Prevalence and odds of *Staphylococcus aureus* carriage in atopic dermatitis: a systematic review and meta-analysis.

J.E.E. Totté
W.T. van der Feltz
M. Hennekam
A. van Belkum
E.J. van Zuuren
S.G.M.A. Pasmans

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ABSTRACT

Background

Staphylococcus (S.) aureus is increasingly implicated as a possible causal factor in the pathogenesis of atopic dermatitis (AD). However, the reported prevalence rates of skin and nasal colonization in the literature vary widely.

Objective

This study evaluates the prevalence and odds of skin and nasal colonization with *S. aureus* in patients with AD.

Methods

A systematic literature search was conducted. Odds ratios (ORs) for colonization in patients vs. controls and the prevalence of colonization in patients were pooled using the random-effects model.

Results

Overall, 95 observational studies were included, of which 30 had a control group. The Newcastle-Ottawa Scale was used to assess study quality, with the majority of studies being of fair to poor quality. Patients with AD were more likely to be colonized with *S. aureus* than healthy controls [OR 19.74, 95% confidence interval (CI) 10.88-35.81]. Differences were smaller in nonlesional skin (OR 7.77, 95% CI 3.82-15.82) and in the nose (OR 4.50, 95% CI 3.00-6.75). The pooled prevalence of *S. aureus* colonization among patients was 70% for lesional skin, 39% for nonlesional skin and 62% for the nose. In lesional skin, meta-regression showed that the prevalence of colonization increased with disease severity. Study heterogeneity should be taken into consideration when interpreting the results.

Conclusions

The results demonstrate the importance of colonization with *S. aureus* in AD. Further evaluation of the mechanisms by which *S. aureus* influences inflammation is required in addition to the development of targeted strategies to decrease skin and nasal *S. aureus* load.

INTRODUCTION

Increased colonization with *S. aureus* in the skin of patients with atopic dermatitis (AD) was first described in the 1970s. Multiple studies confirmed this finding, reporting a prevalence of skin colonization with *S. aureus* ranging from around 30% to nearly 100%.[1-4] The underlying pathogenic mechanisms of *S. aureus* in relation to AD have still not been fully elucidated. However, recent studies suggest a causal role in the complex pathogenesis of AD by showing that *S. aureus* colonization precedes (flares of) the disease.[5-9] *S. aureus* can facilitate skin barrier defects and inflammation in AD using different mechanisms.[4,10] Examples of this include the stimulation of mast-cell degranulation by staphylococcal delta toxin, the induction of keratinocyte apoptosis by alpha toxin, the stimulation of T cells by enterotoxins that act as superantigens and the modulation of inflammation by staphylococcal surface proteins, protein A and lipoteichoic acid.[10-14]

As *S. aureus* contributes to both skin barrier defects and to inflammation, a more proactive control of *S. aureus* in certain patients may help to reduce disease severity. However, use of antibiotics can result in resistance of *S. aureus* and perturbation of healthy microbiota, which has been shown to have potentially deleterious health effects.[15-18] At present, new targeted anti-microbial therapies (such as lysins) are being developed, which are directed against single bacteria (e.g. Staphefekt SA.100 against *S. aureus)*.[19-22] Therefore it is important to identify patients with AD who can potentially benefit from antistaphylococcal treatment.

Defining the prevalence of *S. aureus* skin and mucosal colonization in (subgroups of) patients with AD might provide more insight into the importance of *S. aureus* as a contributor to the disease and its severity.

Current prevalence rates of *S. aureus* colonization reported in AD vary widely, mainly depending on the type of patients included, the sample size and the methods used to collect and detect *S. aureus* or its products. The swab and the scrub method are frequently used to collect microorganisms from the skin.[23] Swabs collect bacteria from the superficial layer of the skin, whereas a scrub technique allows collection of superficial skin cells and associated microbes.[24] The detection of *S. aureus* was predominantly based on culture-based methods. In recent years DNA sequencing methods have allowed determination of the complete microbial composition at species level and recently upcoming metagenomics techniques can be used for identification at strain level.[25]

In this systematic review we aim to provide an overview and a pooled estimate of the prevalence and odds of colonization with *S. aureus* in patients with AD.

MATERIALS AND METHODS

Type of study

Both experimental and observational (original, human) studies were included, however, case reports were excluded. No restrictions were made relating to publication date and language.

Type of participants

Patients of all ages with a diagnosis of AD confirmed by a physician were included.

Type of outcome measures

The primary outcome was the proportion of patients with presence of *S. aureus* on the skin (lesional and nonlesional) or in the nose. Secondary outcomes were (i) the presence of *S. aureus* virulence factors on the skin and (ii) the relation between AD severity and colonization with *S. aureus.* In case of intervention studies, only the baseline measurement was included in this review. When studies reported multiple measurements over time taken from the same skin site (without treatment regimen), or when multiple locations were sampled at the same time point, the mean was included in the meta-analysis. Studies that reported solely on methicillin-resistant *S. aureus* were excluded.

Search strategy

The search was conducted in Embase (from 1974), Medline (from 1946), OvidSP (from 1946), Pubmed (from 1947), Web of Science (from 1945) and The Cochrane Central Register of Controlled Trials (CENTRAL) up to 16 September 2014 (table S1). A cross-reference check was performed to identify further relevant studies.

Study selection and data extraction

The titles and abstracts were screened for relevance. Articles or abstracts were selected based on predefined inclusion and exclusion criteria (appendix S1; see Supporting information). Non-English articles were translated by an official translation service when considered relevant. The methodological quality of the articles was rated using an adapted version of the Newcastle-Ottawa Scale (NOS).[26,27] Uncontrolled studies could reach a maximum score of 7 points and studies including a control group could reach a maximum score of 8 points. Using a scoring algorithm (appendix S2; see Supporting information), the controlled studies were classified as being of poor, fair or good methodological quality, based on their NOS scores for patient selection, comparability and outcome.[28] Study selection and quality assessment was conducted independently by two researchers (J.E.E.T. and W.T. v.d.F., J.E.E.T. and M.H. or W.T.v.d.F. and M.H.). Disagreements were resolved and consensus was reached. If identical populations were

described in different publications within an overlapping time period, the study with the most extensive reporting of results was included.

Statistical analysis

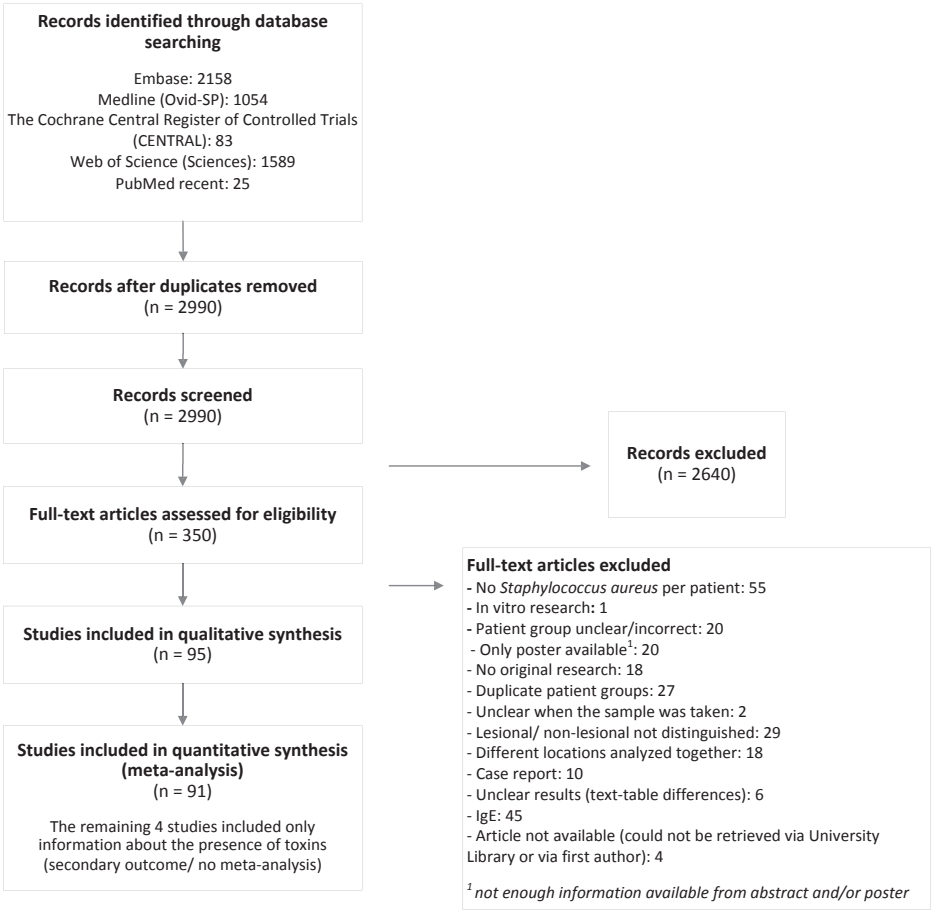
A meta-analysis was performed using a random-effects model. A weighted prevalence of colonization with *S. aureus* on the skin and in the nose was calculated. In controlled studies the prevalence of colonization in patients and controls was compared, expressed as an odds ratio (OR) with a 95% confidence interval (CI). Heterogeneity was assessed using I^2. In cases of substantial heterogeneity between studies ($I^2 > 50\%$) the reasons for heterogeneity were explored using meta-regression (using the unrestricted maximum likelihood method and in cases where there were more than 10 available studies) for the variables NOS score, age and AD severity. For the meta-regression on severity, studies that used the Eczema Area Severity Index (EASI) score or the SCORing Atopic Dermatitis (SCORAD) score were selected. Cut-off values for mild, moderate and severe AD were used as previously described.[29,30] Subgroup analysis was performed for variables that were significant in the meta-regression. Additional subgroup analysis was carried out for studies in which patients were not receiving antibiotic treatment. All statistical analyses were performed using Comprehensive Meta-Analysis Version 2.2 (Biostat, Englewood, NJ, U.S.A.). Publication bias was evaluated using funnel plots, Egger's regression and the trim-and-fill method.[31] The present systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[32]

RESULTS

Study characteristics

The search yielded a total of 4909 articles, of which 2990 articles remained after deduplications. We used article title and abstract to identify 350 studies (figure 1). After reading the full article texts, 95 studies met our inclusion criteria. All studies had an observational design and 30 studies compared patients with AD with healthy controls. In 77% of the studies AD was diagnosed by clinical assessment (dermatologist or another specialized physician). The other studies did not clearly report who diagnosed the patients. The overall percentage of male patients was 52% and the mean age was 14 years (range 0.8-68.9) based on 58 studies. A total of 11 studies measured disease severity using the EASI, with nine studies reporting a mean EASI [17.7 (range 4.5-51.6)]. Twenty-two of the 40 studies that used SCORAD reported a mean score [48.2 (range 13.5-73.5)]. The remaining studies did not measure the disease severity, used other measuring methods or did not report mean EASI or SCORAD values. Overall, 54% of the studies were conducted

Figure 1. Flow chart of the search strategy and study selection.



in Europe, 27% in Asia and 13% in the U.S. Study characteristics including the methods used to collect and identify *S. aureus* are described in table S2.

Quality of the studies

We rated the quality of the 30 articles that included a control group as good (n=4), fair (n=4) and poor (n=22). The quality of the 65 uncontrolled studies varied from 1 to 6 points out of 7 points on the NOS. (table S2). The main reason for downgrading the quality of controlled studies was incomparability of the patient and control groups. Uncontrolled studies were mainly downgraded owing to a limited description of the methods used for collection and identification of *S. aureus.* The low NOS scores were also partly due to the inclusion of abstracts in this review, which provided limited information on methods.

Prevalence of nasal- and skin colonization with *S. aureus*

Overall, 81 studies (5231 patients) reported on colonization of the lesional skin and 30 studies (1496 patients) reported on colonization of the nonlesional skin. Pooled analysis showed that 70% of the patients with AD carried *S. aureus* on the lesional skin (95% CI 66-74; I^2= 88.31) and 39% on the nonlesional skin (95% CI 31-47; I^2 = 87.39). Pooled results of the 43 studies (2476 patients) that address nasal colonization estimated that 62% of the patients with AD carry *S. aureus* in the nose (95% CI 57-68; I^2 = 85.20) (table 1 and figure S1). The prevalence varied substantially among studies (28% to 99% in lesional skin, 3% to 79% in nonlesional skin and 4% to 95% in the nose). This variation probably resulted in the considerable heterogeneity among studies and might be partly explained by the variation in disease severity and the age of patients included in these studies.

Odds of colonization with *S. aureus*

A total of 26 studies compared colonization of the lesional skin in patients with AD with healthy controls. From 10 studies the OR could not be obtained as the reported percentage of patients colonized with *S. aureus* or controls was either 100% or 0%. A pooled OR based on the remaining 16 studies (including 823 patients and 688 controls) showed that patients were significantly more likely than controls to be colonized with *S. aureus* on the lesional skin (OR 19.74; 95% CI 10.88-35.81; p<0.001; I^2 = 66.04). Overall, 12 out of 20 studies were eligible for inclusion in the pooled analysis for the nonlesional skin (550 patients and 446 controls) (OR 7.77, 95% CI 3.82-15.82; p<0.001; I^2 = 63.08). Pooled analysis of the 19 of 21 studies that evaluated nasal colonization (1051 patients and 1263 controls) showed that 57% of the patients was positive for *S. aureus* in the nose vs. 23% of the controls (OR 4.50; 95% CI 3.00-6.75; p<0.001; I^2 = 70.31) (table 2).

Meta-regression and subgroup analysis

Heterogeneity between the studies was considerable, mainly in the pooled analysis of prevalence (>85%). A meta-regression for the variables AD severity, NOS score and age was performed to identify possible sources of heterogeneity. The prevalence of lesional skin colonization was independent of the NOS score but increased with AD severity (1.02; 95% CI 0.21-1.82) and age (0.64; 95% CI 0.15-1.14). A subgroup analysis of the studies that included patients with mild AD showed colonization of the skin in 43% of the patients (95% CI 31-57; I^2 =79.15) whereas the pooled prevalence for severe AD was 83% (95% CI 74-89; I^2 = 65.78). For the nonlesional skin, colonization decreased with a higher NOS score (-0.27; 95% CI -0.50-(-0.04)). Subgroup analysis of the studies with a higher quality (NOS > 4) showed a pooled prevalence of 31% (95% 23-40; I^2 = 64.62), which is lower than the overall prevalence of 39%. Colonization of the nose was independent of the three variables (table 1).

Table 1. Colonization with *S. aureus* in patients with atopic dermatitis

	Number of studies	Pooled proportion of patients positive for colonization (95% CI)	Heterogeneity (I^2)	Pooled proportion of patients positive for colonization adjusted for publication bias	Meta-regression NOS, B (95% CI)	Meta-regression Severe AD, B (95% CI)	Meta-regression age B (95% CI)
Lesional skin							
All studies	81	0.70 (0.66-0.74)	88.31	0.57 (0.52-0.62)	0.07 (-0.10-0.24)	1.02 (0.21-1.82)[1]*	0.64 (0.15-1.14)[3]*
Studies including mild AD	4	0.43 (0.31-0.57)	79.15				
Studies including severe AD	9	0.83 (0.74-0.89)	65.78				
Studies excluding AB/steroid use	17	0.67 (0.58-0.75)	86.44				
Studies including age<18	29	0.78 (0.71-0.84)	84.19				
Studies including age>18	40	0.65 (0.59-0.71)	89-64				
Nonlesional skin							
All studies	30	0.39 (0.31-0.47)	87.39	0.38 (0.30-0.46)	-0.27 (-0.50-(-0.04))*	-	0.76 (-0.01-1.52)[4]
Studies with a NOS score >4	9	0.31 (0.23-0.40)	64.62				
Studies excluding AB/steroid use	11	0.24 (0.16-0.36)	85.22				
Nose							
All studies	43	0.62 (0.56-0.68)	85.20	0.53 (0.48-0.60)	-0.05 (-0.25-0.15)	0.62 (-0.15-1.39)[2]	0.12 (-0.47-0.72)[5]
Studies excluding AB/steroid use	8	0.58 (0.47-0.69)	78-23				

All estimates were calculated using the random effects model.
See supplementary figures 1 for individual forest plots
- = meta-analysis not performed because <10 studies
[1] 28 studies included
[2] 15 studies included
[3] 69 studies included
[4] 27 studies included
[5] 35 studies included
* = significant result

Table 2. Colonization with *S. aureus* in patients with atopic dermatitis versus healthy controls

	Number of studies	Pooled OR colonization in patients vs controls (95% CI)	Hetero-geneity (I^2)	Pooled OR in patients vs controls adjusted for publication bias	Meta-regression NOS, B (95% CI)	Meta-regression Severity, B (95% CI)	Meta-regression age B (95% CI)
Lesional skin						-	
All studies	16	19.74 (10.88-35.81)*	66.04	10.21 (5.44-19.16)	-0.05 (-0.47-0.37)		-0.55 (-1.84-0.74)[1]
Studies excluding AB/steroid use	6	27.43 (11.20-67.16)*	47.46				
Non- lesional skin						-	
All studies	12	7.77 (3.82-15.82)	63.08	3.82 (2.18-6.72)	-		0.36 (-1.23-1.95)[2]
Studies excluding AB/steroid use	5	9.70 (3.60-26.13)*	51.06				
Nose						-	
All studies	19	4.50 (3.00-6.75)	70.31	#	0.13 (-0.12-0.39)		0.68 (-0.48-1.84)[3]
Studies excluding AB/steroid use	7	5.54 (3.55-8.65)*	23.70				

All estimates were calculated using the random effects model. Studies that reported event rates of 0 or 1 were excluded as ORs cannot be calculated with these event rates. See supplementary figures 1 for individual forest plots

- = meta-analysis not performed because <10 studies

= no studies were trimmed according to the Trim and Fill method

* = significant result

[1] = 14 studies included

[2] = 10 studies included

[3]= 16 studies included

The ORs for colonization in patients with AD vs. controls were independent of the NOS and age. Severity was not tested as fewer than 10 studies that measured this variable were available (table 2). Additional subgroup analysis, performed with studies that excluded patients who used antibiotics and corticosteroids at the time of inclusion, showed pooled ORs that were higher than the original pooled estimate of all studies (tables 1 and 2).

Enterotoxins prevalence

The prevalence of at least one toxin-producing *S. aureus* strain on the lesional skin in patients varied between 31.5% and 80%. Staphylococcal enterotoxin B was the toxin found most often, with a prevalence of up to 70%. One study reported a prevalence of toxin-producing *S. aureus* of 11.5% on nonlesional skin. Three studies reported the presence of at least one toxin-producing *S. aureus* in the nose, with prevalence rates varying between 32% and 80%. Other studies reported combined results of skin and nose samples and were not taken into consideration in this study (table S3).

Publication bias

The funnel plots for the prevalence of skin and nasal *S. aureus* in patients with AD showed asymmetry (figure S2). The Eggers test confirmed the presence of publication bias with intercepts of 3.68 (95% CI 2.71-4.65, p<0.001) for lesional skin, 0.76 (95% CI -3.06-4.85, p=0.69) for the nonlesional skin and 2.63 (95% CI 0.84-4.42, p=0.005) for the nose. Also the pooled analysis of the odds for colonization showed publication bias with an Eggers regression intercept of 2.47 (95% CI 1.66-3.28, p<0.001) for lesional skin, 1.71 (95% CI 0.45-2.97, p=0.010) for nonlesional skin and 2.08 (95% CI 0.64-3.52, p=0.023) for the nose. Adjusted prevalence rates and ORs according to the trim-and-fill method were all lower than the original estimates (table 1 and 2).

DISCUSSION

In this systematic review we demonstrate that patients with AD are significantly more likely to be colonized with *S. aureus* than healthy controls on both the lesional and nonlesional skin and in the nose. Pooled prevalence of *S. aureus* carriage among patients is 70% for lesional skin, 39% for nonlesional skin and 62% for the nose. For lesional skin the prevalence appeared to be dependent on disease severity and age, however, this could not be confirmed for nonlesional skin or nasal colonization. Substantial to considerable heterogeneity, incomparability of patient and control groups, variation in methods used for sampling and poor description of exposures (such as treatment) downgraded the

quality of the included articles, which should be taken into consideration when interpreting the results.[33]

The typical features of AD skin, such as a comprised barrier integrity, altered sphingolipid metabolism and antimicrobial peptide expression probably facilitate colonization with *S. aureus*.[34,35] The meta-regression analysis finds a higher prevalence of colonization among patients with more severe AD. However, the causal relationship between colonization with *S. aureus* and AD still has to be further clarified. Recent studies often suggest colonization with *S. aureus* as a primary cause rather than only a secondary effect of skin damage or an insufficient antistaphylococcal immune status. According to Kong *et al.* flares in AD accompany temporal microbial dysbiosis, dominated by *S. aureus*.[5] Microbiome analysis of lesions in mice with an eczematous phenotype revealed that dysbiosis was a driving factor for dermatitis formation and bacterial inoculation experiments showed that *S. aureus* could accelerate eczematous inflammation.[36] Despite these studies that suggest a causal relationship, a systematic review by Bath-Hextall *et al.* did not demonstrate a beneficial clinical effect of untargeted anti-*S. aureus* therapy combined with steroids over steroids alone.[37,38] However, other studies including treatment with mupirocin and bleach baths did show a reduction in clinical severity together with a reduction of *S. aureus* skin load.[39,40] In our review we did not investigate the relation between antistaphylococcal interventions and AD severity. We did conduct a subgroup analysis; including patients who were not receiving any antibiotic or corticosteroid treatment. This showed a lower prevalence of *S. aureus* on the skin and nose, which is not in line with the antibacterial effect of both antibiotics and corticosteroids.[41,42] One explanation might be that the inclusion of patients who did not require treatment resulted in a selection of patients with mild AD who were less likely to be colonized with *S. aureus.*

Several natural and technical factors that are known to cause variation in microbiome outcomes might have influenced our results. There is variation between methods used to collect and detect *S. aureus* and its virulence factors on the human skin.[43,44] Also, *S. aureus* might be present not only on the surface of the skin but also in deeper layers.[45] These differences highlight the importance of interpreting the results carefully, taking the methods used into consideration. Subgroup analysis for culture- vs. DNA-based detection methods were not performed owing to a small number of studies using DNA-based methods. Although DNA-based methods only include nonviable bacteria, they might provide more accurate results for quantifying *S. aureus* in the microbiome.

Furthermore, the impact of exposures such as treatment regimen and duration of the disease at the moment of collection were often poorly reported, which might have resulted in performance bias. A subgroup analysis excluding patients using antibiotics or steroids was performed to take the influence of treatment on the results into consideration. However, the use of other (aseptic) products might have also influenced the microbial composition. The duration of the disease might influence the activity of the

host's immune response, which, in turn, could influence the presence of *S. aureus* via an antimicrobial effect.[46] The presence and quantity of microorganisms on the skin is influenced by many factors that naturally give rise to changes in diversity of the microbiota over time and skin site (e.g. ethnicity and climate).[24,47-50 51,52] It should be noted that our review reports on the proportion of *S. aureus* on the skin and mucosa determined at one specific time point.

As a result of underlying factors such as the (genetic) barrier defect and immune pathways enhancing a defective skin barrier, dysbiosis dominated by *S. aureus* is a chronic and recurring factor in AD. [8,53-55] It is important to evaluate further the pathways by which *S. aureus* leads to inflammation and how current therapies already influence these pathways. Antibiotics and antiseptics are used in infected or severe AD.[56,57,58] Functional textiles that are used as complementary treatment in AD might also decrease *S. aureus* colonization.[59] Glucocorticosteroids might also have an antibacterial effect besides their anti-inflammatory effect, probably via an effect on antimicrobial peptides, and even emollient monotherapy was shown to reduce bacterial colonization.[9,60] The current use of antistaphylococcal therapies, together with literature that points to *S. aureus* as a driver in AD pathogenesis, underlines the importance of antistaphylococcal treatment in AD. However, long-term (preventive) use of antibiotics and glucocorticosteroids is undesirable as they can cause side-effects and antibiotic resistance.[16]

To date this is the most comprehensive review that systematically summarizes data regarding *S. aureus* colonization in patients with AD. A large number of studies were included. These studies were mainly observational and often consisted of small numbers of patients. By not restricting the language of the search, selection bias was kept to a minimum. However, selection might have occurred owing to the exclusion of studies that did not report whether samples were taken from lesional or nonlesional skin. The covariate 'severity' in the meta-analysis was based on the level of the study, which may have led to an aggregation bias. As determining the prevalence of *S. aureus* colonization was not the primary objective in a substantial number of the studies, indirectness of evidence with regard to the study population might have occurred. Publication bias changed the outcomes considerably according to the trim-and-fill method. The quality of a large portion of the individual studies was considered to be low. Future studies into the prevalence of *S. aureus* in patients vs. controls should take these quality criteria into consideration to raise the confidence in pooled estimates.

CONCLUSIONS

Despite the low quality of the included studies and the presence of publication bias, this systematic review and meta-analysis demonstrates that patients with AD are more

frequently colonized with *S. aureus* than healthy controls and that colonization is increased in more severe AD. These results provide an indication of the importance of colonization as a factor in the pathogenesis of AD and encourage evaluation of targeted antistaphylococcal therapy for the skin (and nose), for example based on the use of anti-*S. aureus* lysins. Prospective or experimental studies should further investigate causality and the mechanisms by which *S. aureus* colonization leads to inflammation. Host factors such as age and ethnicity, in addition to host-pathogen interaction, should be taken into consideration when investigating these mechanisms. The possible relevance of other microbes in the pathogenesis of AD should also be explored using metagenomic approaches. Additional examination of colonization in patients with different phenotypes (sensitized and non-sensitized, early onset vs. late onset) might provide insight in the type of patients who are likely to benefit most from targeted therapy against *S. aureus.*

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SUPPORTING INFORMATION

Appendix S1. Criteria for selecting studies

Types of studies

- All original human studies that assess the incidence of (virulence factors of) *S. aureus* on the skin and/or nares in patients with atopic dermatitis
- All study designs, except for case reports (<10 studies)

Participants

- Patients with atopic dermatitis of all ages, diagnosed by a medical doctor, included in hospital setting or general population. All disease severity states were included.

Controls

- Subjects with no known skin disease

Outcome measures

- *Primary: S. aureus* (both MRSA and MSSA) on skin (either lesional or non-lesional) and/or nares, isolated through culture or DNA based methods. Samples taken at any time during the disease or treatment were included. Studies that only report on MSSA were excluded.
- *Secondary:* Incidence rate of *S. aureus* and virulence factors on the skin and/or in the nares, measured by PCR.

Appendix S2. Quality assessment score

Modified Newcastle – Ottawa quality assessment scale for cohort or cross sectional studies

Stars indicate the points allocated if the item criterion is met. A maximum score of 8 can be allocated to each article. Uncontrolled studies can reach a maximum score of 7.

Selection

1. Representativeness of the exposed cohort

a) Truly representative of the general atopic dermatitis population *
b) Somewhat representative of the general atopic dermatitis population *
c) Selected group of atopic dermatitis patients (hospital based, tertiary center, inpatients, outpatients)
d) No description of the derivation of the cohort

2. Selection of the non-exposed cohort

a) Representative of the average community (healthy control, community control)*
b) Selected group of controls (hospital controls, other dermatological condition)
c) No control group or no description of control group

3. Ascertainment of atopic dermatitis

a) Diagnosed by dermatologist *
b) Diagnosed by physician other than dermatologist*
c) Diagnosed by clinical assessment*
d) Based on self-report
e) No description of atopic dermatitis case definition

4. Assessment of disease severity

a) Disease severity was assessed with validated score (doctor assessed) EASI, SCORAD, EASI, TIS, POEM*
b) Disease severity was assessed with a validated score (patient assessed). PO-SCORAD, SA-EASI*
c) Disease severity was assessed using another score
d) No disease severity reported

Comparability

1. Comparability of atopic dermatitis and healthy controls on the basis of design or analysis

a) Study controls for confounding using a multivariate model*

b) Atopic dermatitis patients and healthy controls are matched (for age/gender)*
c) No controlling for confounding or matching

Outcome

1. Assessment of outcome: colonization or presence of virulence factors (measurement)

a) Determined by culture, PCR, ELISA or sequencing*
b) Not mentioned

2. Assessment of outcome: method of sample taking

a) Method or sample taking was well described*
b) Not well described or not mentioned

3. Was there treatment during sampling

a) No treatment *
b) Systemic treatment
c) Topical treatment
d) Not mentioned

4. Adequacy of follow up (only in case of cohort studies (prospective))

a) complete follow-up*
b) subjects loss to follow-up unlikely to introduce bias (<10% lost)*
c) follow-up > 10%
d) no statement

Modified Scoring algorithm controlled studies [28]

Quality rating	Points in Selection Domain	Points in Comparability Domain	Points in Outcome domain
Good	≥ 3	≥ 1	≥ 2
Fair	2	0	≥ 2
Poor	0-1	0	0-1

SUPPLEMENTARY FIGURES

Figure S1a. Forest plot: Odds of lesional skin colonization (all studies)

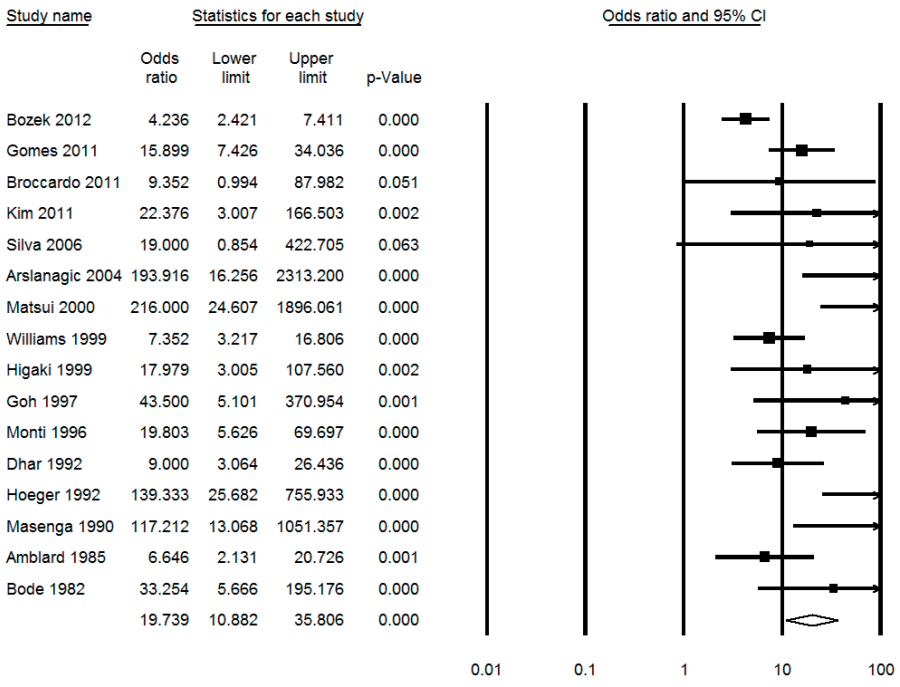


Figure S1b. Forest plot: Odds of non-lesional skin colonization (all studies)

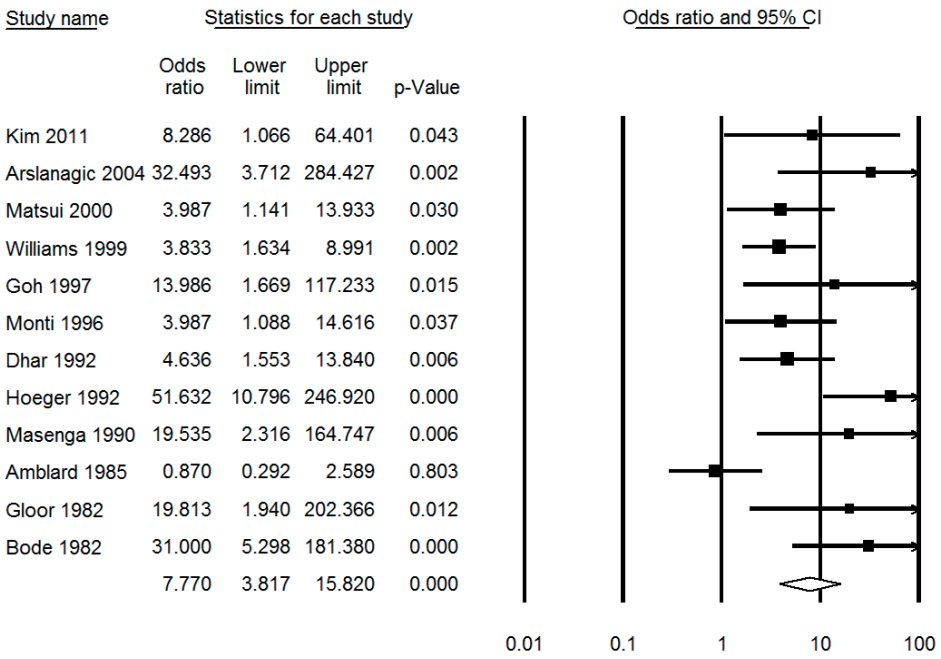


Figure S1c. Forest plot: Odds of nasal colonization (all studies)

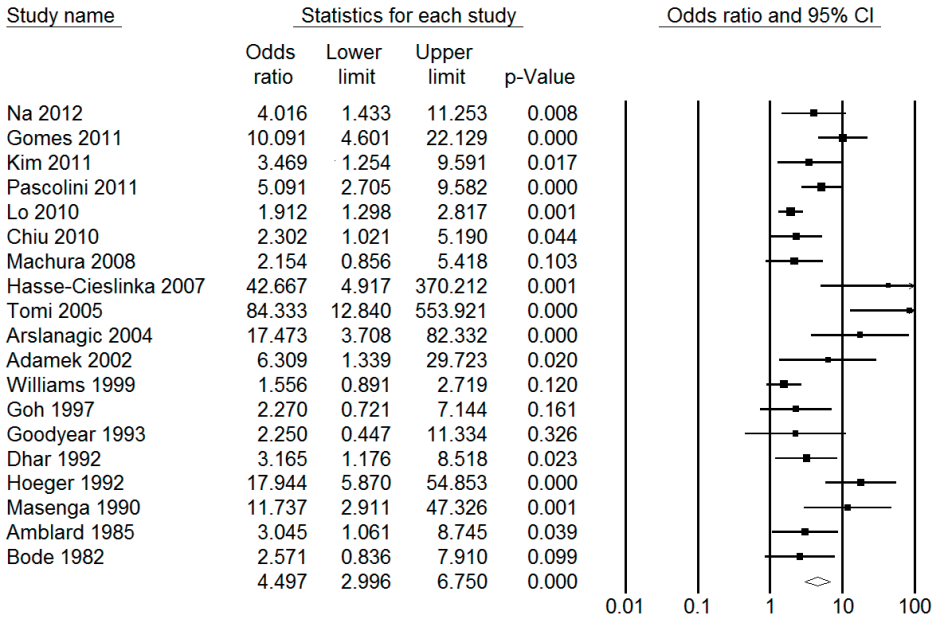


Figure S2a. Funnel plot of studies reporting prevalence of lesional skin colonization with *S. aureus* in patients

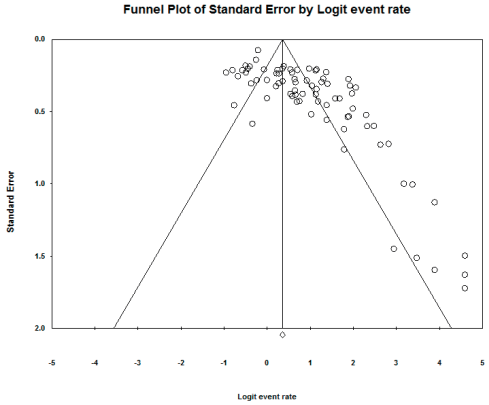


Figure S2b. Funnel plot of studies reporting prevalence of non-lesional skin colonization with *S. aureus* in patients with AD

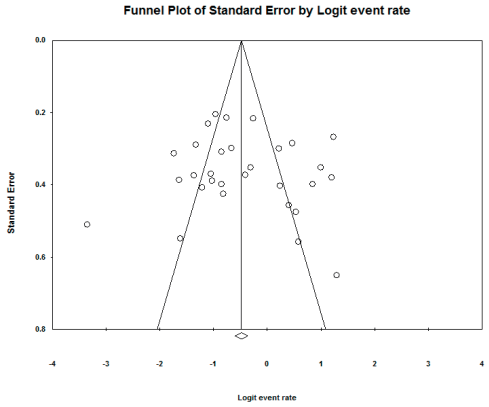


Figure S2c. Funnel plot of studies reporting prevalence of nasal skin colonization with *S. aureus* in patients with AD

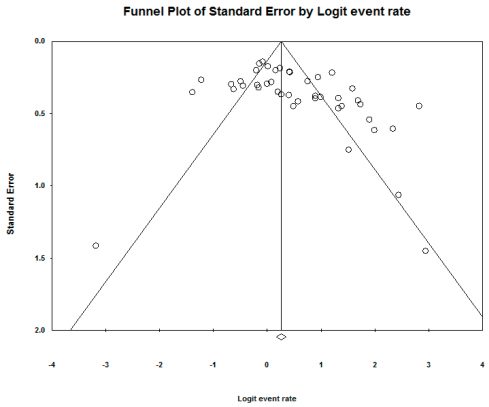


Figure S2d. Funnel plot of studies reporting odds of lesional skin colonization with *S. aureus* in patients

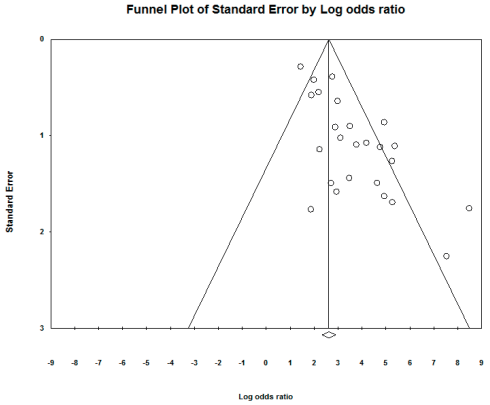


Figure S2e. Funnel plot of studies odds prevalence of non-lesional skin colonization with *S. aureus* in patients with AD

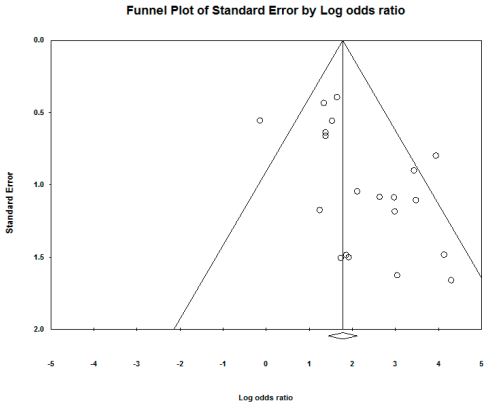
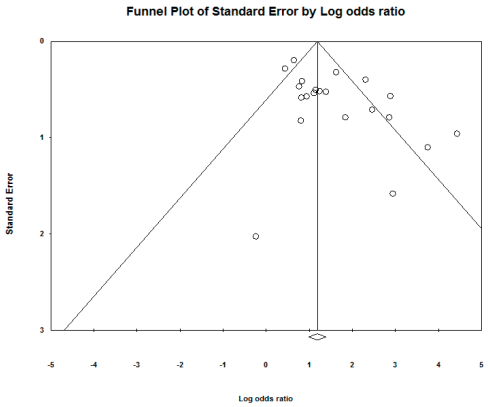


Figure S2f. Funnel plot of studies reporting odds of nasal skin colonization with *S. aureus* in patients with AD



SUPPLEMENTARY TABLES

Table S1. Digital search strategy (last updated 16th of September 2014)

Database	Search string
Embase	('Staphylococcus aureus'/exp OR 'Staphylococcal skin infection'/de ***OR*** 'Microbiome'/de OR 'Skin flora'/de OR ***'Staphylococcus alpha toxin'/de OR 'Staphylococcus toxin'/de OR 'Staphylococcus enterotoxin'/de OR 'Staphylococcus enterotoxin A'/de OR 'Staphylococcus enterotoxin B'/de OR 'Staphylococcus enterotoxin C'/ de OR 'Staphylococcus protein A'/de OR 'Panton Valentine leukocidin'/de OR 'Superantigen'/de OR*** (((cutan* OR skin* OR derma* ***OR nasal OR nose OR nare* OR mucos****) NEAR/3 (flora* OR microflora* OR microbio* OR bacteri* OR staph*)) OR ((staph* OR S OR St) NEAR/3 (aureus* OR pyogenes))):ab,ti OR (***(staph*:ab,ti OR 'Staphylococcus infection'/exp OR 'Staphylococcus'/exp) AND ('Alpha toxin'/de OR 'Bacterial toxin'/ de OR 'Exfoliatin'/de OR 'Leukocidin'/de OR 'Leukotoxin'/de OR 'Bacterial antigen'/de OR 'Cytotoxin'/de OR 'Enterotoxin'/de OR 'Hemolysin'/de OR 'Exotoxin'/de OR (superantigen* OR toxin* OR cytotoxin* OR hemoly* OR haemoly* OR enterotoxin* OR exotoxin* OR exfoliatin* OR leucotoxin* OR leukotoxin* OR leukocidin* OR leucocidin* OR epidermoly* OR dermoly****):ab,ti)))) AND ('Atopic Dermatitis'/de OR ***'Hand eczema'/de*** OR ***'Eczema'/de OR 'Neurodermatitis'/de*** OR (((atopic* OR infant* OR flexur* OR constitution*) NEAR/3 dermatit*) OR neurodermatit* OR eczema*):ab,ti) ***NOT ([animals]/lim NOT [humans]/lim) NOT nare*:ab,ti***
Medline via OvidSP	(exp "Staphylococcus aureus"/ OR "Staphylococcal skin infections"/ ***OR exp*** "Microbiota"/ OR (***staphylococcal alpha toxin OR enterotoxin A, staphylococcal OR enterotoxin B, staphylococcal OR enterotoxin C, staphylococcal OR enterotoxin D, staphylococcal OR enterotoxin E, staphylococcal OR enterotoxin G, staphylococcal OR enterotoxin I, staphylococcal OR staphylococcal enterotoxin J OR staphylococcal enterotoxin H OR SEIO enterotoxin, Staphylococcus aureus OR SEIM enterotoxin, Staphylococcus aureus OR Hlb protein, Staphylococcus aureus OR Gamma-hemolysin, Staphylococcus aureus OR Panton-Valentine leukocidin).mp. OR "Staphylococcal protein A"/ OR "Superantigens"/ OR*** (((cutan* OR skin* OR derma* ***OR nasal OR nose OR nare* OR mucos****) ADJ3 (flora* OR microflora* OR microbio* OR bacteri* OR staph*)) OR ((staph* OR S OR St) ADJ3 (aureus* OR pyogenes))).ab,ti. OR (***(staph*.ab,ti. OR "Staphylococcal infections"/ OR "Staphylococcus"/) AND ("Bacterial toxins"/ OR "Leukocidins"/ OR "Leucocidins"/ OR leukotoxin.mp. OR "Antigens, Bacterial"/ OR exp "Cytotoxins"/ OR "Enterotoxins"/ OR "Hemolysin Proteins"/ OR exp "Exotoxins"/ OR (superantigen* OR toxin* OR cytotoxin* OR hemoly* OR haemoly* OR enterotoxin* OR exotoxin* OR exfoliatin* OR leucotoxin* OR leukotoxin* OR leukocidin* OR leucocidin* OR epidermoly* OR dermoly****).ab,ti.))) AND ("Dermatitis, Atopic"/ OR exp***"Eczema"/ OR "Neurodermatitis"/*** OR (((atopic* OR infant* OR flexur* OR constitution*) ADJ3 dermatit*) OR neurodermatit* OR eczema*).ab,ti.) ***NOT (animals NOT humans).sh.***
Web of Science	TS=((((cutan* OR skin* OR derma* ***OR nasal OR nose OR nare* OR mucos****) NEAR/3 (flora* OR microflora* OR microbio* OR bacteri* OR staph*)) OR ((staph* OR S OR St) NEAR/3 (aureus* OR pyogenes)) OR (***staph* AND (superantigen* OR toxin* OR cytotoxin* OR hemoly* OR haemoly* OR enterotoxin* OR exotoxin* OR exfoliatin* OR leucotoxin* OR leukotoxin* OR leukocidin* OR leucocidin* OR epidermoly* OR dermoly****))) AND (((atopic* OR infant* OR flexur* OR constitution*) NEAR/3 dermatit*) OR neurodermatit* OR eczema*) NOT ((animal* OR pig* OR sheep* OR horse*) NOT (human* OR patient*)))
Cochrane Central	((((cutan* OR skin* OR derma* ***OR nasal OR nose OR nare* OR mucos****) NEAR/3 (flora* OR microflora* OR microbio* OR bacteri* OR staph*)) OR ((staph* OR S OR St) NEAR/3 (aureus* OR pyogenes))):ab,ti OR (***staph*:ab,ti AND ((superantigen* OR toxin* OR cytotoxin* OR hemoly* OR haemoly* OR enterotoxin* OR exotoxin* OR exfoliatin* OR leucotoxin* OR leukotoxin* OR leukocidin* OR leucocidin* OR epidermoly* OR dermoly****):ab,ti)))) AND ((((atopic* OR infant* OR flexur* OR constitution*) NEAR/3 dermatit*) OR neurodermatit* OR eczema*):ab,ti)
Pubmed	(((cutan*[tiab] OR skin*[tiab] OR dermal[tiab] OR dermatol*[tiab] ***OR nasal[tiab] OR nose[tiab] OR nare*[tiab] OR mucos*[tiab]***) AND (flora*[tiab] OR microflora*[tiab] OR microbio*[tiab] OR bacterial[tiab] OR bacterio*[tiab] OR staph*[tiab])) OR ((staph*[tiab] OR S[tiab] OR St[tiab]) AND (aureus*[tiab] OR pyogenes[tiab])) OR (***staph*[tiab] AND (superantigen*[tiab] OR toxin*[tiab] OR cytotoxin*[tiab] OR hemoly*[tiab] OR haemoly*[tiab] OR enterotoxin*[tiab] OR exotoxin*[tiab] OR exfoliatin*[tiab] OR leucotoxin*[tiab] OR leukotoxin*[tiab] OR leukocidin*[tiab] OR leucocidin*[tiab] OR epidermoly*[tiab] OR dermoly*[tiab]***))) AND (((atopic*[tiab] OR infant*[tiab] OR flexur*[tiab] OR constitution*[tiab]) AND dermatit*[tiab]) OR neurodermatit*[tiab] OR eczema*[tiab]) AND publisher[sb]

Table S2 can be found in the published article online: https://onlinelibrary-wiley-com.eur.idm.oclc.org/doi/abs/10.1111/bjd.14566

Table S3. Presence of enterotoxins in lesional skin of patients with AD and healthy controls

Author	Patients, n/total (%)								Healthy controls, n/total (%)							
	SEA	SEB	SEC	SED	SEG	TSST1	Alpha toxin	At least positive for 1 toxin	SEA	SEB	SEC	SED	SEG	TSST1	Alpha toxin	At least positive for 1 toxin
Lesional skin																
Bozek 2012* [69]	3/121 (2.5)	56/121 (46.3)	8/121 (6.6)	29/121 (24.0)				67/121 (55.4)								5/106 (4.7)
Casas 2011* [74]				7/18 (38.8)	9/18 (50.0)											
Matsui 2000* [2]	4/26 (15.4)	1/26 (3.8)	5/26 (19.2)		0/26 (0.0)	3/26 (11.5)		10/26 (38.5)	2/49 (4.1)	0/49 (0.0)	0/49 (0.0)	0/49 (0.0)	0/49 (0.0)	1/49 (2.0)		2/49 (4.1)
Nada 2012* [71]	1/30 (3.3)	8/30 (26.7)	4/30 (13.3)	1/30 (3.3)		4/30 (13.3)		14/30 (46.7)								
Kozman 2010^ [84]	8/89 (9.0)	20/89 (22.5)		2/89 (2.2)		3/89 (3.4)		28/89 (31.5)								
Wichmann 2009[&] [92]							30/127 (23.6)									
Silva 2006[$] [105]	1/10 (10.0)	7/10 (70.0)	2/10 (20.0)					8/10 (80.0)	0/10 (0.0)	1/10 (10.0)	0/10 (0.0)			0/10 (0.0)		1/10 (10.0)
Leung 1993^ [133]	7/42 (16.7)	8/42 (19.0)	0/42 (0.0)	1/42 (2.4)		7/42 (16.7)		24/42 (57.1)								

* Toxins detected with PCR

^ Toxins detected with ELISA

[&] Toxins detected with synergistic haemolysis test

[$] Toxins detected with dialysis membrane over-agar-method