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Received Date : 23-Aug-2016

Revised Date : 30-Jan-2017

Accepted Date : 08-Feb-2017

Article type : Review Article

The Role of the Skin Microbiome in Atopic Dermatitis: A Systematic Review

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Conflict of interest: None.

Funding: A grant from Danish Environmental Protection Agency is supporting salary of the scientists at the National Allergy Research Centre.

What's already known about this topic?

- Dysbiosis is a hallmark of atopic dermatitis: *Staphylococcus aureus* colonisation is frequent and affects disease severity adversely.

- Recent availability of culture-independent methods to profile microorganisms has enabled studies of whole microbial communities and their role in dermatitis.

What does this study add?

- The atopic dermatitis skin has low bacterial diversity, high non-*Malassezia* fungal diversity, high abundance of *Staphylococcus aureus* and *Staphylococcus epidermidis* and reduced abundances of other genera.
- An animal study indicates that dysbiosis is a driving factor in eczema.
- More data are warranted for better characterization of the role of the microbiome in atopic dermatitis and the influence of methodological approaches needs to be resolved.

Summary

Background: Dysbiosis is a hallmark of atopic dermatitis. The composition of skin microbiome communities and the causality of dysbiosis in eczema have not been well established.

Objective: To describe the skin microbiome profile in atopic dermatitis and address if there is a causal relationship between dysbiosis and atopic dermatitis.

Methods: The protocol is registered in PROSPERO (CRD42016035813). We searched PubMed, Embase, Scopus and ClinicalTrials.gov for primary research studies applying culture-independent analysis on the microbiome on atopic dermatitis skin of humans and animal models. Two authors independently full-text screened studies for eligibility and assessed risk of bias. Because of heterogeneity no quantitative synthesis is made.

Findings: Of 5735 texts, 32 met the inclusion criteria and 17 of these are published; 11 human and 6 animal studies. The studies varied in quality and applied different methodology. The skin in atopic dermatitis had low bacterial diversity (lowest at dermatitis involved sites) and 3 studies showed depletion of *Malassezia* species and high non-*Malassezia* fungal diversity. The relative abundance of *Staphylococcus aureus* and *Staphylococcus epidermidis* were elevated and other genera were reduced, incl. *Propionibacterium*. A mouse study indicated that dysbiosis is a driving factor in eczema pathogenesis.

Conclusion: The data is not sufficiently robust for good characterisation; however, dysbiosis in atopic dermatitis does not only implicate *Staphylococcus* species, but also microbes such as

Propionibacterium and Malassezia. A causal role of dysbiosis in eczema in mice encourages future studies to investigate if this applies in humans too. Other important aspects are temporal dynamics and the influence of methodology on microbiome data.

Introduction

Recent availability of culture-independent methods to profile microorganisms and study microbial communities has increased our understanding of the microbiome and its impact in health and disease. Much research has focused on the gut microbiome where findings demonstrate associations between dysbiosis and diseases such as diabetes and asthma [1]. The number of skin microbiome studies is rising. The skin is composed of a variety of niches selecting for colonization by specific microorganisms [2]. Host factors, e.g. sex [3], age [4], and environmental exposures [3, 5, 6], also affect the niches and microbiome communities and it is becoming increasingly apparent that the skin microbiome in turn influences vital functions in the host such as immunity and colonisation by pathogenic microorganisms [5].

Atopic dermatitis (AD) is a chronic skin disease affecting up to 20% children, with lesser prevalence in adults [7]. It manifests with dry, itchy skin, relapsing eczema at sites depending on age: The cheeks on infants are typically the first place to be affected, extensor aspects of joints in toddlers, flexures in older children and a various presentation in adults. AD is characterised by immune dysregulation predisposing to IgE production [8]. Conventional culture-based work has established that dysbiosis is a hallmark too [9], 70% of lesional and 39% non-lesional skin sites are colonised by *S. aureus* [10], which adversely affects disease severity. Not only bacteria but also the fungi are implicated [11]. Conventional culturing fails to grow about 80% of bacterial species [12]. By applying culture-independent molecular methodology dysbiosis is broadly described and the relative amount of present microbes becomes evident, which is also true for microbes not present. Though skin dysbiosis and the microbiome are anticipated an important role in development of treatments, there has been no systematic review on the skin microbiome profile in AD. AD is a multifactorial disease, but the gene-environment interactions leading to development of AD are not fully understood. Controversy remains as to

distinguishing between primary events leading to AD and secondary events resulting from AD [13]. Whether the skin microbiome is a primary factor in AD pathogenesis is uncertain.

This systematic review provides an overview of the AD skin microbiome profile. It is questioned if causal relationships between the skin microbiota and disease exist. To elaborate on this question animal studies are also included and the effect of treatment of AD on the microbiome is evaluated. A discussion of future directions in AD microbiome research is included.

Methods

Complete methods of the literature search, risk of bias and data extraction were specified in advance and documented in a protocol registered in PROSPERO (CRD42016035813).

A systematic literature search was conducted October 21 2016 in PubMed, Embase, Scopus and ClinicalTrials.gov using search terms from the categories: Skin, microbiome and AD – without language and date limitations. After an initial screen of title and abstracts, two authors independently screened full texts for eligibility. Primary research studies (observational and interventional) were included if they applied culture-independent methods and whole community analyses to characterise the AD skin microbiome of humans and animal models. Studies were excluded if they did not present data, included a wrong study population, investigated the microbiome of other body sites or investigated selected microbial taxonomic units. Duplicate studies were excluded. Disagreements on eligibility were resolved by contacting the authors of the original studies.

Two authors assessed risk of bias. For the human studies we used the Cochrane Collaboration's tool for randomised controlled trials (RCT's) and adjusted Newcastle-Ottawa Scales for analytical non-randomized case-control studies and cohort studies without a control group. For the animal studies we used adjusted versions of the Systematic Review Centre for Laboratory Animal Experimentation's (SYRCLE) risk of bias tool [14]. Highest-quality evidence received greatest emphasis.

Two authors collected study characteristics and relative abundances of microbial taxonomic units (when >1% and significant differences were found compared to a reference).

The criteria for study inclusion allow for heterogeneity in study population, design and methods. Therefore no quantitative synthesis was carried out.

Results

5735 studies were identified (fig. 1). After review of title and abstract, 90 were full text screened. Based on selection criteria, 32 records were included – 17 were published (table 1) and 15 were ongoing (supplementary table 1). The published studies were examined in most detail.

Human studies

Study description

Eleven human studies were identified (table 1): 2 RCTs, 7 case-control studies and 2 cohort studies. The studies included 355 AD patients. Oh et al. [15] included also patients with primary immunodeficiencies (N=41), characterised with AD-like eczema. Their data is regarded as from an AD population. The age of the participants spanned from 2 months to 62 years and both sexes were included in 10/11 studies [15-22]. AD was clinically characterised by SCOring of Atopic Dermatitis (SCORAD) in 8/11 studies [15-19, 21-23], Eczema Area and Severity Index in 1/11 studies [24] and Rajka-Langeland in 1/11 studies [4]. Patients with mild AD were included in 2 studies [16, 20], moderate in 9 studies [4, 15-20, 23, 24] and severe in 7 studies [4, 15-17, 19, 20, 24, 25]. Only one study [20] distinguished microbiome compositions according to disease severity. The skin microbiome of anatomically defined skin area(s) were investigated in 9/11 studies [4, 15, 17, 19-21, 23, 25]. Other compared affected and non-affected skin sites [4, 16, 18, 23, 24]. Well defined criteria for treatment allowed before and during the studies were provided in 10/11 studies [4, 15, 16, 18-25].

Methodology

The primary sampling technique of skin was swabs. No biopsies were taken. Different protocols were used for DNA extraction. One study applied a metagenomic sequencing approach profiling all microbes [25]. For bacterial microbiome analyses 10/11 studies used 16S rRNA sequencing [4, 15-19, 21-24] applying either broad-range16S gene primers [17, 19] or targeting hypervariable region 1-3 (V1-V3) [4, 15, 21, 22], V3 [16], V4[24], V1-V2 [18] or V2-V3 [23]. The fungal microbiome was characterised in 2 studies [15, 20], using either the Internal Transcriber Spacer sequence and 18S rDNA as targets for amplification [15] or

the D1/D2 hypervariable region of the 28S rDNA gene [20]. The amount of PCR cycles differed from 30 [16, 20, 23] to 35 [18, 24] to 40 [17]. Five studies did not provide information on the number of PCR cycles [4, 15, 19, 21, 22]. Relative abundances of microbial taxonomic units were provided in percentages in 7/11 studies [4, 15-17, 19, 20, 25], in 5 studies estimations were made from readings of figures [18, 21-24]. Taxonomic classification was performed either on genus- [15, 17-19, 21, 24], family- [22, 23] or species-level [4, 17, 20, 25]. More studies included additional species-level identification of *Staphylococcus* [15, 18, 19, 22] or only *S. aureus* [21]. The study by Bourrain [16] only identified *S. aureus* versus diversified microbiota.

Risk of bias

The quality of the human studies varied (table 2). We rated them as very good (total score=9 and one RCT rated low in risk of bias; N=4), good (total score=7-8; N=4), fair (total score=5; N=2) and poor (a poorly reported RCT; N=1). The main reason for downgrading the quality of the "fair" studies was either lack of information on cases and controls [20] or missing a proper non-exposed control [18].

AD skin microbiome profile

S. aureus was abundant on AD skin compared to control [4, 15, 19] and correlated positively to disease severity [15] (table 3). Affected skin sites were more *S. aureus* dominated than unaffected [4, 15, 16, 26]; especially inflamed areas (compared to xerotic) [16] – and during a flare the abundance increased dramatically in untreated patients [19]. Besides *S. aureus*, other species from the genus *Staphylococcus* increased on involved sites [24]. These included *S. epidermidis* [15, 19, 26] and *S. haemolyticus* [15].

The bacterial diversity on AD skin was low compared to control [15, 19] and reduced during a flare [19]. Reductions in species from the genera *Streptococcus*, *Propionibacterium* [4], *Acinetobacter*, *Corynebacterium* and *Prevotella* were found – not solely attributed to *S. aureus* increase [19]. *Propionibacterium acnes* was also found less frequent on facial AD skin compared to control [17] and was inversely correlated to disease severity [15]. Interestingly, though *Corynebacterium* decreased during AD flares [19], it was increased in the antecubital flexure of primary immunodeficiency patients [15]. After a flare, the species that were reduced increased in relative abundance [19].

The fungal microbiome showed that AD patients had overall depleted *Malassezia* family members[25], however enrichment of *M. dermatis*[25] and more diverse non-*Malassezia* species compared to healthy controls [15, 20]. These included *Aspergillus* [15], *Candida albicans* and *Cryptococcus diffluens* [20].

Effect of treatment on the skin microbiome in AD

Compared to no treatment, intermittent-treatment decreased *S. aureus* predominance and loss of bacterial diversity during a flare [19] (table 3) – with no improvement in SCORAD (data in original paper by Kong). In contrast, Oh et al. found no such treatment-associated shifts in bacterial community diversity [15].

One study evaluated the effect of dilute blech baths and found that 10 days of baths improved SCORAD and number of lesional sites colonised by *S. aureus* [16]. Another study evaluated the effect of topical corticosteroid treatment alone or in combination with dilute bleach baths. Both treatments improved the clinical eczema representation and suppressed *Staphylococcus* on both lesional and non-lesional sites – concluding no effect of the additional dilute bleach baths [24].

Emollient usage improved SCORAD and resulted in minor changes in the microbiome: 28 days of emollient usage did not induce changes in genus-level microflora at unknown skin site(s) but *S. aureus* increased in the non-emollient control group only [21]. 84 days of emollient usage on affected and unaffected sites improved SCORAD in 26 individuals out of 36 [26]. These 26 individuals had less relative abundance of *Staphylococcus* spp. and significantly more *Stenotrophomonas* – which also was inversely correlated to disease severity [15]. However, *Stenotrophomonas maltophilia* was found in facial skin in AD patients (not in controls) [17].

Association between dysbiosis and AD

Two months old infants who later were diagnosed with AD and had affected skin at the age of 12 months had demonstrated significantly lower number of commensal *Staphylococcus* species in their antecubital fossae than children with unaffected skin at the age of 12 months [22]. These data suggest that cutaneous dysbiosis might play a role in initiation of AD and further that exposure to commensal staphylococci during early infancy might be important.

Animal studies

We included 6 animal studies (table 1) either with AD dogs or mouse models; 4 non-interventional and 2 interventional. Four studies sampled the skin by swabbing [27-30] and 2 by biopsies [31, 32]. Different DNA extraction protocols were used. The bacterial microbiome was analysed in 5/6 studies by 16S

rRNA sequencing [27, 29-32]. The fungal microbiome was characterized in one study [28]. No information on the amount of PCR amplification cycles were given in 4/6 studies [27-30].

Relative abundances of microbial taxonomic units was provided in percentages in 3/6 studies [27, 28, 32] and estimated from readings of figures in 3 studies [29-31]. Taxonomic classification was performed either on family-level [29, 32] with additional analysis of *Staphylococcus* species in one study [29], genus- [27, 28, 31] or phylum- with species-level identifications of *Staphylococcus* and *Corynebacterium* [30].

The animal studies were mostly unclear in risk of bias (table 2) due to poor reporting, which is common for animal studies [14].

Animal AD skin microbiome profile and effect of treatment

Like humans, AD dogs [27, 29] and Adam17-deficient mice [33] had decreased bacterial diversity, increased abundance of *Staphylococcus* species [29] and *S. aureus* at the onset of eczematous inflammation [33] (table 4). *Corynebacterium* species were also increased [29, 31, 33].

Antimicrobial treatment of dogs presenting AD lesions [29] decreased the clinical eczema score and transepidermal water loss. No difference was found in skin pH. Furthermore, bacterial diversity normalised with decreased relative abundance of *Staphylococcus* species.

Causality between dysbiosis and AD

In Adam17-deficient mice [33] a prescreening of microbial composition was used to target systemic antimicrobial therapy. Therapy resulted in decreased clinical scores and transepidermal water loss along with decreased relative abundance of the targeted species, *S. aureus* and *C. bovis,* and increased bacterial diversity. Withdrawal of treatment dissipated the improvements in diversity. Eczema and dysbiosis re-appeared after 2 weeks, as shown in a cross over design, where systemic antibiotics was shown to protect the Adam17-deficent mice from developing eczema and loosing microbiome diversity. These data suggest a causal relationship between dysbiosis and AD in an animal model.

Discussion

In this systematic review we demonstrated that AD skin in humans is characterised by low bacterial diversity and high non-*Malassezia* fungal diversity. On involved skin the bacterial diversity was even

lower. The relative abundance of both *S. aureus* and *S. epidermidis* was elevated and the abundance of *Propionibacterium* was reduced, along with other genera; *Streptococcus*, *Acinetobacter*, *Corynebacterium* and *Prevotella*. A birth cohort study indicated that absence of early colonization with commensal staphylococci might precede AD presentation and an animal study indicated that dysbiosis was a driving factor in pathogenesis of eczema. In interpreting this data synthesis, it should be emphasised that the data was drawn from few studies with substantial heterogeneity and varied quality. Many of the included studies (15 of 17) analysed the microbiome using 16S rRNA sequencing, and eventhough the 16S rRNA gene is widely accepted as a biological fingerprint for bacterial species, there are some limitations. Some bacterial species have multiple copies of 16S rRNA genes, which may lead to an artificial overrepresentation in data [34]. In addition, technical aspects may introduce uncertainty too; these include sampling technique [35], DNA extraction [36] and sequencing protocol [37]. For instance classification accuracy varies with the specific regions of the 16S rRNA gene chosen to be sequenced [37]. The limitations to 16S surveys have made the newer approach whole metagenome shotgun sequencing attractive. This method allows for analysis of the entire gene content of the microbial population, catch most species and may sequence deep enough to identify strains [37]. This is crucial when it comes to understanding the physiological implications of a modified microbiome. Only 1/17 studies applied this method. Sequences obtained have short read lengths and many have no representative within databases. Therefore the different methodology applied in the included studies likely affect outcome in microbiome composition and underline the importance of transparency in methodological approach. Not all studies included provided enough information on each methodological step. This shows a need for a guideline for good reporting on microbiome studies.

A common criticism using DNA-based technology to identify microbial communities is that DNA from dead and viable microorganisms are not distinguished. In the future, attempts to reduce DNA from dead microorganisms or performing RNA (cDNA) based community analysis may help minimizing detection of dead microorganisms. Such approaches would also contribute to enlighten potential interplays and communication between host and microbiome, e.g. in processes such as eczematous inflammation. Studies are moving from describing the microbiome to focus on

interactions by implicating also RNA, protein and/or metabolite data. A study by Fyhrquist showed a positive correlation between the relative abundance of skin *Acinetobacter* species and expression of anti-inflammatory molecules among healthy subjects, which was not present in atopic individuals [38]. In the study by Kong [19], the relative abundance of *Acinetobacter* increased post flare – which supports a potential anti-inflammatory role of *Acinetobacter* in AD.

Ongoing studies investigate the effect of age and treatment of AD (supplementary table 1). The findings of *Corynebacterium* being reduced in AD flares, but increased in the antecubital flexure of primary immunodeficiency patients suggest that underlying genetics may affect the microbiome. Mutations in the gene encoding the protein filament aggregating protein, filaggrin, leading to a functional absence of the protein predisposes individuals to develop atopic eczema [39], increase stratum corneum pH [40] and increase susceptibility to recurrent bacterial skin infection among patients with AD [41]. Filaggrin deficiency in ichthyosis vulgaris is associated with a low abundance of proteolytic Gram-positive anaerobic cocci, which are shown better at inducing expression of antimicrobial peptides in cultured keratinocytes [42]. This could be a mechanism favoring growth of *S. aureus* or infection. A trend for lower bacterial diversity in one control and two AD filaggrin-null mutation subjects was seen in the study by Chng [25]. However, the role of filaggrin on the skin microbiome in AD is not known and none of the studies included in this review could elaborate thoroughly on this.

In line with the *S. aureus* data in this review, a recent meta-analysis showed that patients with AD were more likely to be colonized with *S. aureus* than healthy controls, with higher odds rations on lesional skin (19.74, 95% CI: 10.88-35.81) compared to non-lesional (7.77, 95% CI: 3.82-15.82) [10]. With *S. aureus* being more abundant on non-lesional skin suggests that the skin is susceptible to pathogen colonization and in risk to progress toward diseased state. This indicates that anti-staphylococcal treatment could be beneficial. However, a systematic review by Bath-Hextall [43] showed that reducing the numbers of *S. aureus* in people with uninfected eczema, did not result in reduced disease activity. Targeting specific *S. aureus* strains could potentially improve the outcome of anti-staphylococcal treatment. This is supported by the finding of a single nucleotide polymorphism in a staphylococcal lipase gene being preferentially hosted in AD [25]. However, targeting other bacteria

might also be beneficial. An idea of a critical window early in life where exposure to certain microbes are important for development of the immune system and allergic diseases has arisen and is supported by studies showing reduced microbial diversity in the gut before atopy development [1, 44, 45]. Further, tolerance to the skin commensal *S. epidermidis* is preferentially established in neonatal life in mice [46]. Current data [22] is limited and it is difficult to evaluate whether the cutaneous microbiome play a role in initiation of AD. Hypothesising that dysbiosis precede AD flares and severity, studies are currently investigating prevention and treatment targeting dysbiosis. Moisturisers are key in AD management to restore and preserve skin barrier integrity. A RCT showed that emollient therapy from birth in high risk AD babies enhanced the skin barrier and reduced the relative risk of AD incidence with 50% after 6 months [47]. An ongoing study by Glatz (supplementary table 1) investigates if shifts in the skin microbiome are associated with this improvement. Preliminary data show that preventative emollient usage lowers pH, does not change transepidermal water loss and increases the number of bacterial taxonomic units and Streptococcus spp. [48]. Since *Streptococcus* was reduced during flares [19] but increased in the abscense of commensal staphylococci in infants before AD presentation [22] future studies should investigate the role of *Streptococci* species in AD. *Stenotrophomonas* spp. may also have an important role with restoration of the skin microbiome [18].

Another approach to manipulate the skin microbiome is adding beneficial bacteria to moisturisers. A RCT showed that cream containing 5% lysate of the nonpathogenic Proteobacteria *Vitreoscilla filiformis* significantly improved SCORAD, transepidermal water loss, the AD patient's assessment of itch and loss of sleep compared to placebo [49]. Ongoing studies by Gallo and colleagues apply the same principle: In attempt to decrease *S. aureus* colonisation in AD skin, they isolate beneficial *Staphylococcal* species from the patients themselves and place them in a moisturiser, applied to the subjects own arms (supplementary table 1).

To utilize the microbiome in prevention and treatment strategies of AD, more data from human studies are needed on the skin microbiome dynamics related to clinical measures, temporal resolution and how different factors modify the microbial abundances to be able to predict responses in the

microbiome to perturbations. Good speciation and strain-level identification in combination with RNA, protein and metabolite data would strengthen such data and provide valuable insight.

Conclusion

While the microbiome draw increasingly attention as target in prevention and treatment of AD, new methodological approaches have not yet brought us far in understanding the impact of dysbiosis in AD. Staphylococcal species are key players in worsening of AD, and may also be important in the establishment of the disease. Other microbes such as *Propionibacterium*, *Streptococcus*, *Acinetobacter and Malassezia* have been found to be implicated in AD dysbiosis. However, robust data are missing on the influence of methodological procedures, characteristics on the microbiome structure related to temporal dynamics, clinical measures and factors altering the microbiome.

Acknowledgements

We would like to thank scientists conducting primary research for providing information regarding eligibility for this review. We would also like to thank Eik Bjerre for his methodological advice on usage of systematic tools.

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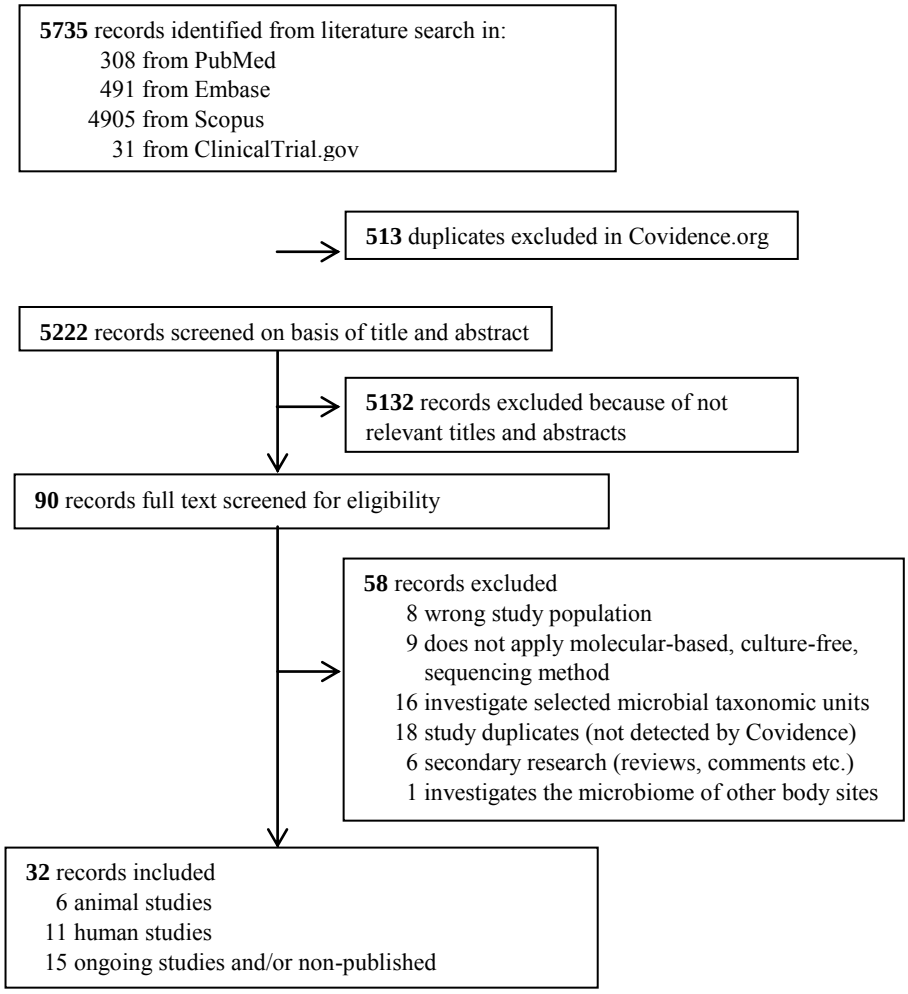
Figure 1: Flow diagram of study selection



	First author	Samp-ling	Area sampled	Setting	Study population	Treatment	N	Study type	Samp-le #	Method Extraction and sequencing	Physiological and clinical measures
Human studies	Bourrain [16]	Swab	5 cm^2 **I**nflam., **N**on-lesional and **X**erotic sites Body site: NA (dry, moist, seb.)	France	Mild-severe AD 18-40 years Mixed sex	Before and during the study: 1 wk: No use of top. steroids. 2 wk: No use of top. or oral immunomodulators, antibiotics, antiseptics or antifungal	25	Prospective cohort study: 18 days of hydrotherapy	4	DNeasy Blood and Tissue kit (Qiagen) 16S rRNA (V3), 30 PCR cycles Diversified microflora or *S. aureus* abundant	SCORAD
	Dekio[17]	Swab-scrub	4.9 cm^2 facial skin	Japan	Mod.-severe AD, Healthy ctrl 19-54 years Mixed sex	Not specified	13 AD 10 Ctrl	Case-control	1	Extraction buffer, glass beads 16S rRNA (V1-V9), 40 PCR cycles, Terminal Restriction Fragment Length Polymorphism	SCORAD
	Flores [18]	Swab	1 cm^2 of affected and nearby unaffected skin Body site: Diverse	France, Slovakia and USA, Californi a and Colorado	Mod. AD 3-39 years Mixed sex	During the study: Instucted not to use other emollients or drugs, incl. corticotherapy and antibiotherapy	49	Prospective cohort study: 84 days emollient treatment	2	MoBio PowerSoil DNA isolation kit 16S rRNA (V1-V2), 35 PCR cycles, 454-pyrosequencing	SCORAD, erythema, dryness, desquamation
	Kong [19]	Swab	Antecubital and popliteal creases, volar forearms, nares	USA, Maryland	Mod.-severe AD Healthy ctrl 2-15 years Mixed sex	"No": No top. for 1 wk, no oral antibiotics for 4 wk prior to sampling. "Intermittent": Top. in the prev. 1 wk and/or oral antibiotics in the prev. 4 wk	12 AD 11 Ctrl	Case-control: Baseline-flare-post flare Treatment (No N=7, intermittent N=5)	3	Lysis buffer and lysozyme, bead-beated, Invitrogen PureLink Genomic DNA kit 16S rRNA (V1-V8), Sanger sequencing	SCORAD
	Oh [15]	Swab and scrape	4 cm^2. Nares, retroauricular crease, antecubital fossa, volar forearm	USA, Maryland	PID patients (2-37 y) with 1) **H**yper IgE, 2) **W**iskott-Aldrich, 3) **D**OCK8 deficiency. Mod.-severe AD (2-17 y). Healthy ctrl (2-40 y). Mixed sex	Only data on PID patients: 22/25 H patients got antifungals and/or antibiotics. 6/10 W patients got antibiotics. 4/6 D patients got antibiotics	41 PID: 25H, 10W, 6D. 13 AD 49 Ctrl	Case-control	1	Lysis buffer and lysozyme, bead-beated, Invitrogen PureLink Genomic DNA kit 16S rRNA (V1-V3) 18SF and ITS1 (Only H patients) Sanger and 454 Sequencing	SCORAD
	Zhang [20]	Strip (x3)	63 cm^2 facial skin	Japan	Mild, mod., severe AD Healthy ctrl Mixed sex	Intermittent medium/strong top. steroids. No systemic or top. antibiotics or antifungals	3+3+3 AD 10 Ctrl	Case-control	1	Lysing solution, ethanol precipitation 28S rDNA (D1/D2), 30 PCR cycles, Sanger (3730x)	
	Bianchi [21]	Scratch	Right antecubital fossa (unaffected)	France, Italy	Children with mild AD 1-4 years Mixed sex	No immunosuppressant's a month before. Systemic antibiotics, probiotics or anti-inflammatory treatment 2 wk before, local top. a wk and no cream 48 h before	55	RCT: 28 days of 1) hygiene product or 2) hygiene product + emollient	2	QIAamp DNA Investigator Kit 16S rRNA (V1-V3), 454-pyrosequencing	SCORAD TEWL
	Drago [23]	Scrape	Behind the ear (lesional + non-lesional)	Italy	3 first cousins: mod. AD, mod. psoriasis, healthy ctrl 50 y Males	No pharmacological therapy or probiotics 1 month before sampling. Restricted on lifestyle, diet, sexual activity, personal care	1 AD 1 Ctrl	Case-control	1	Geneaid Genomic DNA Mini Kit (tissue) 16S rRNA (V2-V3), 30 PCR cycles Torrent PGM	SCORAD
	Kennedy [22]	Swab	Antecubital and popliteal fossae, nasal tip, cheek	Ireland USA, Maryland	AD and healthy ctrl infants from the Cork BASELINE Birth Study Mixed sex	Emollient usage in 6/10 AD infants and 2/10 healthy. No differences in bathing frequency or antibiotic usage	10 AD (4 affected at 12 months of age) 10 Ctrl	Case-control from a prospective birth cohort study. Swabbed at months 2, 6 and 12 and alsoclinical assessed at 24 months of age	3	Epicentre MasterPure Kit, bead-beated, Invitrogen PureLink Genomic DNA Kit, 16S rRNA (V1-V3), 454-pyrosequencing (GS FLX)	SCORAD (month 24). Filaggrin genotype (no mutations)

	Chng [25]	Tape-strip	Antecubital fossae	Singa-pore	Singaporean Chinese population, non-flare AD > 18 years Mixed sex	Only restricted from using antibiotics	19 AD 15 Ctrl	Case-control	1	Qiagen EZ1 DNA Tissue Kit, Shotgun whole-metagenome sequencing	Filaggrin genotype (mutations in 2 AD, 1 Ctrl) TEWL, pH
	Gonzalez[24]	Swab	3 lesional (2 representative + the worst) and 1 contralateral or adjacent non-lesional site. Ctrl at 4 sites with AD predilection	USA, New York	Mod.-severe AD Healthy ctrl 3 months – 5 years Mixed sex	Excluded if overt infection, concurrent chronic skin disorders or use of antibiotics, systemic or top. corticosteroids or calcineurin inhibitors in the prior 2 wk	21 AD 14 Ctrl	RCT: 4 wk treatment of 1) top. corticosteroid (plus water baths) or 2) top. corticosteroid plus bleach baths	2	MoBio PowerSoil DNA Isolation kit 16S rRNA (V4), 35 PCR cycles, Illumina MiSeq	Hanifin and Rajka, EASI
	Shi [4]	Swab	25 cm^2 lesional and adjacent non-lesional skin on volar forearm	USA, Cali-fornia	Mod-severe AD Healthy ctrl 2-12, 13-17 and 18-62 years Mixed sex	Excluded if temp > 38.5 Prior sampling: 20 days: No phototherapy or immunosuppressant's 1 wk: No antibiotics, topicals, bleach baths 24 h: No creams/lotions, bathes.	128 AD 68 Ctrl	Case-control: Comparison among age groups	1	QIAamp DNA micro kit incl. bead beating. 16S rRNA (V1-V3) Illumina MiSeq	Rajka-Langeland
Animal studies	Rodrigues Hoffmann [27]	Swab	**A**xilla, **g**roin, **n**asal, skin **in**-between digits	USA, Texas	Allergic dogs (6, 5 with AD) Healthy ctrl dogs	No syst. antibiotics 30 d prior to sampling. 3 got glucocorticoids or cyclosporine, 3 got allergen-specific immunotherapy	6 A 12 Ctrl	Case-control	1	MoBio Power Soil DNA isolation kit 16S rRNA (V1-V3), 454-pyrosequencing	
	Meason-Smith [28]	Swab	**A**xilla, **g**roin, **n**asal, skin **in**-between digits, ear canal, lumbar	USA, Texas	Allergic dogs (8, 6 with AD) Healthy ctrl dogs 1.5-11 y Mixed sex	No syst. antibiotics or antifungals in the allergic dogs 1 month prior sampling (6 in the healthy). Top. allowed	8 A 10 Ctrl	Case-control	1	MoBio Power Soil DNA Isolation kit Internal Transcribed Spacer region (1F and 4R), Illumina MiSeq	
	Bradley [29]	Swab	Axilla, groin, pinna, mouth	USA, Pennsyl-vania	AD dogs with active lesions Healthy control dogs	4 used antibiotics within 45 d before. Targeted antimicrobial therapy in the interventional period	14 AD 16 Ctrl	Prospective cohort study: Flare-post therapy-post conclusion	3	Lysozyme, bead-beating, protein precipitation, Genomic DNA Isolation Kit (Life Tech) 16S rRNA (V1-V3) Illumina MiSeq	Clinical scoring, TEWL, pH
	Kobayashi [33]	Swab	Cheek	JapanUSA, Maryland and Minnesota	Disintegrin and metalloproteinase 17 deficient mice in Sox9-tissue, incl. epidermidis ($AD17^{fl/fl}Sox9\text{-}^{Cre}$).		A) 3 WT 3 AD17 B) 8 WT 8 AD17 C)12 AD17	A) Tanner stage B) Antibiotics targeting *S. aureus* and *C. bovis* C) Crossover D) Characteristics	A) 7 B) 3 C) 2 D) 1	Incubated in lysis buffer and lysozyme, (maybe bead-beated), Invitrogen PureLink Genomic DNA kit. 16S rRNA (V1-V3), 454-pyrosequencing	TEWL
	Kubica [32]	Punch biopsy (4 mm)	Ear	Belgium	Caspase-14 (involved in filaggrin degradation) knock out hairless mice		5 WT 4 KO	Animal study, case-control	1	QIAamp DNA Stool Mini Kit, 16S rRNA (V3-V5), 25 PCR cycles, 454-pyrosequencing	
	Schar-schmidt [31]	Biopsy	Ear flexure	USA, Maryland	Ichthyotic model: Matripase (degrades profilaggrin) deficient Mice, 1% of WT levels ($St14^{hypo/-}$)		3 WT + 3 $St14^{hypo/-}$	Animal study, case-control	1	DNAeasy kit (Qiagen), protocol for Gram-pos. bacteria (incl. bead-beating) 16S rRNA (V1-V8), 23 PCR cycles, Sanger	

Table 1: Characteristics of included published studies. Inflam.: Inflammatory. NA: Not available. Seb.: Sebaceous. NIH: National Institutes of Health. AD: Atopic dermatitis. Mod.: Moderate. Wk: Week. Top.: Topical. Prev.: Previous. PID: Primary Immunodeficiency. H: Hyper-IgE. W: Wiskott-Aldrich. D: DOCK8 deficiency. Syst.: Systemic. H: Hours. D: Days. EGFR: Epidermal Growth Factor Receptor. AD17: $AD17^{fl/fl}Sox9\text{-}^{Cre}$ (AD17=ADAM17, a metallopeptidase involved in epidermal barrier integrity). WT: Wild Type. KO: Knock Out. $St14^{hypo/-}$: Mice with one null and one hypomorphic allele of "Suppressor of tumorigenicity 14", matriptase = a serine protease. Ctrl: Control. A: Allergic. AD: Atopic dermatitis. RCT: Randomised Controlled Trial. *S. aureus: Staphylococcus aureus. C. bovis: Corynebacterium bovis*. PCR: Polymerase Chain Reaction. rRNA: ribosomal RNA. ITS1: Internal Transcribed Spacer region 1. V3: Variable region 3 of the 16S rRNA gene. Gram-pos.: Gram-positive. SCORAD: SCORing Atopic Dermatitis. TEWL: TransEpidermal Water Loss. EASI: Eczema Area and Severity Index.

(a): Cochrane Collaboration's tool for assessing risk of bias in randomised controlled trials			
Study	**Domain**	**Review authors judgement**	**Support for judgement**
Bianchi [21]	Random sequence generation	Unclear	No information
	Allocation concealment	Unclear	No information
	Blinding of participants and personnel	Unclear	Patients not blinded, but no information on personnel.
	Blinding of outcome assessment	Unclear	No information
	Incomplete outcome data	Low risk	Reason given for one exclusion
	Selective reporting	Unclear	No study protocol available
	Other sources of bias	Unclear	Insufficient rationale: No sample size calculation. Objective is given but no clear hypothesis. No specified setting
Gonzalez [24]	Random sequence generation	Low risk	Shuffling envelopes
	Allocation concealment	Low risk	Numbered containers
	Blinding of participants and personnel	Low risk	Participants (incl. parents) and clinical personnel blinded
	Blinding of outcome assessment	Low risk	Investigators, data analysts, and sequences blinded to treatment until unblinding was necessary for comparative data analysis after ended experiment
	Incomplete outcome data	Low risk	Reasons for missing outcome data and balanced across intervention groups
	Selective reporting	Unclear	No study protocol available
	Other sources of bias	Low risk	The study appears to be free of other sources of bias

(b): Newcastle-Ottawa Scale for assessing quality of case-control studies				
Studies	**Selection** Definition and selection of cases and controls (max=4*)	**Comparability** of cases and controls (max=2*)	**Exposure** Blinding, same method, rel. abundances as outcome, complete data (max=4*)	**Total** (max=10*)
Dekio [17]	***	**	**	7
Kong [19]	***(*) (4/11 healthy children have fam. history of AD)	**	***	9
Oh [15]	***	**	***	8
Zhang [20]	*	*	***	5
Drago [23]	****	**	**	8
Kennedy [22]	****	**	***	9
Chng [25]	***	**	***	8
Shi [4]	****	**	***	9

(c): Newcastle-Ottawa Scale for assessing quality of cohort studies				
Studies	**Selection** True and/or somewhat representatives of AD, ascertainment of exposure, outcome at baseline (max=4*)	**Comparability** +/- treatment of matched skin areas, controlling for additional factors (max=2*)	**Outcome** Blinding, time to follow-up, complete follow-up, bias due to missing follow-ups (max=4*)	**Total** (max=10*)
Bourrain [16]	***	*	****	9
Flores [26]	**	*	**	5

(d): Adjusted SYRCLE's tool for assessing risk of bias in animal studies							
Type of bias	**Domain**	**Scharschmidt [31]**	**Kubica [32]**	**Rodrigues Hoffmann [27]**	**Meason-Smith [28]**	**Kobayashi [33]**	**Bradley [29]**
Selection bias	**Group similarity (sex, age)**	Low risk	Low risk	High risk	High risk	Low risk	High risk
Performance bias	**Random housing**	Unclear	Low risk	Low risk	Unclear	Unclear	Unclear
Detection bias	**Blinding**	High risk	Unclear	Unclear	Unclear	Unclear	High risk
Detection bias	**Blinding of outcome assessor**	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Attrition bias	**Incomplete outcome data**	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk
Reporting bias	**Selective outcome reporting**	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Biases associated with interventional studies	**Allocation**					Unclear	Low risk
	Baseline characteristics					B) Unclear C) Low risk	Low risk

Table 2: Review authors scores of risk of bias of included studies using the Cochrane Collaboration's risk of bias tool (a), an adjusted Newcastle-Ottawa Scale for case-control studies (b) and cohort studies (c) where points (*) are assigned for no biases and an adjusted SYRCLE's tool for non-interventional (6 entries) and interventional (8 entries) animal studies (d).

Phylum	Family	Genus or species	Bourrain [16] # Baseline/D1 D10 D18 **X I N**	De-kio [17] ¤ C / AD	Flores [26] Pre-tr Post-tr U A Resp Non U+A U+A	Kong [19] Antecub & popl C B F P I N	Oh [15] Antecub Volar forearm C PID AD H W D	Zhang [20] AD C M Mo S	Bianchi [21] ¤ D0 D28 C E	Drago [23] C AD U A	Kennedy [22] Antecub M2 U A M12	Chng [25] C / AD	Gonzalez [24] Baseline Post-tr **C Tr+bl Tr-bl L N L N**	Shi [4] C / AD L/N Ch Teen-Adu
Firmicutes	Staphylococca-ceae									33 32 33	50 7			
		Staphylococcus		75 54	17 33* 15 52	16 35 31 90 20	11 28* 7 35*47* 6 18* 7 11 8*					9 7	12 62 31 58 34 12 24*6* 24* 40	6 9 37/21*38/29*
		S. aureus	36 52/56*16 48 44 24 24 28 20		1 8	1 17 15 65* 6	0 10* 1 8		28 28 NA 28 (6.5x↑)*					0 1 24/13*20/13*
		S. capitis				2 2 6 1 3					3 0			
		S. epidermidis			11 19	9 7 7 20* 8	5 13* 2 7*				27 4			1 4 9/4 11/9
		S. hominis				3 5 2 2 2								2 2 2/2 4/4
		S. haemolyticus					0 1* 0 1*							
		S. cohnii									19 1			
	Alicyclobacilla-ceae				5 4 6 4									
	Streptococca-ceae										5 24			
		Streptococcus		80 54	8 7 6 5	15* 2 14*						1 3*	16 9 8 7 9 20 13 8 13 8	26 14 20/26* 10/11
		S. mitis										1 2*		
	Neisseriaceae	*Neisseria*												2 1 2/2 1/1
	Veillonellaceae	*Veillonella*												2 2 1.5/2* 1/1
Proteo-bacteria	Rhodobactera-ceae									1 1 1				
	Moraxellaceae	*Acinetobacter*			2 1.2 2 1	1 0 3*							7 3 3 3 3 11 3 3 11 4	1 1 1/1 1/1
	Xanthomonada-ceae	*Stenotropho-monas*			7 1.5*									
		S. maltophilia		0* 38										
	Alcaligenaceae	*Alcaligenes xylosoxidans*		0 7										
	Enterobacteria-ceae	*Serratia marcescens*					0 8* 3 0 0 0 8* 3 0 0							
Actino-bacteria	Dietziaceae	*Dietzia maris*		80* 15										
	Propionibacteria-ceae									18 14 15	5 13			
		Propioni-bacterium			11 8 11 5	6 1 12*	24 11 26 9 7					56 67		13 28 5/5 11/14

		P. acnes		75* 35										13 28 4/5 10/13
	Corynebacteria-ceae									3 2 1	2 4			
		Coryne-bacterium			4 3 8 3	9* 1 9*	9 17* 14 15 5 8 18 9 17 5					6 2		3 8 3/4* 8/11*
	Dermacocca-ceae											1 0.5*		
	Actinomycetace ae	*Rothia*												2 2 2/2 1/1
Bacte-roidetes		*Prevotella*			1 2	1 0 1								3 3 2/2 2/2
Asco-mycota	Trichocomaceae	*Aspergillus*					1 4* 0 7*							
	Saccharomyce-tales	*Candida*					0 0.4* 0 0.3*							
		C. albicans						1 2 3 0						
	Davidiellaceae	*Cladosporium*						5 5 6 3						
	Capnodiales	*Toxicoclado-sporium irritans*						2 2 1 0						
Basidio-mycota	Malasseziaceae											2 1*		
		Malassezia					96* 71 96* 67	69(all) 79						
		M. restricta						48 49 34 59						
		M. globosa						15 16 27 14				19 10*		
		M. dermatis										2 8*		
	Tremellaceae	*Cryptococcus diffluens*						2 1 3 1						
Shannon diversity (- *S. aureus*)					A=6.0; U=6.3 Pre-post: ΔU=0.2 ΔA=0.08	3.4 2.8 2.7 0.7* 3.4 *2.8 2.5 2.5 1.5* 2.8*	2.8 2.4 2.7 2.3 2.1* 2.8 2.7 2.9 2.8 2.7 No treatment effect in P at any site		2 2 2 2		NS	1.7 1.4	Improved with no differences between tr-groups. Inversely corr. to EASI	
SCORAD			Reduction at D18 (30.8±7.2 to 20.0±10.2)	36	Δ = -12. 78% sites had ↓severity	NA 21.8 42.1 18.1	0 22 6 11 28		10 12 8* 6*	32	Not relevant			
EASI													Improved with no differences between tr-groups	
Spearman corr.							To SCORAD, inverse: *Stenot., P. acnes, Neisseria, Streptococcus.* Pos.: *S. aureus*					Inverse: *P. acnes* and *S. epidermidis*. *Dermacoccus* and *S. aureus*		
TEWL (g/m^2/hour)									D28: No change in C, 34% ↓ in E			No diff		
Skin pH												No diff		

Table 3: Summary of relative abundance (in percent) of microorganisms found on skin, clinical and physiological outcomes, human studies. Taxonomic units with % relative abundance ≤ 1 are not included in this table.
#: Percentage of total amount of samples dominated by *S. aureus* (vs. diversified microbiota)
¤: Percentage of individuals in the study population with a specific microorganism (in percent)
X: Xerotic. I: Inflammatory. N: Non-lesional. L: Lesional site. .D1: Day 1. M2: Month 2. AD: Atopic Dermatitis. Antecub: Antecubital Fossa. Popl: Popliteal region. C: Control. Tr: Treatment. U: Unaffected. A: Affected. Resp: Responders. B: Before. F: Flare. I: Intermittent (treatment). N: No (treatment). P: Post flare. NA: Not available. PID: Primary Immunodeficiency. H: Hyper-IgE. W: Wiskott-Aldrich. D: DOCK8 deficiency. M: Mild. Mo: Moderate. S: Severe. E: Emollient (group). Ch: Children. Teenagers-Adults. SCORAD: SCORing Atopic Dermatitis. EASI: Eczema Area and Severity Index. TEWL: TransEpidermal Water Loss. * Indicate statistical differences found in the original papers.

Phylum	Family	Genus or species	Meason-Smith [28] C/A # Diff. between C and A, all sites Ax G I N E L	Rodrigues Hoffmann [27] C/A Ax G I N	Kobayashi [33] Time (wk) after birth WT/AD17 2 4 6 8 10 12 14	Kobayashi [33] Antibiotic treatment AD17 −AB/+AB 2 4 8	Kobayashi [33] Antibiotic treatment WT −AB/+AB 2 4 8	Kobayashi [33] Crossover, AD17 -AB→+AB 10 13	Kobayashi [33] Crossover, AD17 +AB→-AB 10 13	Kobayashi [33] Mechanism	Bradley [29] C/AD Flare Ax G P	Bradley [29] C/AD Post TR Ax G P	Bradley [29] C/AD Followup Ax G P	Kubi-ca [32] WT/KO	Schar-schmidt [31] WT/St14hypo/−
Firmicutes															2 9*
		Other than *Streptococcus* + *Staphylococcus*			82 53 76 60 46 41 36 83 15 10 3 1 0 7	82 13 0 94 35 48	86 41 49 92 50 48	0 33	38 0						
	Class: Bacilli													5 2*	
	Order: Bacillales													2 8	
	Bacillaceae	*Bacillus*		3 1 1 0 4 2 0* 0											
	Staphylococcaceae													92 77*	
	Staphylococcaceae	*Staphylococcus*		1 1 1 0 0 3 1 0							3 12 4 33*43*45*	6 11 6 12 9 17	4 11 6 6 9 20	50 52	
		S. aureus			0 0 0 0 0 0 0 0 12 8 49 45 30 25	0 16 39 0 1 2	0 0 0 0 0 0	23 5	5 17		Across all skin sites: Flare: 10 Post TR: 1 P: 11 10 7 5				
		S. lugdunensis									Across all skin sites: Flare: 20 Post TR: 18 P: 20 2 10 12				
		S. pseudintermedius									Across all skin sites: Flare: 52 Post TR: 62 P: 52 82 68 68				
		S. lentus			3 5 2 2 0 0 0 4 1 0 0 0 0 0	0 1 0 0 1 0	0 0 0 0 0 0	0 4	3 1						
		Other than *aureus and lentus*			0 0 0 0 0 0 0 1 2 4 0 0 1 0	0 0 0 0 0 0	0 0 0 0 4 0	0 2	6 3						
	Alicyclobacillaceae	*Alicyclobacillus*		0 0 0 0 1 1 2 0											
	Streptococcaceae	Streptococcus			0 1 0 16 3 10 11 0 4 0 2 1 1 0	1 2 0 1 1 0	0 10 5 0 1 0	1 1	5 2		3 10 4 3 2 3	4 8 7 4 5 6	4 4 5 5 10 5		0 6*
Proteobac-teria					4 16 3 3 8 3 3 1 5 2 1 0 0 0	3 4 0 3 19 2	3 14 9 3 6 5	0 12	16 0						97 75*
	Class: Beta-proteobacteria	Dominated by *Janthinobacterium*													35 31
	Neisseriaceae	*Conchiformibius*									2 6 3 0 1 1	4 7 3 1 2 1	2 7 2 3 4 4		
	Class: Gamma-proteobacteria	Dominated by *pseudomonas*													48 33
	Pasteurellaceae										3 3 4 2 1 1	2 2 2 3 1 2	3 2 2 2 2 2		
	Rhodobacteraceae	*Rubellimicrobium*		1 0 0 0 1 1 0* 0											
	Ralstoniaceae	*Ralstonia*		4 2 7 17 0 0* 0* 0*											
	Sphingomonadaceae	*Sphingomonas*		0 1 0 0 3 2 0 0											
	Xanthomonadaceae													1 3*	
		Stenotrophomonas												0	

							4*	
Actinobac-teria								2 13*
	Propionibacteriaceae	*Propionibacterium*				5 1 6 3 1 7 2 1 3 3 1 2 3 1 3 6 1 5		
	Corynebacteriaceae	*Coryonebacterium*				3 6 4 4 3 4 3 3 4 6 12*11 7 14 11 6 9 8		0 13*
		C. bovis			0 0 0 0 0 0 0 0 50 59 0 0 0 74 15 7 13 0 0 12 26 51 67 54 0 15 5 0 0 3			
		C. mastitidis			0 0 0 0 0 0 0 0 9 1 0 0 0 0 1 1 0 0 51 63 15 0 0 0 0 7 1 0 0 0			
		Other than *bovis, mast., jeikeium, tuberculostearicum*			2 11 2 11 9 11 19 0 0 0 0 16 7 0 6 7 0 0 0 0 0 0 0 0 1 8 12 0 12 47			
Bacteroidetes					6 9 3 13 29 28 25 7 2 0 6 16 26 0 17 4 0 6 6 2 0 0 0 5 6 16 6 6 25 8			
	Porphyromonadaceae	*Porphyromonas*				7 8 6 5 8 7 9 10 6 3* 3 1* 3 3 4 4 5 4		
	Flavobacteriaceae					1 1 1 1 1 1 2 2 1 1 0 0 4 2 1 2 1 1	0 6*	
Tenericutes	Mycoplasmataceae	*Mycoplasma*		0 0 0 0 2* 0 0 0				
Ascomycota	Pleosporaceae	*Alternaria*	30 28 22 33 23 32 20 20 26 30 11 22					
		Epicoccum	5 5 9 11 7 16 10 9 10 10 14 15					
	Davidiellaceae	*Cladosporium*	33 31 37 16 17 16 35 37 30 16 36 22					
	Saccharomycetales	*Candida*	# 0 1 0 0 0 0 0 4 0 0 0 0					
	Clavicipitaceae	*Claviceps*	# 1 1 0 0 0 1 0 4 0 0 0 0					
	Nectriaceae	*Fusarium*	1 2 3 0 2 0 2 5 2 0 0 2					
Basidiomyco ta	Malasseziales	*Malassezia*	1 1 0 5 1 1 1 2 2 0 2 0					
	Wallemiaceae	*Wallemia*	# 0 0 4 14 9 1 0 0 0 12 22 5					
	OTHER		# 2 4 5 0 7 4 5 1 2 5 12 2					
Shannon Diversity			All sites: $\frac{1.9}{1.7}$. Only diff in ear (C>A)	AGI: N: 6 2.9 5.4 2	2.3 1.3*0.8* 2 3.5 3.3 2.2 3 2.5 1.9 3 2.5	8 7 8 8 8 7.5 8.5 7.5 8 6*6 3* 7.5 7 7.5 7.5 6.5 7.5		
Chao1 richness				432 100 168* 40*				
Struc. similarity (θ)								WT ≠ KO
TEWL					5 6 8 NA 8 NA 9 7 19 NA 30 13*10 7*23*27*NA 34*NA 40* 7 12*NA 37 9 18	14 10 9 13 11 13 16 10 14 26 14 14 14 14 14 17 10 13		
Clinical score					NA 20 37 38 15* 5 43 NA 12*8*	0 0 0 22.0 14.9 15.9		
Antimicro-bial activity							KO> WT	

Table 4: Summary of relative abundance (in percent) of microorganisms found on skin, clinical and physiological outcomes, animal studies. Taxonomic units with % relative abundance ≤ 1 are not included in this table. C: Control. A: Allergic. Ax: Axilla. G: Groin. I: In-between digits. N: Nasal. E: Ear Canal. L:lumbar. Wk: week. WT: Wild Type. AD: Atopic dermatitis. AD17: AD17$^{fl/fl}$Sox9-^{Cre}. AB: Antibiotics. EGFR: Epidermal Growth Factor Receptor. P: Pinna. KO: Knock Out. St14$^{hypo/-}$: Mice with one null and one hypomorphic allele of "Suppressor of tumorigenicity 14", matriptase = a serine protease. * Indicate statistical differences found in the original paper.