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BRIEF REPORT

History of *S. aureus* Skin Infection Significantly Associates with History of Eczema Herpeticum in Patients with Atopic Dermatitis

Mary C. Moran · Alanna Klose · Takeshi Yoshida · Anna De Benedetto · Lynda C. Schneider · Peck Y. Ong · Eric L. Simpson · Donald Y. M. Leung · Benjamin L. Miller · Christopher L. Seplaki · Lisa A. Beck

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ABSTRACT

Introduction: Patients with atopic dermatitis (AD) are uniquely susceptible to a number of serious viral skin complications, including eczema herpeticum (EH), caused by herpes simplex virus. This study explored the associations between biomarkers of epithelial barrier dysfunction, type 2 immunity, *Staphylococcus aureus* infection, and *S. aureus*-specific immunoglobulin responses in a cohort of AD subjects with and without a history of EH (EH+ and EH−, respectively).

Methods: A total of 112 subjects with AD (56 EH+, 56 EH−), matched by age and AD severity, were selected from a registry of over 3000 AD subjects. Logistic regression was used to test the association between history of *S. aureus* skin infection and history of EH, while controlling for a number of confounders.

Results: Compared to those without a history of *S. aureus* skin infection, subjects with a history of *S. aureus* skin infection were found to have more than sixfold increased odds of having a history of EH (6.60, 95% confidence interval [CI]: 2.00–21.83), after adjusting for history of other viral skin infections (molluscum contagiosum virus, human papillomavirus), serum total IgE, and IgG against the *S. aureus* virulence factor SE*l*X.

Conclusions: These findings indicate an important relationship between *S. aureus* skin infections and EH.

Keywords: Atopic dermatitis; *S. aureus*; Eczema herpeticum; Viral skin infections; Immunoglobulins

M. C. Moran · A. Klose · T. Yoshida · A. De Benedetto · B. L. Miller · L. A. Beck (✉)
Department of Dermatology, University of Rochester Medical Center, Rochester, NY, USA
e-mail: lisa_beck@urmc.rochester.edu

L. C. Schneider
Division of Allergy-Immunology, Department of Pediatrics, Boston Children's Hospital–Harvard Medical School, Boston, MA, USA

P. Y. Ong
Division of Clinical Immunology and Allergy, Children's Hospital Los Angeles–University of Southern California, Los Angeles, CA, USA

E. L. Simpson
Department of Dermatology, Oregon Health and Science University, Portland, OR, USA

D. Y. M. Leung
Division of Allergy-Immunology, Department of Pediatrics, National Jewish Health–University of Colorado School of Medicine, Denver, CO, USA

C. L. Seplaki
Department of Public Health Sciences, University of Rochester Medical Center, Rochester, NY, USA

Key Summary Points

Why carry out the study?

The relationship between eczema herpeticum (EH) and a history of *Staphylococcus aureus* skin infections or immune responses to *S. aureus* has not been explored in a highly matched cohort of deeply phenotyped atopic dermatitis (AD) subjects while controlling for key confounders/covariates.

Despite the high prevalence of *S. aureus* skin colonization and/or infection in subjects with AD, little is known about the immunoglobulin (Ig) G immune response to *S. aureus* antigens in this patient population.

We hypothesized that IgG levels against *S. aureus* antigens would associate with a history of *S. aureus* skin infections and that a history of *S. aureus* skin infections would significantly associate with a history of EH.

What was learned from this study?

IgG against the *S. aureus* virulence factor SE*l*X was significantly associated with a history of *S. aureus* skin infection and a history of EH in AD subjects.

Subjects with a history of *S. aureus* skin infection(s) have more than a sixfold increased odds of also having experienced a case of EH even after controlling for critical confounders.

INTRODUCTION

Atopic dermatitis (AD) is a complex disease in which *Staphylococcus aureus* skin colonization, epithelial barrier disruption, and type 2 immune polarization are all thought to contribute to disease severity, allergen sensitization, and enhanced susceptibility to cutaneous bacterial and viral infections. There are unique and AD-specific viral skin complications that can be serious and even life-threatening, including eczema herpeticum (EH, caused by herpes simplex [HSV] infections), eczema molluscatum (caused by molluscum contagiosum [MCV] infection), eczema coxsackium (caused by coxsackievirus A16), eczema vaccinatum (caused by vaccinia virus), and the newly identified eczema monkeypoxicum (caused by monkeypox virus) [1, 2]. A previous study reported that patients with AD with a history of *S. aureus* skin infections are at higher risk for developing EH, while another study found a high association between EH and skin colonization specifically with *S. aureus* strains that produce toxic shock syndrome toxin-1 (TSST-1) [3, 4].

The aim of this study was to explore the associations between *S. aureus* and viral skin infections in AD subjects after controlling for key confounders using a cohort of 112 AD subjects with and without a history of EH. We tested (1) whether an adaptive response to *S. aureus* antigens was associated with either a history of *S. aureus* skin infections or a history of EH; (2) whether a serum biomarker of skin barrier or epithelial damage (lactate dehydrogenase) was associated with these histories; and (3) whether type 2 biomarkers commonly measured as part of routine clinical management of AD (absolute eosinophils and total immunoglobulin [Ig] E) were associated with these histories.

METHODS

Study Procedures

A subset of subjects (and their samples) collected as part of the National Institute of Allergy and Infectious Diseases (NIAID)-funded, Atopic Dermatitis Research Network (ADRN) were studied. This multi-center, clinical registry study was designed to examine factors associated with susceptibility of AD participants to cutaneous viral dissemination and bacterial colonization/infection as well as the biomarkers related to AD sub-phenotypes

(ClinicalTrials.gov Identifier: NCT01494142 [ADRN02]). The ADRN02 protocol was approved at the institutional review board (IRB) at each academic center (Ann & Robert H. Lurie Children's Hospital of Chicago; Boston Children's Hospital; Children's Hospital of Los Angeles; Mount Sinai School of Medicine; National Jewish Health; Oregon Health & Science University; University of Rochester Medical Center; IRB: RSRB00015368) and was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Written informed consent was provided by the participant or parent/legal guardian, and written consent was provided by the participant, as applicable, before participation. Detailed medical history and case reports, disease severity assessments, and serum were available from the biorepository. Serum tests including total IgE, complete blood counts, and the Immunocap™ Phadiatop test for aeroallergens had been previously performed [3]. We received IRB approval to perform additional serum assays on these samples (IRB: RSRB00007325).

Medical History Questions

Subjects were considered to have had a history of *S. aureus* skin infections if they answered "yes" during the medical history questionnaire to the question "Have you ever had a Staph infection?" and answered "skin" to the question "Was this staph infection of the skin, bloodstream, bones, or orthopedic hardware?". Subjects were considered to have had a history of EH if they answered "yes" during the medical history questionnaire to the question "Have you ever been diagnosed with eczema herpeticum by a health care provider?" and answered "yes" to the question "Did you ever have the following skin condition?", after being read a description of EH and being shown photographs of EH. Subjects were considered to have a history of cutaneous MCV or human papillomavirus (HPV) if they answered "yes" to either of the following questions: "Have you ever had a skin infection with molluscum contagiosum?", after being shown photographs of molluscum contagiosum infections, or "Have you ever had a skin infection with HPV (also called warts)?", after being shown a photograph of HPV infection.

Sample Selection

Subjects were selected based on classification by history of EH (n = 56 EH+, n = 56 EH−) (Fig. 1). Subjects were matched by disease severity (Eczema Area and Severity Index [EASI] ± 6 points) and age (± 10 years) and, when possible, by race and gender (Table 1).

Biomarker Measurements

Serum Lactate Dehydrogenase

Serum lactate dehydrogenase (LDH) was measured by routine laboratory assay in the UR Medicine Labs at the University of Rochester Medical Center.

Serum IgG Measurements

Serum IgG measurements against 17 *S. aureus* antigens (Fig. 2) were determined utilizing arrayed imaging reflectometry (AIR). A previously described array termed StaphAIR consisting of 17 *S. aureus* antigens (Fig. 2) along with control proteins on the AIR platform was used for antigen-specific serum IgG measurements [5]. Briefly, *S. aureus* antigens were printed on amine-reactive silicon/silicon dioxide chips to create a microarray of probe spots, background blocked, and then stabilized for storage. Human serum was diluted 1:50 in Enhanced Assay Buffer (EAB: 25 mM Tris Base, 250 mM NaCl, 250 KCl, 3% w/v propylene glycol, 0.125% w/v Triton X-100, 1% w/v bovine serum albumin, pH 7.2 in nanopure water) with 20% fetal bovine serum (FBS) and incubated with the chips overnight with shaking at 4 °C. The chips were then washed with Assay Wash Buffer (AWB: 150 mM NaCl, 10 mM Na_2HPO_4, 10 mM NaH_2PO_4, 0.005% Tween-20, pH 7.2), incubated for 1 h with 5 μg/mL anti-human IgG in EAB with 20% FBS, washed again, and then dried with nitrogen gas. Chips were then imaged by AIR to detect molecular binding. Images were captured at 6, 11, 25, 50, 100, 250, 500 and 1000 ms CCD exposure times. Pixel intensity

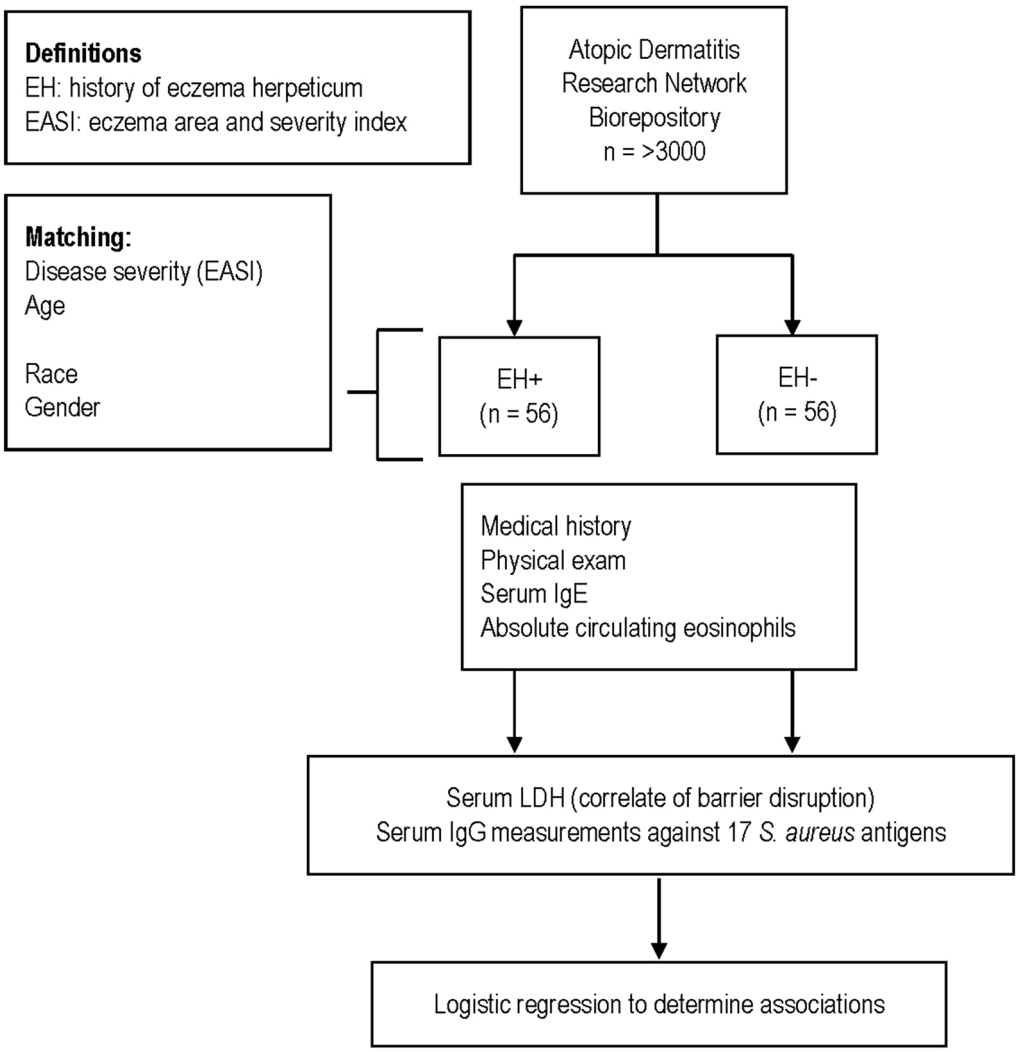

Fig. 1 Flow chart of study design, matching criteria, and metrics. *EASI* Eczema Area and Severity Index, *EH* eczema herpeticum, *Ig* immunoglobulin, *LDH* lactate dehydrogenase. Figure created using BioRender (https://www.biorender.com/)

was quantified and applied to an intensity versus thickness calibration curve to calculate the thickness of IgG build onto the probes.

Data Analysis

The thickness of IgG was calculated as described above and in previous studies [5]. Case reports, IgG measurements, and serum LDH measurements were imported into R for data manipulation, organization and creation of plots. Linear correlations and logistic regressions were performed in SAS OnDemand for Academics. The Bonferroni correction for multiple comparison was applied resulting in a $p < 0.001$ being used as the threshold for significance in our logistic regression models [6].

RESULTS

The StaphAIR assay was used to measure IgG against 17 *S. aureus* antigens in serum samples collected from 112 AD subjects. We selected *S. aureus* antigens representing five main classes of

Table 1 Demographics for atopic dermatitis patients with or without a history of eczema herpeticum

Demographics	Study group	
	EH+ (n = 56)	EH− (n = 56)
Gender, n		
Male	25	27
Female	31	29
Race, n		
Caucasian	37	43
Black or African American	15	6
Asian	2	2
Multi-racial	1	5
Native Hawaiian or other Pacific Islander	1	0
Current Staphylococcus aureus skin culture, n		
Positive (SA+)	28	28
Negative (SA−)	28	28

Mann-Whitney t-test Confounders	EH+ group (n = 56)	EH− group (n = 56)	p
Age	22.94	22.95	0.874
EASI score	13.67	12.80	0.534
Total IgE (kU/L)	2549.06	3294.10	0.018
Absolute eosinophils (cells/mL)	492.93	330.13	0.016
LDH (U/L)	185.46	190.91	0.588
SE*l*X (thickness)	15.4	10.7	0.0003

Subjects had been matched into the two groups by Eczema Area and Severity Index (EASI) score (± 6), age (± 10 years), and race and gender when possible. n = 56 subjects per group

EH+, *EH—* With or without a history of eczema herpeticum, respectively, *IgE* immunoglobulin E, *LDH* lactate dehydrogenase, *SA Staphylococcus aureus*, *SElX* staphylococcal enterotoxin-like X (superantigen)

S. aureus proteins important for pathogenesis (see Fig. 2):

1. Iron acquisition proteins (iron-regulated surface determinant proteins IsdA, IsdB, IsdH)
2. Cell division proteins (autolysin domains glucosaminidase [Gmd] and amidase [Amd])
3. Immune evasion proteins (chemotaxis inhibitory protein of *Staphylococcus* [CHIPS]; staphylococcal complement inhibitory protein [SCIN])
4. Superantigens (staphylococcal enterotoxin A [SEA], B [SEB], and C [SEC]; staphylococcal enterotoxin-like G [SE*l*G], I [SE*l*I], and X [SE*l*X], and TSST-1)

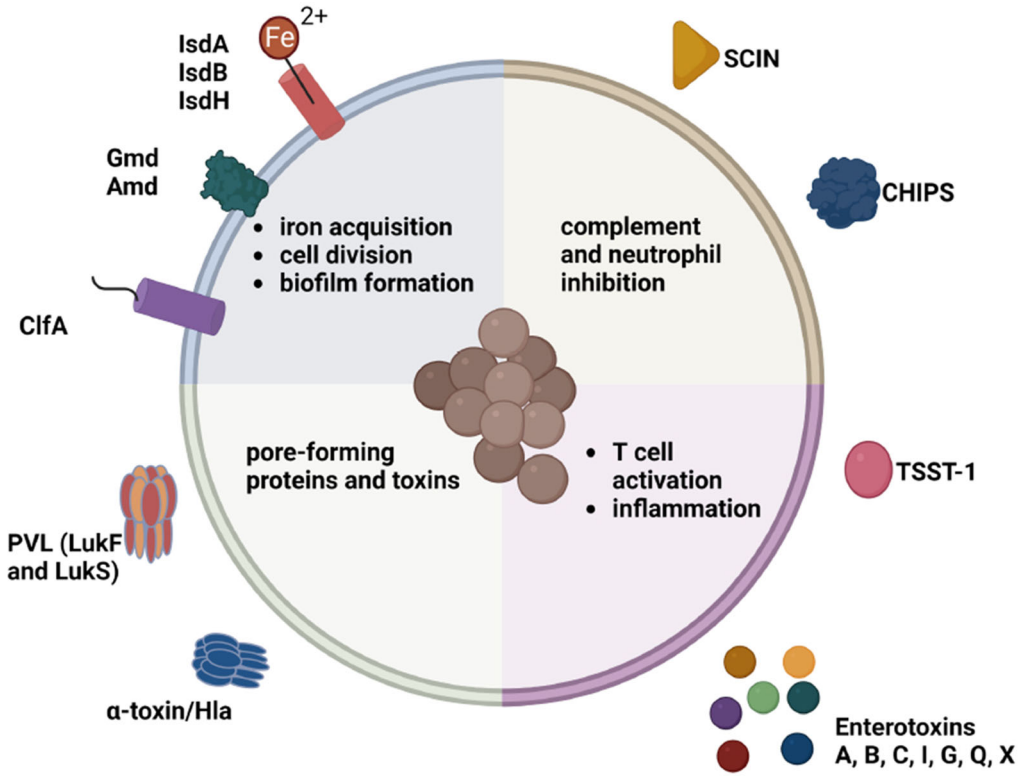

Fig. 2 Schematic of *Staphylococcus aureus* antigen classes included in the StaphAIR assay. *Amd* Autolysin domain amidase, *CHIPs* chemotaxis inhibitory protein of *Staphylococcus*, *ClfA* staphylococcal clumping factor A, *Gmd* autolysin domain glucosaminidase, *Hla* alpha-hemolysin, *Isd* iron-regulated surface determinant protein, *PVL* Panton-Valentine leukocidin, *SCIN* staphylococcal complement inhibitory protein, *TSST-1* toxic shock syndrome toxin-1 Figure created using BioRender (https://www.biorender.com/)

5. Cytotoxins (leukocidin F [LukF] and S [LukS], and alpha-hemolysin [Hla]).

A previous study had found associations between specific *S. aureus* IgG levels and AD severity (self-administered EASI), including immunomodulatory proteins [7]. We sought to determine if there were significant associations between specific *S. aureus* IgG levels and two clinical AD phenotypes: history of *S. aureus* skin infections and history of EH, while controlling for disease severity (EASI) measured by AD experts.

Logistic regressions were run for each *S. aureus* antigen to determine the relative odds of having a history of *S. aureus* skin infection, or history of EH, associated with each 1 unit increase in IgG thickness. The Bonferroni correction was used to set a p value < 0.001 as the threshold for significance and inclusion into the models [6]. Of the 17 antigens measured, only IgG against SE*I*X was significantly associated with both a history of *S. aureus* skin infections and a history of EH (Table 2). IgG against SE*I*X was significantly greater in the EH+ group than the EH- group (Table 1).

A previous study found that AD subjects with EH had more severe disease, greater type 2 immune polarization, and increased incidence of cutaneous infections with *S. aureus* or MCV [3]. We sought to test if the association of *S. aureus* skin infections and EH held true when controlling for confounders (factors influencing both independent and dependent variables) and covariates (correlated with independent variable). We controlled for the main confounder of disease severity in our study design, and subjects were matched into the EH+ and EH− groups based on AD disease severity which

Table 2 *Staphylococcus aureus* antigens and relative odds of history of *S. aureus* skin infection or history of eczema herpeticum as determined by logistic regression

Antigen[a]	History of *S. aureus* skin infection			History of EH		
	Odds ratio	95% Confidence interval	Type III *p* value	Odds ratio	95% Confidence interval	Type III *p* value
IsdA	1.014	0.972, 1.057	0.5337	1.013	0.971, 1.057	0.5455
IsdB	1.028	0.973, 1.087	0.3195	1.052	0.994, 1.113	0.0805
IsdH	1.026	0.996, 1.057	0.0946	1.028	0.997, 1.060	0.0729
Amd	1.032	0.998, 1.067	0.0618	1.002	0.971, 1.034	0.9071
Gmd	1.037	0.996, 1.080	0.0767	1.007	0.969, 1.046	0.7361
CHIPS[b]	1.12	1.038, 1.208	0.0035	1.097	1.021, 1.178	0.0111
SCIN[b]	1.045	1.017, 1.073	0.0013	1.028	1.004, 1.052	0.0239
SEA	0.999	0.986, 1.013	0.8997	1.006	0.993, 1.020	0.3549
SEB	1.015	0.994, 1.036	0.1606	1.008	0.988, 1.029	0.4396
SEC	1.006	0.965, 1.048	0.775	1.011	0.971, 1.054	0.5937
SE/G	1.018	0.963, 1.076	0.5305	1.002	0.948, 1.059	0.9345
SE/I	1.04	0.989, 1.095	0.1268	1.05	0.997, 1.106	0.0653
SE/X[b]	1.129	1.058, 1.204	0.0003*	1.118	1.049, 1.190	0.0006*
TSST1	0.986	0.950, 1.023	0.4427	1.004	0.969, 1.41	0.8263
LukF[b]	1.064	1.012, 1.120	0.0161	1.061	1.008, 1.117	0.0233
LukS[b]	1.035	1.007, 1.064	0.0151	1.024	0.997, 1.052	0.0836
Hla	1.02	0.988, 1.053	0.2127	0.99	0.960, 1.021	0.5309

Odds ratios and 95% confidence intervals (CIs) are for every 1 unit increase in IgG (thickness)

*$p < 0.001$

[a]IsdA, IsdB, IsdH, Iron-regulated surface determinant proteins A, B, H, respectively; Gmd, Amd, autolysin domains glucosaminidase and amidase, respectively; CHIPS, chemotaxis inhibitory protein of *Staphylococcus*; SCIN, staphylococcal complement inhibitory protein; SEA, SEB, SEC, staphylococcal enterotoxin A, B, C, respectively; SE/G, I, X, staphylococcal enterotoxin-like G, I, X, respectively; TSST-1, toxic shock syndrome toxin-1; LukF, S, leukocidin F, S, respectively; H1a, alpha-hemolysin

[b]*S. aureus* virulence factors with the most significant IgG response associated with a history of *S. aureus* skin infection or history of EH

was measured by AD experts (EASI). We considered the inclusion of additional variables into the model based on their associations with history of EH, history of *S. aureus* infection, their correlations with EASI, and our understanding of AD.

Serum LDH is thought to be a marker of barrier dysfunction, as serum LDH correlates with two key measures of skin barrier integrity: transepidermal water loss and stratum corneum hydration [8]. This barrier biomarker was used because no physiological measures of barrier function were collected in the ADRN02 registry

Table 3 Relative odds of history of *S. aureus* skin infection and history of eczema herpeticum infection as determined by logistic regression

Variable	Odds ratio	95% Confidence interval	Type III *p* value
History of S. aureus skin infection			
History of MCV or HPV Skin Infection	5.112	2.251, 11.607	< 0.0001*
Serum LDH	1.02	0.953, 1.091	0.5689
Serum total IgE (log10)	1.913	1.225, 2.987	0.0043
Absolute eosinophils (log10)	1.555	0.609, 3.972	0.3564
History of EH			
History of MCV or HPV Skin Infection	1.538	0.730, 3.239	0.2578
Serum LDH	0.983	0.920, 1.050	0.6096
Serum total IgE (log10)	1.559	1.034, 2.353	0.0341
Absolute eosinophils (log10)	3.518	1.308, 9.461	0.0127

Odds ratios and 95% CIs are for every 10 unit increase in LDH (U/L), 1 unit increase in total IgE (kU/L) (log10 transformed), or 1 unit increase in absolute eosinophils (cells/mL) (log10 transformed)
HCV Herpes simplex virus, *MCV* molluscum contagiosum virus
*$p < 0.001$

study. We found that LDH did not associate with a history of *S. aureus* skin or EH infections and that LDH was not significantly different between EH+ and EH− groups (Tables 1, 3). This is likely due to the fact that EH+ and EH− samples were matched for disease severity (EASI), which may explain the lack of differences in LDH. We did observe a significant correlation (Pearson correlation coefficient of 0.32, $p = 0.0005$) between LDH and EASI, further supporting that matching by EASI score will mask any differences in LDH among the groups and reconfirming the observation that barrier dysfunction is greater in those with more severe disease [9–13].

We also evaluated the importance of two markers of type 2 immunity, namely, serum total IgE and absolute eosinophil count in the circulation. IgE and absolute eosinophils have been shown to be elevated in AD patients with a history of EH, and IgE has been implicated as a risk factor for EH among AD patients [3, 14]. These measurements have also been shown to be associated with disease severity [3, 15, 16]. We observed a significant correlation (Pearson correlation coefficient of 0.36, $p = 0.0001$) between IgE (log10 transformed) and EASI, and between absolute eosinophil count and EASI (Pearson correlation coefficient of 0.27, $p = 0.0047$). Nevertheless, we observed a significant difference in total IgE (log10 transformed; Mann–Whitney test, $p = 0.0136$) and absolute eosinophils (log10 transformed; Mann–Whitney test, $p = 0.0143$) between the EH+ and EH− groups, even when matching by EASI. This suggests that our matching by disease severity did not fully correct for changes in these variables. When added to the model, serum total IgE (log10 transformed) changed the odds ratio (5.48, 95% CI 2.33–12.92) by > 10% and, therefore, it was considered to be a confounder and significant contributor to the model in this study (Table 4: model 3).

History of cutaneous MCV or HPV infection was included as a co-variate, as a previous study found that patients with EH had a greater incidence of MCV infections [3]. Furthermore, we found a history of MCV or HPV to be

Table 4 Relative odds of history of eczema herpeticum associated with subject characteristics, as determined by logistic regression

Model	Variable	Odds ratio	95% Confidence interval	Type III *p* value
1	History of *S. aureus* skin infection	6.11	2.65, 14.11	< 0.0001*
2	History of *S. aureus* skin infection	6.13	2.63, 14.32	< 0.0001*
	Serum LDH	0.97	0.90, 1.04	0.413
3	History of *S. aureus* skin infection	5.48	2.33, 12.92	0.0001*
	Serum total IgE (log10)	1.27	0.82, 1.97	0.289
4	History of *S. aureus* skin infection	6.08	2.55, 14.47	< 0.0001*
	Absolute Eosinophils (log10)	3.57	1.23, 10.32	0.019
5	History of *S. aureus* skin infection	6.9	3.07, 15.51	< 0.0001*
	History of MCV or HPV Skin Infection	0.56	0.26, 1.20	0.134
6	History of *S. aureus* skin infection	5.6	2.44, 12.89	< 0.0001*
	History of MCV or HPV Skin Infection	0.6	0.27, 1.30	0.195
	Serum total IgE (log10)	1.41	0.98, 2.04	0.643
7	History of *S. aureus* skin infection	6.6	2.00, 21.83	0.002
	History of MCV or HPV skin infection	0.49	0.15, 1.60	0.239
	Serum total IgE (log10)	0.9	0.48, 1.71	0.757
	IgG SE*l*X	1.11	1.00, 1.22	0.045

Odds ratio and 95% CI are for every 10 unit increase in LDH (U/L), 1 unit increase in Total IgE (kU/L) (log10 transformed), 1 unit increase in Absolute Eosinophils (cells/mL) (log10 transformed), or 1 unit increase in IgG (thickness)
*$p < 0.001$

significantly associated with history of *S. aureus* skin infection (Table 3). Lastly, we added IgG against SE*l*X, as this significantly associated with both history of *S. aureus* skin infection and EH and was therefore treated as a confounder (Table 3). When adjusting for history of MCV or HPV infection, total IgE (log10 transformed) and IgG against SE*l*X, those with a history of *S. aureus* skin infections had 6.60-fold increased odds of a history of EH compared to those without a history of *S. aureus* skin infections. (Wald Chi-Square type III $p = 0.002$, 95% CI 2.00–21.83) (Table 4: model 7).

DISCUSSION

In this study we utilized a large, deeply phenotyped cohort of AD subjects with and without a history of EH to investigate associations between this serious AD-associated viral skin infection and a history of *S. aureus* infections, *S. aureus* immunoglobulin responses, and a biomarker of skin barrier disruption. Notably, this is the first study to measure IgG against 17 different specific *S. aureus* antigens in AD patients with and without a history of EH, and little is known about how antibody response against *S. aureus* antigens contribute to AD disease severity, barrier defects, or associated infections.

We found IgG against the *S. aureus* superantigen SE*l*X to be significantly associated with

history of *S. aureus* skin infection and history of EH. In addition to the traditional superantigen function of activating T cells, SE*I*X is also able to bind neutrophils and disrupt IgG-mediated phagocytosis [17]. SE*I*X is also unique because its gene is chromosomally located, as opposed to being located on a mobile genetic element like many other virulence factors [18, 19]. The chromosomal location of the SE*I*X gene means that nearly all strains of *S. aureus* are able to produce SE*I*X, which may increase the likelihood of developing an immune response to this antigen. When we quantified virulence factors produced by *S. aureus* strain USA300 in our previous study, the expression level of SE*I*X was the highest among three superantigens, SE*I*K, SE*I*Q, SE*I*X, secreted in the culture media of this strain [20]. We also observed that the five *S. aureus* virulence factors with the most significant IgG response associated with a history of *S. aureus* skin infection or history of EH were all immune evasion proteins (Table 2). These virulence factors (SE*I*X, CHIPS, SCIN, LukS, LukF) are able to act on neutrophils and inhibit their immune function. Neutrophils are the first line of immune cells to respond to *S. aureus* infection and are able to secrete antimicrobial factors, produce reactive oxygen species, phagocytose bacteria, and release neutrophil extracellular traps [21]. The importance of neutrophils in clearing *S. aureus* infection has been made clear in patients with congenital and acquired diseases of impaired neutrophil number and/or function [22]. Arguably, antibodies capable of neutralizing the activity of these immune-evasion proteins would give the host more time to recruit immune cells to the site of infection to clear the bacteria.

Our study has a number of limitations. One limitation is that this is a cross-sectional study and that the history of *S. aureus* skin infection and EH were assessed at one point in time and not over time or at the time of an acute infection. Because of this, we are unable to address temporality. These medical histories are subject to recall bias, which could result in misclassification of history of *S. aureus* skin infection, history of MCV or HPV infection, and history of EH.

A limitation of the StaphAIR assay is that antibodies against many of these antigens are not commercially available and, therefore, we were unable to create standard curves that would allow us to determine the concentration of each of the antigen-specific antibodies in the serum. Instead, we have a semi-quantitative measurement of antibody build on the probes (measured as thickness) [5]. Importantly, for our purposes it was more important to compare values across samples rather than to know the absolute amount. While our platform included 17 *S. aureus* antigens, this is in no way exhaustive of all the potentially relevant *S. aureus* virulence factors important for human colonization and/or infection.

CONCLUSIONS

This study has demonstrated that there is a significant association between a history of *S. aureus* skin infection and history of EH, even after controlling for confounders and covariates such as disease severity, epithelial barrier disruption (using LDH as a surrogate), type 2 immunity, and history of MCV or HPV skin infection. Furthermore, we found that IgG against the *S. aureus* antigen SE*I*X is associated with history of *S. aureus* skin infection and history of EH. These findings support that skin infection caused by *S. aureus* or an increased susceptibility of AD patients to *S. aureus* skin infection significantly impacts susceptibility to viral infection. Reducing *S. aureus* skin infections in patients with AD may help reduce the risk of developing serious viral skin complications, such as EH. A greater understanding of these mechanisms and the key *S. aureus* virulence factors involved may help better identify patients at a greater risk of EH.

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REFERENCES

1. Xia J, Huang CL, Chu P, Kroshinsky D. Eczema monkeypoxicum: report of monkeypox transmission in a patient with atopic dermatitis. JAAD Case Rep. 2022;29:95–9.

2. Ong PY, Leung DY. Bacterial and viral infections in atopic dermatitis: a comprehensive review. Clin Rev Allergy Immunol. 2016;51(3):329–37.

3. Beck LA, Boguniewicz M, Hata T, et al. Phenotype of atopic dermatitis subjects with a history of eczema herpeticum. J Allergy Clin Immunol. 2009;124(2):260–9.e7.

4. Schlievert PM, Roller RJ, Kilgore SH, et al. Staphylococcal TSST-1 association with eczema herpeticum in humans. mSphere. 2021;6(4):e0060821.

5. Klose AM, Daiss JL, Ho L, et al. StaphAIR: a label-free antigen microarray approach to detecting anti-staphylococcus aureus antibody responses in orthopedic infections. Anal Chem. 2021;93(40):13580–8.

6. Armstrong RA. When to use the Bonferroni correction. Ophthalmic Physiol Opt. 2014;34(5):502–8.

7. Totte JEE, Pardo LM, Fieten KB, et al. IgG response against *Staphylococcus aureus* is associated with severe atopic dermatitis in children. Br J Dermatol. 2018;179(1):118–26.

8. Simpson EL, Villarreal M, Jepson B, et al. Patients with atopic dermatitis colonized with *Staphylococcus aureus* have a distinct phenotype and endotype. J Invest Dermatol. 2018;138(10):2224–33.

9. Addor FA, Takaoka R, Rivitti EA, Aoki V. Atopic dermatitis: correlation between non-damaged skin barrier function and disease activity. Int J Dermatol. 2012;51(6):672–6.

10. Agner T. Susceptibility of atopic dermatitis patients to irritant dermatitis caused by sodium lauryl sulphate. Acta Derm Venereol. 1991;71(4):296–300.

11. Finlay AY, Nicholls S, King CS, Marks R. The "dry" non-eczematous skin associated with atopic eczema. Br J Dermatol. 1980;103(3):249–56.

12. Rinaldi AO, Korsfeldt A, Ward S, et al. Electrical impedance spectroscopy for the characterization of skin barrier in atopic dermatitis. Allergy. 2021;76(10):3066–79.

13. Seidenari S, Giusti G. Objective assessment of the skin of children affected by atopic dermatitis: a study of pH, capacitance and TEWL in eczematous and clinically uninvolved skin. Acta Derm Venereol. 1995;75(6):429–33.

14. Wollenberg A, Zoch C, Wetzel S, Plewig G, Przybilla B. Predisposing factors and clinical features of eczema herpeticum: a retrospective analysis of 100 cases. J Am Acad Dermatol. 2003;49(2):198–205.

15. Kagi MK, Joller-Jemelka H, Wuthrich B. Correlation of eosinophils, eosinophil cationic protein and soluble interleukin-2 receptor with the clinical activity of atopic dermatitis. Dermatology. 1992;185(2):88–92.

16. Wuthrich B. Serum IgE in atopic dermatitis: relationship to severity of cutaneous involvement and course of disease as well as coexistence of atopic respiratory diseases. Clin Allergy. 1978;8(3):241–8.

17. Tuffs SW, James DBA, Bestebroer J, et al. The *Staphylococcus aureus* superantigen SElX is a bifunctional toxin that inhibits neutrophil function. PLoS Pathog. 2017;13(9): e1006461.

18. Xu SX, McCormick JK. Staphylococcal superantigens in colonization and disease. Front Cell Infect Microbiol. 2012;2:52.

19. Wilson GJ, Seo KS, Cartwright RA, et al. A novel core genome-encoded superantigen contributes to lethality of community-associated MRSA necrotizing pneumonia. PLoS Pathog. 2011;7(10):e1002271.

20. Moran MC, Cahill MP, Brewer MG, et al. Staphylococcal virulence factors on the skin of atopic dermatitis patients. mSphere. 2019;4(6):e00616–9. https://doi.org/10.1128/mSphere.00616-19.

21. Guerra FE, Borgogna TR, Patel DM, Sward EW, Voyich JM. Epic immune battles of history:

neutrophils vs *Staphylococcus aureus*. Front Cell Infect Microbiol. 2017;7:286.

22. Miller LS, Fowler VG, Shukla SK, Rose WE, Proctor RA. Development of a vaccine against *Staphylococcus aureus* invasive infections: evidence based on human immunity, genetics and bacterial evasion mechanisms. FEMS Microbiol Rev. 2020;44(1):123–53.