particular, induced Tregs (iTregs) with skin-homing capacity were increased in patients with acute EH compared to ADEH⁻ patients. Analysis of their role in ADEH⁺ patients has shown that their suppressive capacity to inhibit proliferation of effector T cells is similar to that of healthy individuals. Investigating the cytokine expression of different lymphocyte subsets revealed reduced IFN- γ and TNF- α production in acute ADEH⁺ by T helper cells, cytotoxic T cells, and NK cells compared to healthy controls. As the depletion of Tregs from

HSV-1 infected PBMCs restored the production of IFN- γ , it was hypothesized that Tregs may contribute to the initiation and progression of EH in AD patients(99).

As previously mentioned, IL-4 and IL-5 are upregulated in acute AD lesions, leading to a decrease in IFN- γ production (14,75). With the knowledge that IFN- γ plays a decisive role in viral defense, its reduction may induce susceptibility to HSV(100,101). Additionally, serum levels of IFN- γ were found to be reduced in AD patients, although it is worth noting that IFN- γ was reduced in both ADEH⁺ and ADEH⁻ subjects (76). Furthermore, significantly decreased levels of IFN- γ in T cell lines of AD patients, particularly ADEH⁺ patients, were observed following stimulation with HSV proteins and peptides(98). In addition, transcriptome analyses of PBMCs from ADEH⁺ patients displayed a reduced IFN- γ and IFN- γ receptor gene expression compared to ADEH⁻ patients (86).

Gao et al. investigated the interferon-pathway in ADEH⁺ patients in detail by sequencing relevant genes (*IFNG*, *IFNGR1*, *IFNAR1* and *IL12RB1*) (102) and subsequently delineated six rare missense-mutations in *IFNGR1* located on chromosome 6 (Val14Met, Val61Ile, Val264Ile, His335Pro, Tyr397Cys and Leu467Pro). These mutations were associated with an IFN- γ Receptor 1 deficiency predisposing for EH in AD patients. These results underlined the finding of Leung et al. showing an increased risk for EH in patients with specific IFN- γ and *IFNGR1* SNPs (86). Of note, Gao et al. identified seven common *IFNGR1* SNPs (rs11914, rs17175127, rs1327475, rs10457655, rs7749390, rs2234711 and rs28515059) to be accompanied with a reduced risk for EH.

Beside the IFN- γ receptor 1, interferon regulatory factors (IRF) play an important role as transcription factors in intracellular signaling pathways. By analyzing the transcriptome of PBMCs after HSV-1 stimulation, Bin et al. revealed that IRF3 and IRF7 are downregulated in ADEH⁺ patients in comparison to ADEH⁻ and healthy individuals (103). This led to a downstream decrease in expression of type I and type III interferon genes. Additionally, Bin et al. showed that ankyrin repeat domain 1 (ANKRD1) is reduced in PBMCs of ADEH⁺ patients (103). Upon further investigation, it was shown that ANKRD1 forms a protein complex with IRF3 and IRF7, contributing to an anti-viral innate immune signaling pathway(104). Moreover, several SNPs in the IRF2 encoding gene, depending on ethnic background, are associated with a higher risk of

developing EH(105). In conclusion, numerous gene expression patterns and SNPs were determined to lead to an impaired IFN-signaling pathway, resulting in a weakened viral defense.

In addition to *IFNGR*, human leukocyte antigen (HLA) is also encoded by chromosome 6. Interestingly,HLA B7 was identified to be associated with EH, approximately doubling the risk of developing the condition(OR: 1.91,95% CI: 1.10-3.31)(106).

Regarding other immune cells, a decreased amount of plasmacytoid dendritic cells can be detected in AD. These cells are known as physiological producers of IFN- α and β , and thus, take part in viral defense. The reduced presence of plasmacytoid dendritic cells in the skin may therefore lead to a higher susceptibility to HSV(107). Indoleamine 2,3-dioxygenase(IDO1), a tryptophan catabolizing enzyme, is a product of dendritic cells. Analyzing the role of IDO1 in ADEH⁺ patients, Staudacher et al. revealed an increased activity of IDO1 during acute EH(108). Additionally, increased IDO1 expression and activity was revealed in Langerhans cells(LC) from ADEH⁺ patients and acute EH individuals. Stimulating ADEH⁺ patient-derived LC in vitro resulted in an exaggerated IDO1 expression and activity. Notably, IDO inhibits T-cell proliferation and IFN- γ production, meaning the increased IDO1 activity in ADEH⁺ patients may contribute to HSV susceptibility (109).

Furthermore, skin-derived antimicrobial peptides (AMP) are involved in local protection against pathogens, e.g., viruses and bacteria. Interestingly, some of these AMPs are reduced in AD patients (110,111). Howell et al. demonstrated that, in antiviral assays, the AMP LL-37 in particular exhibited anti-HSV activity(112). ADEH⁺ patients express significantly lower levels of LL-37 in their skin, which may contribute to HSV susceptibility (112). Notably, an inverse correlation of total IgE and LL-37 was detected identifying a possible surrogate parameter.

Furthermore, the keratinocyte-derived thymic stromal lymphopoietin (TSLP), which stimulates DCs to induce Th2 cell polarization was analyzed by Gao et al. (113). Investigating the TSLP pathway, an association between SNPs in the TSLP gene and the appurtenant receptors(IL7R and TSLPR) and an increased or decreased probability of EH in AD patients was demonstrated when comparing ADEH⁺ and ADEH⁻ patients (113).

Concerning the innate immune system, Kawakami et al. developed an EH mouse model with which they revealed a reduced Natural Killer (NK) cell activity. In their model, mice demonstrated diminished levels of granzyme B⁺ NK cells, IFN- γ ⁺ NK cells and perforin⁺ NK cells alongside low

level of granzyme B(114). However, no differences regarding numbers of mature cytolytic NK cells between EH mice and healthy mice were detected. Of note, it was recently shown that ADEH⁺ patients also exhibit reduced numbers of NK cells and a diminished ability to produce granzyme B following stimulation (115).

Most recently, Cabanillas et al. reported elevated levels of HSV-1-specific IgE in ADEH⁺ patients compared to ADEH⁻ and healthy individuals (116). In more than 50% of these patients, HSV-1 specific IgE recognized glycoprotein D, viral protein 22 and to a lesser extent glycoprotein B. Interestingly, it was shown in a mouse model that the sensitization with the first two proteins induces IL-4 as a cytokine response.

The microbiome of the skin is known to be an important contributing factor to the development of EH in AD (117). AD lesions are characterized by a dysbiosis due to a rise of *S. aureus* and a reduction of commensal skin bacteria (118). ADEH⁺ patients suffer from cutaneous infections with *S. aureus* more frequently than both ADEH⁻ and healthy individuals (78% vs. 29% vs 0%), as shown in a study with 134 ADEH⁺ patients (15). *S. aureus* produces a multitude of different toxins, among them the pore-forming α -toxin as well as the staphylococcal enterotoxins (SEs) SEA, SEB, SEC, SED, SEE, and SEI and toxic shock syndrome toxin 1 (TSST-1). IgE specific to SEA, SEB and TSST-1 can be identified in half of ADEH⁺ patients, whereas it is only identifiable in 20% of ADEH⁻ patients (15). Bin et al. analyzed the effect of the α -toxin, SEB, and TSST-1 on viral susceptibility of keratinocytes and observed an increase in HSV-1 replication following 24h stimulation of keratinocytes with α -toxin (119). These effects were absent under the influence of SEB and TSST-1. In line with this, infection of a VV infected mouse model with an α -toxin deficient strain of *S. aureus* led to a decrease of VV infection severity when compared to wild type *S. aureus*. The pathomechanism seems most likely to depend upon the binding of α -toxin to ADAM10, the disintegrin and metalloprotease 10 receptor, as the silencing of the *ADAM10* gene expression by siRNA inhibited the *S. aureus* induced HSV-1 and VV enhancement.

Regarding external factors, the virus itself has an impact on the development of EH. Two out of 35 genotypes of HSV-1 strains (F1 and F35) were identified to occur mostly in EH patients (120,121).

In conclusion, a variety of genetic polymorphisms as well as different skin and immunological abnormalities were identified that may contribute to an increased susceptibility of a subgroup of

AD patients. A detailed analysis of the barrier – immune system – virus interaction would help to understand the complete pathophysiology.

Therapy

Before the invention of acyclovir, also known as 9-(2-hydroxyethoxymethyl) guanine, in 1978, 10-50% of EH ended fatally, because the treatment with immunoglobulins and immune-stimulating agents was often not sufficient to cure the infection(72,122,123). EH responds effectively to acyclovir, which is nowadays considered as a gold standard treatment for the condition(79). It should be given in a dose of 5-10 mg/kg intravenously for 7 days (see figure 3). The dosage depends on the extent of the manifestation, comorbidities, and complications e.g. encephalitis and immune status. Recurrent flares of EH are often less severe, thus may be treated with valacyclovir 1000mg TID orally for 7 days. Immunocompromised patients have been reported to suffer more frequently from acyclovir-resistant HSV strains (124). In cases of acyclovir resistant HSV strains, foscarnet is recommended for treatment(14). Topical treatments are focused on the prevention of secondary infections, e.g. by *S. aureus*. Therefore, topical antimicrobial substances such as octenidine are suggested. Additionally, adequate analgesia is advised.

Concerning the concurrent use of immunosuppressants, manufacturers' data advises to discontinue methotrexate, mycophenolate mofetil, and cyclosporine in case of severe infections such as EH. Systemic steroids should be reduced during EH if possible. Regarding dupilumab, one may argue continued treatment based on the fact that IL-4 and IL-13 are not necessary for viral response and may even be counterproductive. The manufacturer advises to stop the dupilumab treatment when helminth infections occur; however, no recommendation is given concerning HSV infections.

Several new therapeutic drugs targeting AD are currently under investigation. One of the most promising molecule groups are Janus kinase (JAK) inhibitors (125). As JAK1 and 2 also play an important part in the intracellular signaling of the IFN-pathway, the frequency of EH in patients treated with JAK inhibitors will be interesting to monitor, especially given the importance of IFN pathway aberrations in EH patients. Baricitinib (JAK1/2 inhibitor), tofacitinib (JAK1/3 inhibitor), and upadacitinib (selective JAK1 inhibitor) are already approved for use in treating rheumatoid arthritis and, additionally, tofacitinib for ulcerative colitis. Bechman et al. analyzed the risk of severe infection following JAK inhibitor treatment in a meta-analysis of 21 placebo-controlled

phase II and III studies (126). Focusing on herpes zoster infections, this meta-analysis identified the incidence rate ratio (IRR) of baricitinib vs placebo as 2.86 (95% CI: 1.26, 6.50) in patients with rheumatoid arthritis, whereas no significant IRRs were measured for the other two JAK inhibitors (126). Of note, in a retrospective study of 8030 tofacitinib patients, combined treatment of tofacitinib and oral glucocorticoids increased the risk for herpes zoster by a factor of two (HR 1.96, 95% CI 1.33-2.88) in contrast to tofacitinib with methotrexate (HR 0.99, 95% CI 0.64-1.54) (127). (127,128). Additional studies, especially post-approval surveillance, are needed to comprehensively evaluate the risk for herpes infections in JAK inhibitor treated patients.

For AD, some recent phase II or phase III studies have been communicated as full papers for baricitinib, upadacitinib, and abrocitinib (129-133). So far, no significant increases have been observed for EH or other herpes infections with any of these JAK inhibitors in those studies. It should be mentioned, however, that a history of EH was defined as an exclusion criterion in most of the studies. Additionally, studies on efficacies of novel drugs are usually underpowered with respect to the evaluation of rare adverse events. In the regulatory text of baricitinib, which has been approved in the European Union for AD in November 2020, a history of EH is not included as a contraindication. However, JAK inhibitors should be used with caution in ADEH⁺ patients.

Prevention and outlook

Primary prevention in the context of EH in AD patients would require the prevention of initial HSV infection. A possible approach to achieve this would be the vaccination of AD patients against HSV. In the last three decades, immunization against HSV has been the focus of a multitude of publications. A pivotal protein synthesized by herpes simplex viruses is glycoprotein D, which is encoded in both HSV types but not VZV (134). A vaccination containing glycoprotein D was brought to clinical trials for the prevention of genital HSV-1 and HSV-2 infections in seronegative women. The vaccine, whilst successful against HSV-1, did not provide protection against HSV-2 (135). Recent studies investigating an HSV live attenuated vaccine demonstrated effectiveness in a guinea pig genital HSV-2 infection model (136).

As described above, a multitude of genetic aberrations have been identified that predispose for EH in AD patients. The use of genetic sequencing to identify AD patients at risk of developing EH may be part of a prevention strategy in the future.

Our recent results revealed a type 2 skewing of virus-specific T cells in ADEH⁺ patients; most notably an increase in IL-4(98). Fleming et al. provided a meta-analysis investigating the risk of EH during treatment with dupilumab, a human monoclonal IgG4 antibody targeting the α -chain of the IL-4 and IL-13 receptor(137). This study, which included eight randomized controlled trials with 2706 participants in total, identified a risk reduction of nearly 70% for EH in dupilumab treated AD patients, yet no risk reduction was shown for overall herpesvirus infections(19). Further investigation is needed to determine whether the decreased risk of developing EH upon treatment with dupilumab is based on an improvement of the skin, the reduced type 2 polarized inflammation in the skin, or both. This may lead to the hypothesis that dupilumab, or other anti-type 2 inflammation drugs, can be used for tertiary prevention of EH in patients with recurrent episodes, or even perhaps as secondary prevention in patients with an increased risk. Nowadays, a prophylaxis with acyclovir 200mg twice daily or valaciclovir 500 mg per day over several months is recommended in ADEH⁺ patients with recurrent episodes(14,138).

In conclusion, EH depicts a severe complication in patients with AD. It is caused by specific barrier dysfunctions as well as immunological aberrations such as a type 2 skewing of virus specific T cells and a malfunction of the IFN-pathway. Additionally, a detailed understanding of the contributing genetic factors may lead to the ability to identify AD patients at risk of developing EH. New therapeutic approaches such as dupilumab or other anti-type 2 inflammation drugs may represent a specific prevention measure, particularly in patients with recurrent EH episodes.

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Accepted Article

Skin Barrier		Immune System	
Darier's Disease ⁺	(30-33)	Cutaneous T Cell Lymphoma ⁺	(50)
Epidermolysis Bullosa Simplex ⁺	(34)	Sézary Disease	(51)
Pemphigus Foliaceus ⁻	(35)	Hodgkin's Disease ⁻	(52)
Hailey-Hailey Disease ⁻	(36,139)	Multiple Myeloma ⁺	(53)
Pityriasis Rubra Pilaris ⁺	(37)	Wiskott-Aldrich Syndrome ⁻	(54)
Irritant Contact Dermatitis ⁺	(38)	Immune Compromised Patients ⁻	(55)
Staphylococcal Scalded Skin Syndrome ⁺	(39)		
Grover's Disease ⁺	(40)		
Psoriasis ⁺	(41)		
Rosacea ⁺	(42)		
Patients With Skin Grafts ⁺	(43)		
Burns ⁻	(46,47)		
Trauma ⁻	(44)		
Cosmetic Procedures ⁻	(45)		
Ichthyosis ⁻	(48)		
atopic dermatitis			

Table 1: Diseases associated with eczema herpeticum. The dichotomic differentiation is provided for a better overview. ⁺:Virus was proved by culture, PCR or immunofluorescence.
[±]: Diagnosis was based on clinical appearance and/or Tzanck test.

Clinical Characteristics

1. Non-grouped vesicular eruptions
2. Vesicles and erosions focused on predominant AD lesions
3. Fever, malaise
4. EH episode in the patient history

Diagnostic Tests

- HSV PCR
- Virus culture
- Virus protein detection in the skin by labeled antibodies (immunofluorescence)
- Electronic microscopy
- Tzanck test
- Histology

Table 2: Clinical features and diagnostic tests. Eczema herpeticum displays a typical clinical morphology and features. To underline the diagnosis different diagnostic tests are available.

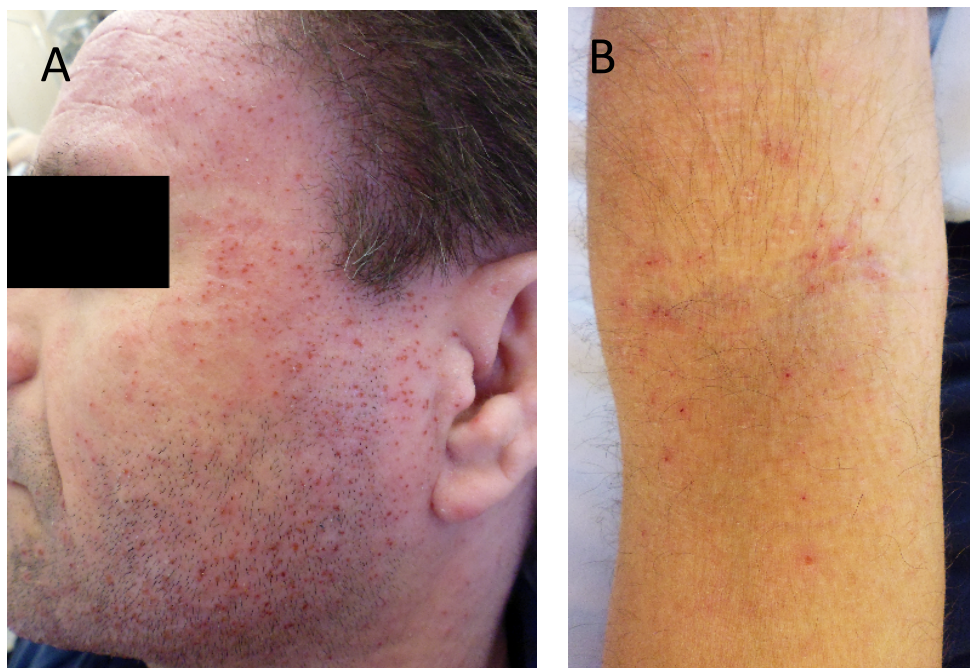


Figure 1. Characteristic efflorescences of an eczema herpeticum. Typical scattered erythematous erosions and vesicles presented by a 41-year-old patient with a history of AD. (A) Lesions on the face left lateral (B) Generalized HSV infections manifests in the right cubital fossa.

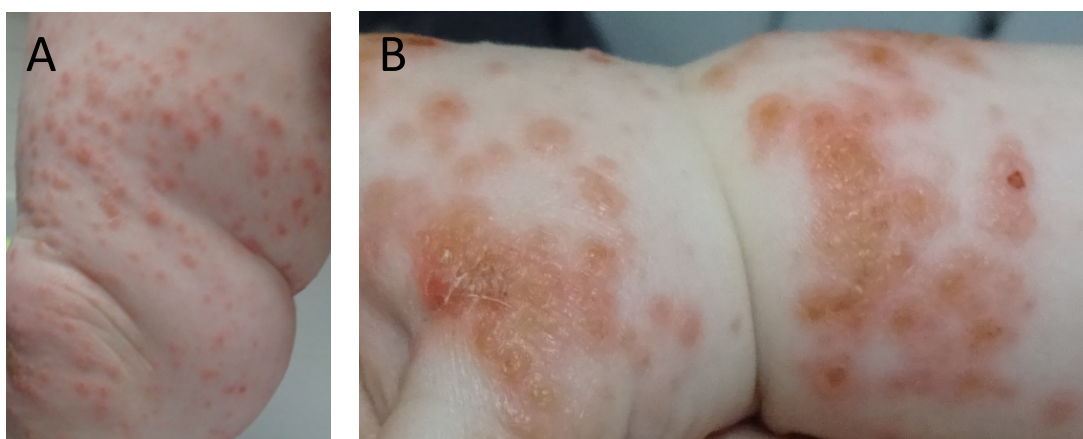
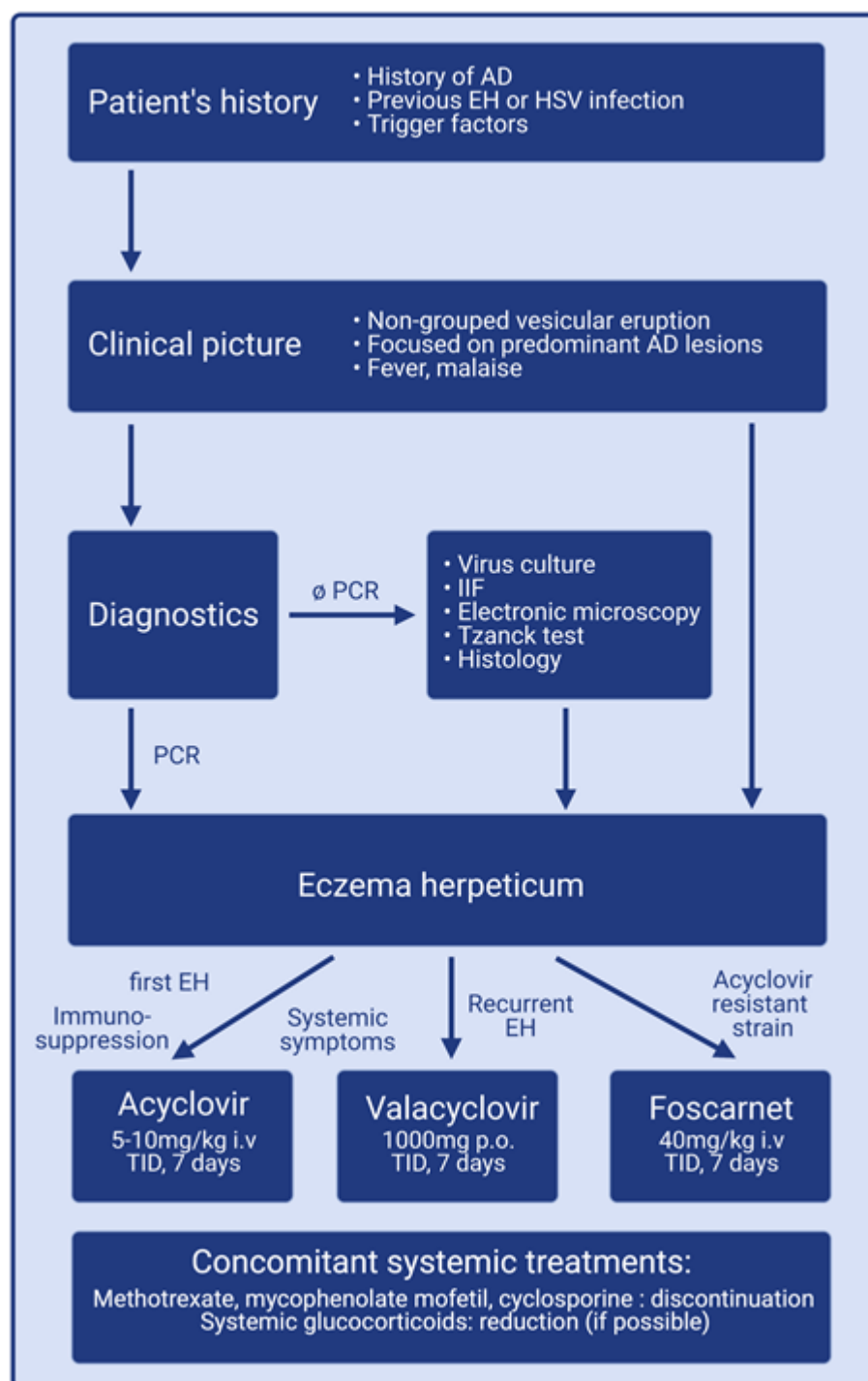


Figure 2. Characteristic efflorescences of eczema coxsackium. Typical vesiculobullous eruption in a young child with EC at the leg (A) and the hand and forearm (B) (kindly provided by PD Dr. Hagen Ott).

**Figure
Possible**



3.

diagnostic and therapeutic algorithm for clinical practice. PCR is recommended to support the diagnosis of EH. The standard therapy is acyclovir given intravenously for 7 days, however, in recurrent EH an ambulant therapy with valacyclovir depicts a possibility. Foscarnet is the alternative for HSV strains resistant to acyclovir. AD: atopic dermatitis, EH: eczema herpeticum, IIF: indirect immunofluorescence, MMF: mycophenolate mofetil, MTX: methotrexate.

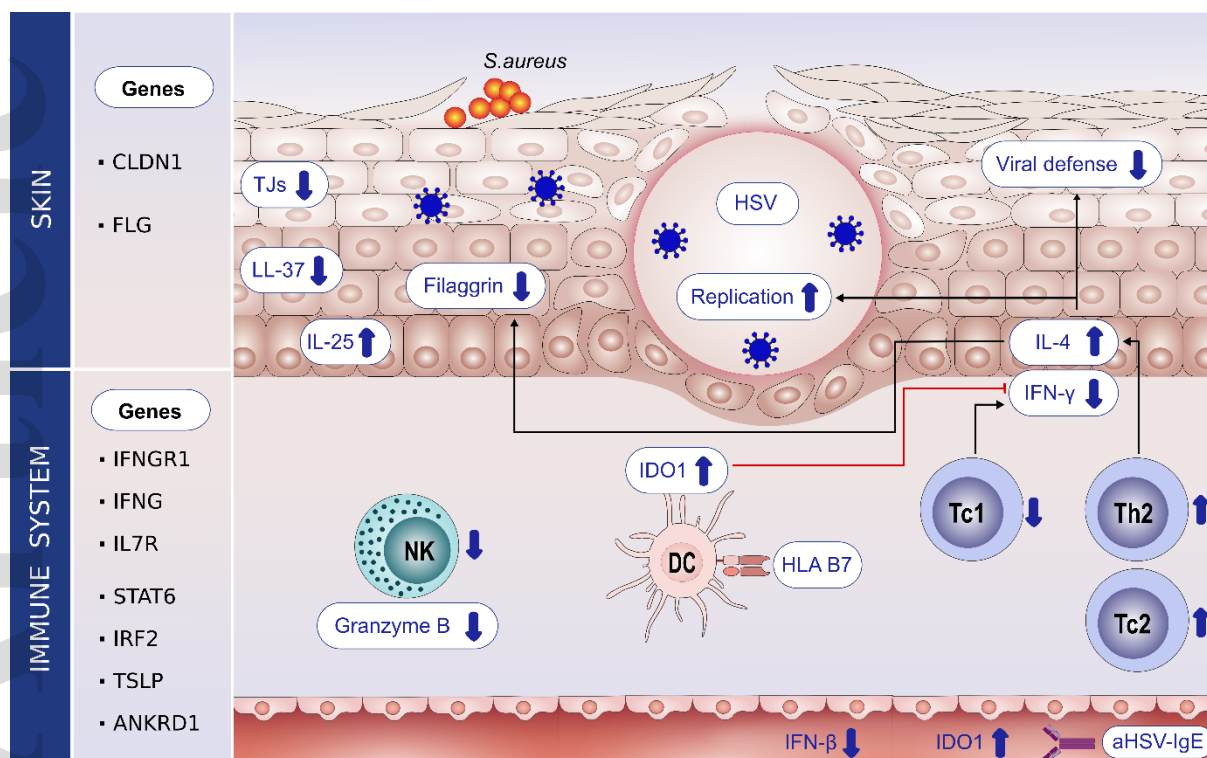


Figure4. Molecular and genetic characteristics of EH patients leading to viral susceptibility.

Abnormalities in the immunological response, skin barrier dysfunction, and environmental factors contribute to the complex pathogenesis of EH. ANKRD1: ankyrin repeat domain 1, CLDN1: claudin 1, DC: dendritic cell, FLG: filaggrin gene, HSV: herpes simplex virus, IDO1: indoleamine 2,3-dioxygenase, IFN: interferon, IFNGR1: interferon γ receptor 1, IRF: interferon regulatory factors, NK: natural killer cell, *S. aureus*: Staphylococcus aureus, STAT: signal transducer and activator of transcription, Tc: cytotoxic T cell, Th: T helper cell, TJs: tight junctions, TSLP: thymic stromal lymphopoietin.