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Colonization with *Staphylococcus aureus* in patients with hand eczema: Prevalence and association with severity, atopic dermatitis, subtype and nasal colonization

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Abstract

Background: While *Staphylococcus aureus* (*S. aureus*) colonization has been thoroughly studied in atopic dermatitis (AD), where *S. aureus* is related to flares and considered a trigger factor, *S. aureus* colonization in hand eczema (HE) has only been sparsely studied.

Objectives: To examine the 1-week prevalence of *S. aureus* colonization in HE patients, and its association with severity, HE subtype, AD, and nasal *S. aureus* colonization compared with healthy controls.

Methods: In a case-control study of 50 adult HE patients and 50 healthy controls, bacterial swabs from lesional skin (patients only), non-lesional skin (dorsal hand), and the nasal cavity were sampled for culturing of *S. aureus* on days 1, 3, 5 and 8. Participants were characterized by demographics, AD, HE subtype, filaggrin gene mutation status, and HE severity.

Results: Twenty-seven HE patients (54%) were colonized with *S. aureus* on the hand compared to one control (2%) ($P < .01$). Nasal *S. aureus* colonization was found in 72% of patients and 22% of controls ($P < .01$). For patients, *S. aureus* colonization on the hands was associated with an atopic HE subtype and HE severity ($P = .01$ and $P < .01$, respectively).

Conclusions: Both hand and nasal *S. aureus* colonization were highly prevalent among HE-patients and may have an impact on the persistence of HE.

KEYWORDS

atopic hand eczema, contact dermatitis, filaggrin, hand eczema, skin barrier function, *Staphylococcus aureus*

1 | INTRODUCTION

Hand eczema (HE) has a 1-year prevalence of nearly 10% in the general population,¹ and in many cases, a chronic relapsing course² as well as considerable physical and psychological consequences for the individual. Moreover, the socioeconomic costs for society are high.^{3,4} The complex aetiology of HE includes both environmental and endogenous factors.^{1,5} In the pathogenesis of HE, an impaired epidermal barrier is fundamental,⁶

caused by irritant or allergic exposure,^{7,8} previous or current atopic dermatitis (AD),⁹ and down-regulation of structural barrier proteins such as filaggrin.^{6,10,11} However, regardless of the aetiology, chronic HE is often the end-stage and possible maintenance factors are still to be clarified.

Colonization with *Staphylococcus aureus* (*S. aureus*) in patients with HE has only been sparsely investigated. The point prevalence of *S. aureus* colonization on the hands of patients with HE in two previous studies was reported as 48% and 69%, respectively, and in both

studies was significantly related to the severity of HE.^{12,13} Both studies used just one sampling to distinguish *S. aureus* non-carriers from carriers, which could lead to misclassification.¹⁴ Although the role and causality of *S. aureus* in relation to HE is unknown, we hypothesize that the presence of *S. aureus* could be an important driver of inflammation and, subsequently, of chronicity.

The nose (anterior nares) is the primary reservoir for *S. aureus* in humans with a reported prevalence varying greatly between 20% and 60%, depending on the study population, sampling, and culture techniques.^{15–18} The prevalence of nasal colonization with *S. aureus* in HE patients has previously been reported as similar to that of healthy individuals, albeit sparsely studied.^{12,13}

The primary objective of our study was to investigate the 1-week prevalence of hand and nasal *S. aureus* colonization in patients with HE compared to healthy controls. Our secondary objective was to investigate possible associations between *S. aureus* hand colonization in HE patients and a history of AD, atopic subtype of HE, HE severity, and nasal *S. aureus* colonization. Furthermore, we hypothesized that factors such as impaired skin barrier function, filaggrin (*FLG*) gene mutation,¹⁹ being a healthcare worker (HCW),^{20,21} younger age, and male sex^{15,18} were associated with increased risk of *S. aureus* colonization.

2 | METHODS

2.1 | Population and study design

Patients with chronic HE, according to the definition in guidelines from the ESCD,²² were included from the outpatient clinic of the Dermatologic Department, Bispebjerg University Hospital of Copenhagen, from February to August 2019. Healthy individuals with no personal history of HE or other currently active skin diseases, recruited during the same period through an advertisement, served as controls. Exclusion criteria for both groups were age <18 or >65 years, pregnancy, breastfeeding, and use of systemic or topical antibiotics within the 2 weeks prior to the first visit. In terms of treatment, patients were included regardless of topical or systemic HE therapy, though this was recorded. No intervention or restrictions were made regarding hand hygiene routines. During the study period (days 1–8), patients had a consultation with a dermatologist comprising a guided talk on HE prevention and all were patch tested with the European baseline series.

Written informed consent was obtained from each participant. The study was approved by the local ethics committee (Project number H-18049625) and the Danish Data Protection Agency (Project number VD-2019-15).

2.2 | Demographics, *FLG* status, skin barrier function, and severity

Demographic characteristics, including age, sex, current or past medical history of AD ("have you had childhood eczema"²³ or "have you

had atopic dermatitis diagnosed by a dermatologist"), and being an HCW (yes/no), were collected. For patients, additional information on any dermatologist-diagnosed subtype of HE (irritant contact dermatitis, allergic contact dermatitis, atopic HE, hyperkeratotic HE, or acute vesicular recurrent HE),⁷ notification as occupational HE (yes/no), and approximate duration of HE was collected. From a blood sample, *FLG* was examined with respect to common single mutations in Scandinavian populations (R501X, 2282del4 and R2447X).²⁴ At the first visit, skin barrier function was assessed by measurements of transepidermal water loss (TEWL) (triplicate values from the non-lesional or least affected skin on the dorsal side of the hand, using DermaLab Combo; Cortex Technology, Hadsund, Denmark²⁵), according to the manufacturer's guidelines.²⁶ Eczema severity, assessed by the Hand Eczema Severity Index (HECSI),²⁷ was registered at the first visit.

2.3 | Sample collection and *S. aureus* identification

Each participant had a total of four visits within a period of 1 week, approximately on days 1, 3, 5 and 8. Bacterial skin samples were collected at all visits using ESwab (Copan, Brescia, Italy). Swabs were taken from lesional skin (patients with most pronounced lesions only), non-lesional skin (preferably the dorsal side of the dominant hand or any location nearest to this area), and the nose (anterior nose cavity). For each participant, the same locations of approximately 2 cm² were swabbed at all four visits. The skin was rubbed vigorously for 30 seconds, and nose samples were collected by rotating swabs five times in the right anterior nares. Swab specimens were plated on *S. aureus* selective plates (SaSelect, Bio-Rad, Marnes-la-Coquette, France) and incubated overnight at 37°C. Identified *S. aureus* colonies were plated on 5% blood agar plates (SSI Diagnostika, Hillerød Denmark) and species classification was validated with MALDI-TOF (Microflex LT/SH System, Bruker Daltonics, Bremen, Germany). Colonization with *S. aureus* on lesional skin, non-lesional skin, and nose, respectively, was defined as *S. aureus* presence at least once during the four visits of the study period.

2.4 | Statistics

Descriptive statistics used included mean and standard deviation ($\pm$ SD) for continuous data, and numbers and frequencies for categorical data. Fisher's exact test was used to compare *S. aureus* skin colonization between patients and controls and a multivariate logistic regression with adjustments for AD was used to compare nasal colonization. Fisher's exact test was used to examine variables associated with *S. aureus* colonization on lesional skin and in the nose of patients with HE. A multivariate logistic regression analysis was performed for selected variables (severity, HE subtype and nasal *S. aureus* colonization) ($P < .2$ from Fisher's exact tests) in association with lesional skin colonization. Geometric means were used when data were not

normally distributed. *P*-values <.05 were considered statistically significant. R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio (Boston, Massachusetts) were used for statistical analysis.

3 | RESULTS

Fifty patients with HE and 50 healthy controls were included in the study. Patients and controls participated in a baseline visit (visit 1) and three follow-up visits. Mean ($\pm$ SD) days from visit 1 to visit 2, 3 and 4, respectively, for patients were 2 ($\pm$ 0.2), 4 ($\pm$ 1.1), and 8 ($\pm$ 1.8) days, and for controls 3 ($\pm$ 0.8), 5 ($\pm$ 0.9) and 8 ($\pm$ 1.1) days. There were no drop-outs. *S. aureus* colonization, demographics, FLG status, TEWL values for patients with HE and healthy controls are given in Table 1 as well as for HE patients, HE subtypes, and HE severity are indicated as well. Mean age was 40 years (range 22–62) in patients and 42 years (range 24–64) in controls, respectively, and fewer patients than

controls were females (28 female patients vs 41 female controls). More patients than controls had a medical history of AD (17 patients [34%] vs four controls [8%]), and fewer patients than controls were HCWs (nine patients vs 24 controls). Eight patients had a FLG mutation, of which six had a history of AD, as compared to three persons in the control group. Mean HESCI score was 22.1 ($\pm$ 2.8, range 2–145). Thirty-four patients (68%) had HE noted as occupational. The mean duration of HE was 2.75 years (range 0.25–40 years). Regarding treatment of HE 1 week prior to the first visit, 33 had used emollients only, 15 patients had used topical corticosteroids (TCS) at least once, and two patients used systemic therapy (acitretin and dupilumab, respectively).

3.1 | Colonization with *S. aureus* in patients vs controls

A total of 54% (95%CI: 39%–68%) of patients with HE were colonized with *S. aureus* on the hands (lesional skin), which was significantly

TABLE 1 *Staphylococcus aureus* (*S. aureus*) colonization and demographics for patients with hand eczema (HE) and healthy controls

	Patients with HE (N = 50)	Healthy controls (N = 50)	<i>P</i> -value
<i>S. aureus</i> on hands ^a , n, (%) [95%CI colonization prevalence]	27 (54%) [39.3–68.2]	1 (2%) [0.05–10.6]	<.01
<i>S. aureus</i> on NLS, n, (%) [95%CI colonization prevalence]	15 (30%) [17.9–44.6]	1 (2%) [0.05–10.6]	<.01
<i>S. aureus</i> in nose, (%) [95%CI colonization prevalence]	36 (72%) [57.5–83.8]	11 (22%) [11.5–36.0]	<.01 ^b
Age, years, mean (SD) (range)	40.1 (11.7) (22–62)	42.5 (12.6) (24–64)	
Sex, female, n (%)	28 (56%)	41 (82%)	
Atopic dermatitis, n (%)			
Past	13 (26%)	4 (8%)	
Current	4 (8%)	0 (0%)	
Ever	17 (34%)	4 (8%)	
Occupation, n (%)			
HCWs	9 (18%)	24 (48%)	
FLG mutation ^c , n (%)	8 (17%)	3 (6%)	
TEWL (g/m ² /h), geometric mean (SD) ^{d,e}	12.1 (1.9)	10.0 (1.7)	
HE subtypes (primary diagnosis), n (%)		-	
Irritant contact dermatitis	15 (30%)		
Allergic contact dermatitis	11 (22%)		
Atopic	13 (26%)		
Hyperkeratotic	8 (16%)		
Vesicular	2 (4%)		
Unknown	1 (2%)		
HECSI, geometric mean (SD) ^e	22.1 (2.8)	-	

Abbreviations: AD, atopic dermatitis; FLG, filaggrin; HCW, health care worker; HE, hand eczema; HECSI, Hand Eczema Severity Index; NLS, non-lesional skin (dorsal side of the dominant hand); SD, standard deviation; TEWL, transepidermal water loss.

^aLesional skin for patients with HE; dorsal hand for healthy controls.

^bSignificantly different after adjustments for AD (multivariate logistic regression analysis with nose colonization, HE vs controls adjusted for AD ever).

^cFLG, $n_{\text{patients}} = 48$. In patients, all mutations were heterozygous for either R2447X, R50X1 or 2282del4. One control had a homozygous mutation (2282del4), two had heterozygous mutations.

^dTEWL, $n_{\text{patients}} = 47$, measured on dorsal hand.

^eGeometric means and standard deviations ($\exp(\log[\text{tewl}])$ and $\exp(\log[\text{hecsi}])$).

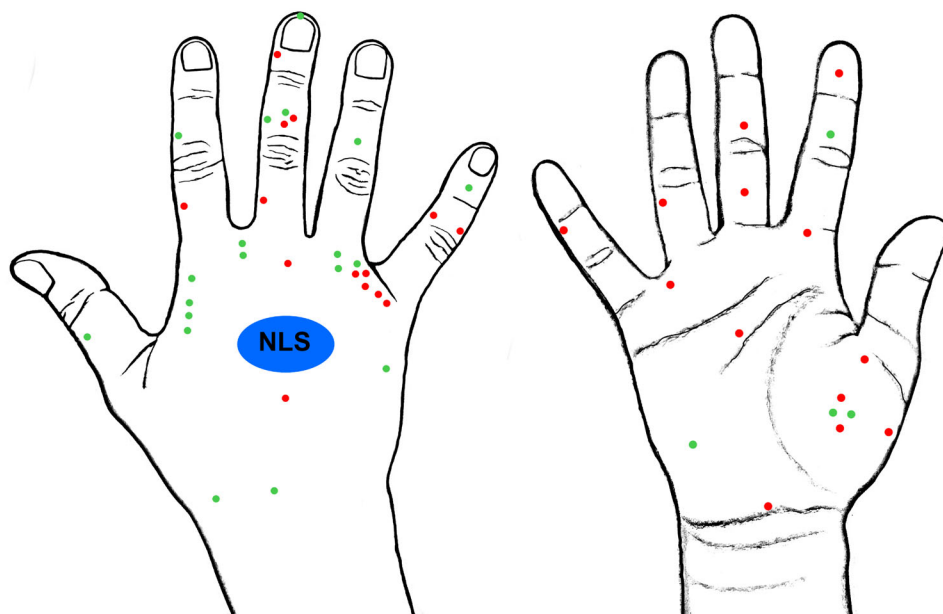


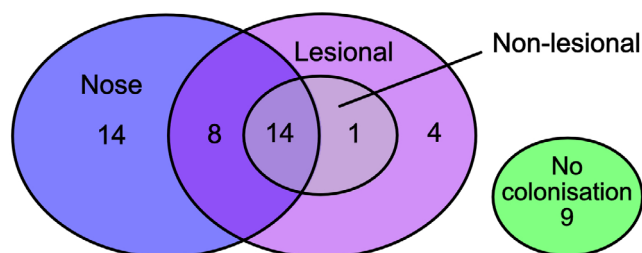
FIGURE 1 Sample sites illustrated by one circle for each patient. Lesional skin swabs with at least one visit with *Staphylococcus aureus* (*S. aureus*) colonization marked as red ($n = 27$) and those without *S. aureus* colonization at all visits marked as green ($n = 23$). Non-lesional skin (NLS) swabs (blue) were collected from the marked area on the dominant dorsal hand of both patients and controls. Each point corresponds to a swabbed area of approximately 2 cm^2

more prevalent than the 2% found in controls (95%CI: 0%–11%) ($P < .01$). Nasal *S. aureus* colonization was 72% (95%CI: 58%–84%) for patients vs 22% (95%CI: 12%–36%) for controls ($P < .01$) (Table 1). Adjusted for AD, the difference in nasal *S. aureus* colonization between patients and controls was still significant ($P < .01$). *S. aureus* colonization from lesional skin samples was evenly distributed on the hand and fingers, and a higher colonization rate in the palm (74%) than on the dorsal hand (42%) was found (Figure 1). Fifteen patients (30%, 95%CI: 18%–45%) were colonized with *S. aureus* on non-lesional skin of the hands, which was significantly higher than the 2% of controls ($P < .01$); all these HE patients were also colonized on lesional skin and/or in the nose (Figure 2).

3.2 | Associations between colonization with *S. aureus* and demographic and clinical data

Demographic and clinical data of HE patients stratified according to *S. aureus* colonization on lesional skin and in the nose are shown in Table 2. *S. aureus* on lesional skin was significantly more prevalent among patients with current or past AD compared to those without a medical history of AD ($P = .04$). Likewise, *S. aureus* on lesional skin was more prevalent in atopic HE compared with the group of other HE subtypes collectively ($P = .01$). Severity of HE was associated with *S. aureus* colonization on lesional skin ($P < .01$), with a geometric mean HECSI score of $36.1 (\pm 2.4)$ for patients colonized with *S. aureus* vs $12.5 (\pm 2.6)$ for patients without *S. aureus*. Age, sex, FLG mutation status, TEWL, duration of HE, and use of TCS 1 week prior to the first visit were not associated with skin colonization. No increased colonization prevalence was found among HCW (33% with *S. aureus*). Nasal *S. aureus* colonization was found in 81% of patients colonized with *S. aureus* on the hands, vs 61% in patients not colonized with *S. aureus*

Patients with hand eczema



Healthy controls

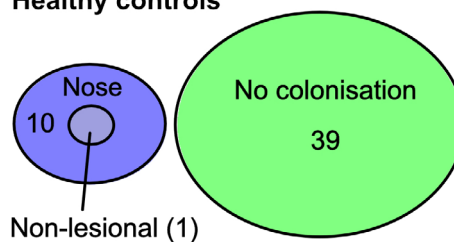


FIGURE 2 *Staphylococcus aureus* (*S. aureus*) colonization in patients with hand eczema (HE) ($N = 50$) and healthy controls (HC) ($N = 50$). *S. aureus* colonization on lesional skin (purple, $n(\text{HE}) = 27$), non-lesional skin (grey, $n(\text{HE}) = 15$, $n(\text{HC}) = 1$), and in the nose (blue, $n(\text{HE}) = 36$, $n(\text{HC}) = 11$). Individuals with no colonization (green, $n(\text{HE}) = 9$, $n(\text{HC}) = 39$).

on the hands ($P = .13$) (Table 2). In a multivariate logistic regression analysis for selected variables (HE subtype, severity, and nasal *S. aureus* colonization) with *S. aureus* colonization on lesional skin on hands as an outcome, atopic HE, and severity were both significant and independent covariates (odds ratio [OR] 10.2, 95%CI: 1.7–101 and OR 3.0, 95%CI: 1.6–7.4, respectively), while there was no

TABLE 2 Demographic and clinical data stratified with respect to *Staphylococcus aureus* (*S. aureus*) colonization on lesional skin and in nose at least once within 1 week (four visits) for patients with hand eczema (HE) and multivariate logistic regression analysis for selected variables with *S. aureus* colonization on lesional skin as outcome

Variable	Patients with HE (N = 50)							
	Hand (lesional skin) <i>S. aureus</i>			Multivariate log. regress.		Nose <i>S. aureus</i>		
	Colonized (n = 27)	Not colonized (n = 23)	P-value	OR (95%CI)	P-value	Colonized (n = 36)	Not Colonized (n = 14)	P-value
Age, mean (SD)	41 (11.7)	39 (12.0)	.61	-	-	39 (11.4)	42 (12.8)	.46
Sex, n (%)								
Male (n = 22)	11 (41%)	11 (48%)	.78	-	-	18 (50%)	4 (29%)	.22
Female (n = 28)	16 (59%)	12 (52%)				18 (50%)	10 (71%)	
AD past or current, n (%)								
No (n = 33)	14 (52%)	19 (83%)		-	-	22 (61%)	11 (79%)	
Yes (n = 17)	13 (48%)	4 (17%)	.036			14 (39%)	3 (21%)	.33
HE-subtype, n (%)								
Non-AD HE (n = 37)	16 (59%)	21 (91%)		1.0 (ref.)		25 (69%)	12 (86%)	
AD HE (n = 13)	11 (41%)	2 (9%)	.012	10.2 (2-101)	.003	11 (31%)	2 (14%)	.30
FLG mutation, n (%)								
Wild type (n = 40)	20 (74%)	20 (86%)	.26	-	-	28 (78%)	12 (86%)	.42
Mutated (n = 8)	6 (22%) (1 NA)	2 (9%) (1 NA)				7 (19%) (1 NA)	1 (7%) (1 NA)	
TEWL dorsal hand, g/m ² /h, geometric mean (SD) ^a	12.3 (1.95) (1 NA)	11.8 (1.76) (2 NA's)	.82	-	-	12.3 (1.91) (3 NA's)	11.6 (1.77)	.76
HECSI, geometric mean (SD) ^a	36.1 (2.39)	12.5 (2.58)	<.001*	3.0 (2; 7)	.004	25.2 (2.88)	15.9 (2.66)	.16
Pos. <i>S. aureus</i> in nose, n (%)						-	-	-
No (n = 14)	5 (19%)	9 (39%)		1.0 (ref.)				
Yes (n = 36)	22 (81%)	14 (61%)	.13	1.7 (0.3;9.2)	.55			

Abbreviations: AD, atopic dermatitis; FLG, filaggrin gene; HECSI, hand eczema severity index; NA, not applicable (missing value); TEWL, transepidermal water loss.

Note: Fisher's exact tests and unpaired t-tests were used to test for association between *S. aureus* colonization and the categorical and the continuous variables, respectively. Significant differences considered at a .05-level, unadjusted. P-values for each of the two sampling sites were adjusted for mass significance using Bonferroni test (0.05/15) and adjusted significant values ($P < .003$) are marked with *.

^aGeometric means ($\exp(\log[\text{tewl}])$ and $\exp(\log[\text{hecsi}])$).

TABLE 3 Dominant subtype of hand eczema (HE) related to *Staphylococcus aureus* (*S. aureus*) colonization on hands (lesional skin) and in the nose

HE-subtype	<i>S. aureus</i> positive, n (%)	
	Hand	Nose
Irritant contact dermatitis (n = 15)	5 (33%)	9 (60%)
Atopic, (n = 13)	11 (85%)	11 (85%)
Allergic contact dermatitis, (n = 11)	6 (55%)	7 (64%)
Hyperkeratotic, (n = 8)	4 (50%)	7 (88%)
Vesicular, (n = 2)	1 (50%)	2 (100%)
Unknown, (n = 1)	0 (0%)	0 (0%)
Total	27 (54%)	36 (72%)

significant association with nasal *S. aureus* colonization (Table 2). The prevalence of hand and nasal *S. aureus* colonization across the specific dominant HE subtypes is presented in Table 3.

4 | DISCUSSION

This is the first study to assess colonization with *S. aureus* in HE over 1 week, and to link this to possible risk factors. We found a markedly higher 1-week prevalence of *S. aureus* skin colonization in patients with HE compared with healthy controls, which is in agreement with the few available previous studies.^{12,13} Our new observation is the significantly higher level of nasal colonization with *S. aureus* in HE patients (72%) than in controls (22%), independent of AD. Furthermore, severity of HE, atopic HE subtype as well as a history of AD, were associated with *S. aureus* colonization on the hands of HE patients. Considering the well-known high prevalence of *S. aureus* colonization in AD patients,¹⁷ this is not surprising; however, colonization was also found in patients with no history of AD, and in all subtypes of HE.

To date, focus on HE prevention has been to minimize exposure to allergens and irritants. Despite the obvious benefits of these

preventive efforts, the prognosis has not improved.²⁸ This indicates that there could be different mechanisms driving the disease, in particular in the chronic phase of HE. Our finding that 54% of HE patients are colonized with *S. aureus* on their hands at least once within a week supports two previous studies reporting a prevalence of 48% and 69%, respectively.^{12,13} Unlike these two studies, however, which report the prevalence based on a single sampling, we performed a total of four samplings over 8 days. In this way we intended to increase the sensitivity of detection of *S. aureus* and prevent false-negative observations due to hand washing or use of alcohol-based hand-rubs immediately before sampling, since no restrictions for hand hygiene were present in our study design. Random contamination with *S. aureus* on the hands seems to be rare, since only one of our controls was colonized with *S. aureus* on the hands. However, from our patient population we observed a higher colonization rate on the ventral hand compared with the dorsal, which might have biased the comparison of lesional skin in patients and the dorsal hand of controls. This supports our hypothesis that *S. aureus* colonization favours an impaired skin barrier. However, *S. aureus* presence is not strictly determined by barrier disruption. As an example of this, skin lesions in psoriatic patients are not colonized with *S. aureus* (prevalence of 35%)²⁹ as often as is observed among HE and AD patients. In the present study we also found an increased prevalence of *S. aureus* colonization on non-lesional skin of HE patients (30%), which is well-known for AD.¹⁷ However, in HE, non-lesional skin is located close to lesional skin, and drawing conclusions from this, therefore, seems more problematic.

Interestingly, a significantly higher prevalence of nasal *S. aureus* colonization in HE patients as compared to controls was found, which was also the case even among patients without skin colonization. By contrast, previous studies did not find nasal colonization prevalence to be increased in patients.^{12,13} Similar findings have been reported for AD; however, our data confirm a significant relationship between HE and nasal colonization also after adjusting for AD. The fact that the increased percentage of nasal carriers in HE patients was not found in previous studies may be explained by a change in methodology with increased sensitivity of the test for bacteria, and assuming that the concentration of bacteria in the nose is low in some people, this would probably not have been detected by the methodology previously used. The route of colonization between nose and skin in HE is unknown and explanations are speculative. Hands are considered the main means of transmitting *S. aureus* from surfaces to the nose and back.³⁰ Because of impaired skin barrier function in HE, bacteria might adhere more easily to skin and subsequently be transferred from skin to nose. As the nose is considered a niche of *S. aureus*, colonizing strains may serve as endogenous reservoirs¹⁶ with a more stable colonization than the transient skin colonization, and a vicious circle of transmission between skin and nose, and back again, would then be established. Thus, nasal carriage could be important in the pathogenesis of disease, and maybe also contribute to the chronicity of HE. Moreover, it seems reasonable to assume that the 14 patients out of the 36 (39%) who were nasal *S. aureus* carriers without an additionally detected skin colonization, could occasionally have *S. aureus*

on the hands as well, increasing the actual skin colonization rate in patients with HE. This would also make the patients more prone to harbour *S. aureus* in the nose compared to the controls. This might explain the surprising finding, that our association between skin and nasal colonization was not significant among patients. From an infection prevention perspective, the frequent *S. aureus* skin and nasal colonization in patients with HE may hamper the work of certain occupations with the risk of transferring *S. aureus*. Previously, a higher skin prevalence of *S. aureus* has been reported among HCWs with damaged skin on the hands,^{20,21,31} though this was not confirmed in the present study. Even HCWs without eczema are reported to carry *S. aureus* on hands,³²⁻³⁴ probably due to occupational exposure. On the other hand, HCWs might be better trained in hand hygiene, and the difference in number of HCWs among patients and controls (nine vs 24) could possibly bias our results.

Patients with atopic HE were more frequently colonized with *S. aureus* on the hands compared with all other HE subtypes, confirming expectations that AD patients by default have a higher risk of *S. aureus* skin colonization. This was, however, not found in a previous study.¹² Severity of HE and, thereby, the degree of an altered epidermal barrier function observed in HE, might increase skin susceptibility towards *S. aureus*. Alternatively, the causal link between these two may be the other way around, in which case *S. aureus* is a decisive factor for aggravating the disease; at the moment there is no definitive answer to this.

FLG mutations are thought to favour *S. aureus* skin colonization in patients with AD.¹⁹ In the present study we also found a trend toward higher prevalence of colonization in HE patients with FLG mutations; though this is probably explained by too few patients with mutations and no results for two patients. This finding was not statistically significant, and a large-scale study would be necessary to determine whether FLG mutations are a risk factor for *S. aureus* colonization in HE patients, independent of AD.

Different sampling techniques for skin and nasal *S. aureus* culturing are available. Some researchers have used the hand-imprinting technique, ie directly pressing fingers on an agar.³⁵⁻³⁷ Others have used the "glove juice method," where the hand is gloved and filled with liquid to release *S. aureus* for sampling.^{13,20,21,33,38,39} The 'glove juice method' is ideal for bacteria sampling from hands, and particularly preferred in quantification of bacterial counts; however, this technique does not allow for comparison of lesional and non-lesional skin, and the method is likely to influence subsequent samplings. Swabs are commonly used successfully to sample from eczematous skin surface of HE and AD.^{12,19,40} Therefore, we used swabs, suitable for both skin and nasal collection of *S. aureus*, for comparison, and repeated sampling.^{12,31,32}

Our "real-life" study design is both a strength and a limitation. We aimed to determine the *S. aureus* colonization in everyday life for patients with HE, regardless of treatment and hand hygiene. Restrictions on this would most likely influence the results, though unpredictably, and the four samplings prevent the risk of such false-negative results. The relatively small sample size of HE patients limits our results on associations. Because of these limitations, the potential

associations between skin colonization and particularly *FLG*, *HCW*, and *TEWL*, might have remained unidentified. A major strength of our study is the 100% follow-up in both groups and for all *S. aureus* samplings, in combination with a well-characterized study population.

In conclusion, results from our study indicate that *S. aureus* colonization is highly prevalent on the hands in HE patients, as well as in the nose. Factors associated with *S. aureus* colonization were disease severity and AD. Our findings underline the potentially influential role of *S. aureus* in disease pathogenesis, severity, and chronicity of HE.

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AUTHOR CONTRIBUTIONS

Sofie Edslev: Conceptualization; formal analysis; methodology; resources; software; validation; visualization; writing-original draft; writing-review and editing. **Paal Andersen:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing-original draft; writing-review and editing. **Frederik Plum:** Data curation; investigation; methodology; resources; visualization; writing-review and editing. **Jette Holt:** Conceptualization; funding acquisition; methodology; supervision; validation; writing-review and editing. **Anne Kjerulf:** Conceptualization; funding acquisition; methodology; supervision; validation; writing-review and editing. **Niels Ebbelhøj:** Conceptualization; formal analysis; funding acquisition; methodology; project administration; resources; supervision; validation; visualization; writing-review and editing. **Maja Lisa Clausen:** Conceptualization; formal analysis; funding acquisition; investigation; methodology; resources; supervision; validation; visualization; writing-review and editing. **Esben Flachs:** Formal analysis; investigation; methodology; resources; software; supervision; validation; writing-review and editing. **Tove Agner:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing-original draft; writing-review and editing.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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