

Cheek Microbial Communities Vary in Young Children with Atopic Dermatitis in China

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Keywords

Atopic dermatitis · Microbiome · Skin isolated bacteria · Keratinocytes

Abstract

Background: Atopic dermatitis (AD) is a chronic, recurrent skin condition with recently increased incidence in younger children. AD development has been correlated with the skin microbiome, and *Staphylococcus aureus* enrichment causes significant increases in skin lesions. **Objective:** Our objectives were to compare the microbial diversity of the cheek skin of children with or without AD aged 0–1 years in China, and to determine whether 4 types of skin-isolated bacteria could inhibit *S. aureus* in vitro. **Methods:** The skin microbial samples of cheek skin of children were sequenced by 16S rRNA V1–V2 region. Four skin isolated bacterial fermentation supernatants were tested for effects on *S. aureus* growth, membrane formation, and induction of cytokine secretion from HaCaT cells. **Results:** Bacterial diversity decreased significantly in skin with severe AD compared to healthy skin ($p < 0.01$). Seven phyla had content $>1\%$, 4 of which differed in AD ($p < 0.05$). 38 genera had content $>1\%$, 15 differed ($p < 0.05$). Differences in 8 species were observed ($p < 0.05$).

In vitro antibacterial and cellular experiments showed that *S. aureus* growth, biofilm formation, and induction of interleukin (IL)-1 α and IL-6 secretion from HaCaT cells were significantly inhibited by *Klebsiella oxytoca*, *Kocuria rhizophila*, and *Staphylococcus epidermidis* culture supernatants ($p < 0.05$). **Conclusion:** Skin microbiome changes in children varied with age and with AD. There were complex interactions between skin isolated bacteria and *S. aureus* which could inhibit *S. aureus* growth and biofilm formation in vitro, suggesting that these microorganisms could be used in AD treatment.

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Introduction

Atopic dermatitis (AD) is a chronic, highly pruritic (itchy) inflammatory skin disease and is one of the most common skin disorders in children [1, 2]. It is highly prevalent in children and often precedes allergic disorders such as asthma and allergic rhinitis. An epidemiological survey

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of AD revealed that its incidence in children and teenagers is 10–20%, with infants under 1 year old accounting for approximately 50% of those cases [3]. In infants and young children, it tends to occur on the face, scalp, and extensor surfaces of extremities [4]. Phenotypic analysis of AD in children aged 1–12 months in China revealed the most commonly seen manifestations in infantile AD were facial dermatitis (72.07%) [2]. The pathogenesis of AD is not completely understood. AD pathogenesis involves a number of factors [5], including microbial infections. In addition to the isolation of *Staphylococcus aureus* from the skin of a large number of patients with AD [6], a number of other factors also supports the hypothesis that microflora plays an important role in disease onset [7]. Recently, assessment of damaged regions has revealed significant differences of the skin microbiome between AD patients and healthy individuals, with a significant elevation in the abundance of *S. aureus* at the lesions and a significant reduction in microbes including *Propionibacterium acnes* [8–10]. Clinical studies have shown that *Lactobacillus* is an effective probiotic bacterium for the prevention and treatment of eczema and can inhibit the growth of *S. aureus* [11, 12]. Recent studies have reported that AD is also correlated with intestinal flora. Since a low abundance of *Lactobacillus* and *Bifidobacteria* or the lack of species-specific *Bifidobacteria* are considered to be strongly associated with AD, AD may be prevented by increasing the abundance of these intestinal bacteria [13–15]. Similarly, the recovery of AD may also be related to the skin microbiome. Manipulation aiming at an increase in the number of selected, potentially beneficial microorganisms using special nutrients (prebiotics) or even living microorganisms (probiotics) has presented a novel avenue. The creams containing a 5% lysate of the nonpathogenic bacterium *Vitreoscilla filiformis* can markedly improve the patient SCORAD index and pruritus [16].

High-throughput DNA sequencing of the bacterial 16S rRNA gene revealed the presence of more diverse bacteria on healthy human skin than that revealed through culture-based methods [17]. High-throughput 16S rRNA gene sequencing enables the examination of many genera and species including rare and fastidious bacteria, therefore providing the examination of skin bacterial communities at a higher resolution. This study explored the differences in cheek skin bacterial diversity of healthy and AD infants from 0 to 1 years old by the bacterial 16S rRNA gene sequencing and demonstrated in vitro interaction between isolated skin bacteria and *S. aureus*. Those may provide a new theoretical basis for the prevention and treatment of infantile AD.

Materials and Methods

For further details, see the online supplementary material (see www.karger.com/doi/10.1159/000502469) (Fig. 1; Table 1).

Results

Effects of Age on Healthy Cheek Skin Microbiome Composition

First, we sorted the healthy group into 3 subgroups by age (0–6, 6–12, and 12–36 months) and compared their microbiomes. Principal coordinate analysis (PCoA) profiles (Fig. 2a) demonstrated that sample distributions in the groups aged 0–6 and 6–12 months were relatively close but were well separated from the 12- to 36-month-old group, indicating changes in facial skin microbiome composition with age.

The difference between the 3 groups was analyzed by one-way ANOVA. There were 3 genera (>1%) that differed significantly between 0- to 12- and 12- to 36-month-old children, including *Streptococcus* (47.92 ± 12.44 , 38.80 ± 12.02 , and $17.06 \pm 8.68\%$ at 0–6, 6–12, and 12–36 months, respectively, $p = 0.00003$), *Rothia* (6.35 ± 5.98 , 5.13 ± 2.46 , and $2.09 \pm 1.69\%$ at 0–6, 6–12, and 12–36 months, respectively, $p = 0.017$), especially *Rothia mucilaginosus* (6.32 ± 6.00 , 4.56 ± 2.38 , and $1.28 \pm 1.35\%$ at 0–6, 6–12, and 12–36 months, respectively, $p = 0.0059$) and *Rothia aerea* (0.03 ± 0.04 , 0.57 ± 0.84 , and $0.81 \pm 0.65\%$ at 0–6, 6–12, and 12–36 months, respectively, $p = 0.0085$), *Leptotrichia* (0.16 ± 0.29 , 0.65 ± 0.73 , and $2.12 \pm 2.18\%$ at 0–6, 6–12, and 12–36 months, respectively, $p = 0.0299$).

Difference of Healthy and AD Cheek Skin Microbiome Composition

Due to a greater effect of age on differences among groups, especially after 1 year old, and in roughly 60% of cases, the disease manifests during the first year of life (i.e., early onset) [1]. Therefore, we selected 0- to 1-year-old healthy children and severe AD cases for bacterial diversity analysis.

Diversity Analysis

The bacterial alpha diversities of the 2 groups are summarized in Figure 2b and c. We analyzed alpha diversity (species richness) in the 2 skin microbiomes based on the estimated (Chao1) richness values and the Shannon diversity values. The Chao1 and Shannon values of healthy groups were significantly higher than those of the severe

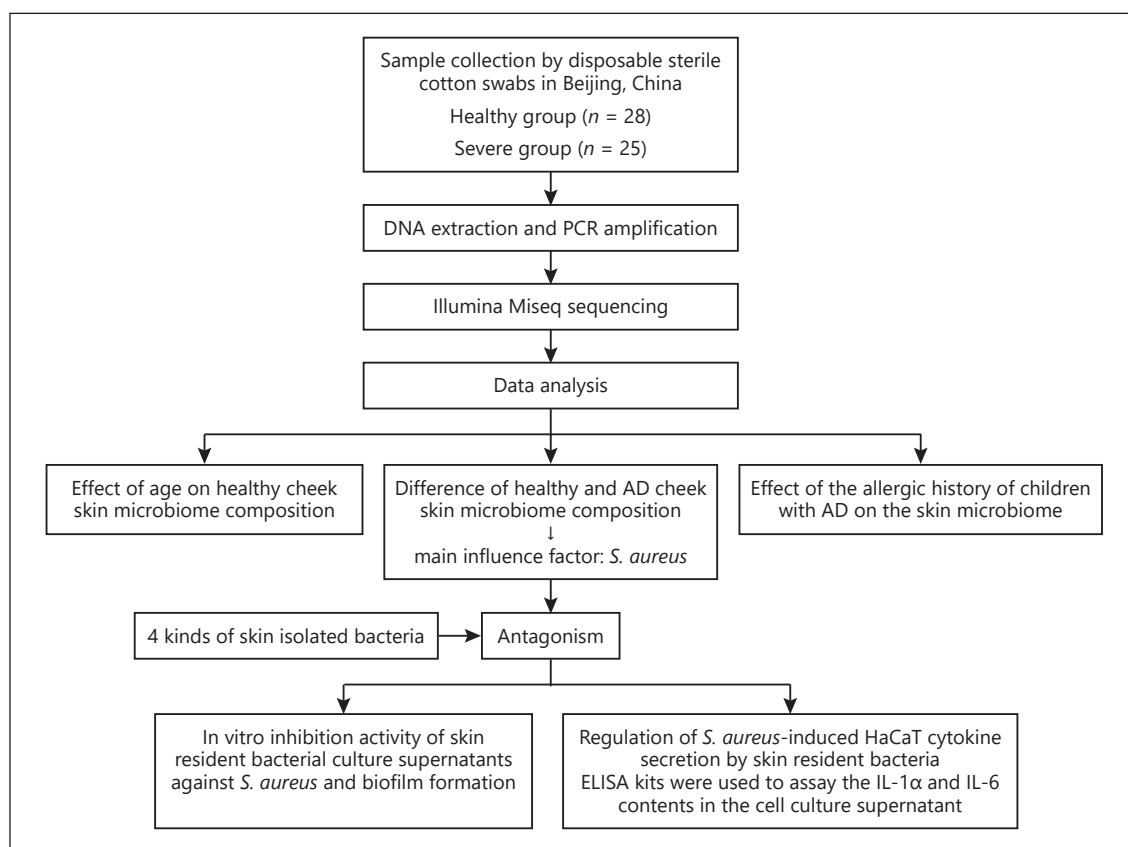


Fig. 1. Flowchart of the Material and Methods.

Table 1. Baseline characteristics of the study population

Groups	Age, months (head count)	Gender (girl/total)	Born (cesarean/total)	Use of an emollient/total	Wash face more than twice a day/total
Healthy group	0–6 (<i>n</i> = 11)	8/11	5/11	5/11	0/11
	6–12 (<i>n</i> = 7)	6/7	4/7	3/7	2/7
	12–36 (<i>n</i> = 10)	7/10	5/10	7/10	4/10
Severe group	0–12 (<i>n</i> = 25)	6/25	11/25	8/25	2/25
No.	AD scores	No.	AD scores	No.	AD scores
S4	10.8	S22	10.8	S7	10.8
S20	10.8	S2	10.8	S24	10.8
S36	8.8	S16	12	S28	12
S17	9.6	S18	9	S13	10.8
S26	10.8	S23	11.4	S21	12
S25	12	S9	10.8	S1	9
S27	8	S35	9	S12	12
S19	12				

These subjects live in northern China, mainly from Beijing; living environment, climate, and family conditions are relatively similar. The AD score in the severe group is also shown.

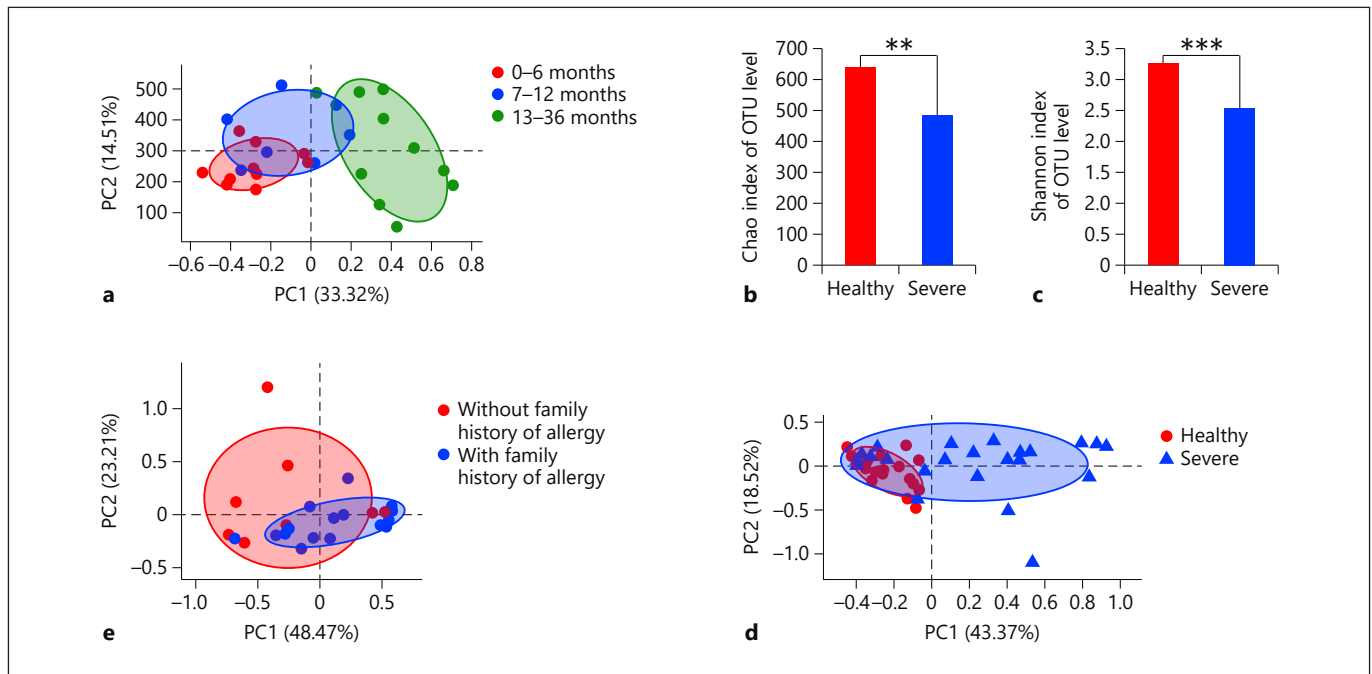


Fig. 2. Diversity comparisons. **a** Principal coordinate analyses (PCoA) of weighted UniFrac distances at different age subgroups in healthy children. PCoA plots with intersample distances represented by 2 principal coordinates (PC1 and PC2), with closely positioned samples being more similar in composition. **b, c** Histo-

gram of Chao and Shannon values. OUT, operational taxonomic unit. ** $p < 0.01$, *** $p < 0.001$. **d** PCoA plots on OTU level between healthy and severe AD samples. **e** PCoA plots between intersample with or without family history of allergy.

AD group (Chao1 value: 635.5 ± 184.7 vs. 482.1 ± 120.3 , $p = 0.0056$; Shannon value: 3.25 ± 0.39 vs. 2.54 ± 0.67 , $p = 0.0002$). These indicated that cheek skin bacterial richness and diversity were significantly lower in infants with severe AD compared to the healthy ones.

We also examined intersample diversity, or beta diversity, based on principal coordinate analyses of weighted UniFrac distances (Fig. 2d). PCoA revealed the significant differences in bacterial composition between the healthy and severe AD groups. The distribution in healthy samples was more concentrated. These indicated there are higher similarities in bacterial species abundance and evolutionary relationship within the healthy group. By contrast, the samples in the severe AD group were more discrete, indicating that the internal microbial community structure is more complex.

Comparison of Bacterial Composition and Differences among Groups

Thirty phyla were detected in the healthy and severe AD groups. Among them, there were 7 phyla (accounted for 99%) with relative abundance $>1\%$ in at least one sample: *Firmicutes*, *Proteobacteria*, *Actinobacteria*, *Bacte-*

roidetes, *Cyanobacteria*, (*Thermi*), and *Fusobacteria*, in descending order, and the relative abundances of 38 genera were $>1\%$ in at least one sample. These included *Streptococcus*, *Staphylococcus*, *Rothia*, *Veillonella*, and so on (Fig. 3a). A total of 27 species were detected of which the relative abundance was $>1\%$ in at least one sample, including *S. aureus*, *R. mucilaginosa*, *Staphylococcus epidermidis*, *Anoxybacillus kestanbolensis*, and so on (Fig. 3b).

Analysis of differences between the healthy and severe AD groups showed that the proportion of *Firmicutes* increased markedly in the severe AD group compared with the healthy group (72.83 ± 17.97 vs. $62.19 \pm 13.18\%$, $p = 0.0087$), while the proportion of *Actinobacteria*, *Bacteroidetes*, and *Fusobacteria* in the severe group was significantly lower than in the healthy group ($p < 0.05$). Of genera with relative abundance $>0.1\%$, 16 differed between the healthy and severe AD groups. The abundance of *Staphylococcus* was significantly higher in the severe AD group than in the healthy group (28.92 ± 26.89 vs. $4.21 \pm 6.30\%$, $p < 0.001$), as were *Finexgoldia* and *Aerococcus* ($p < 0.05$). The abundance of *Veillonella* in the severe AD group was significantly lower than in the healthy group (1.81 ± 2.75 vs. $4.52 \pm 3.55\%$), as were *Actinomyces*,

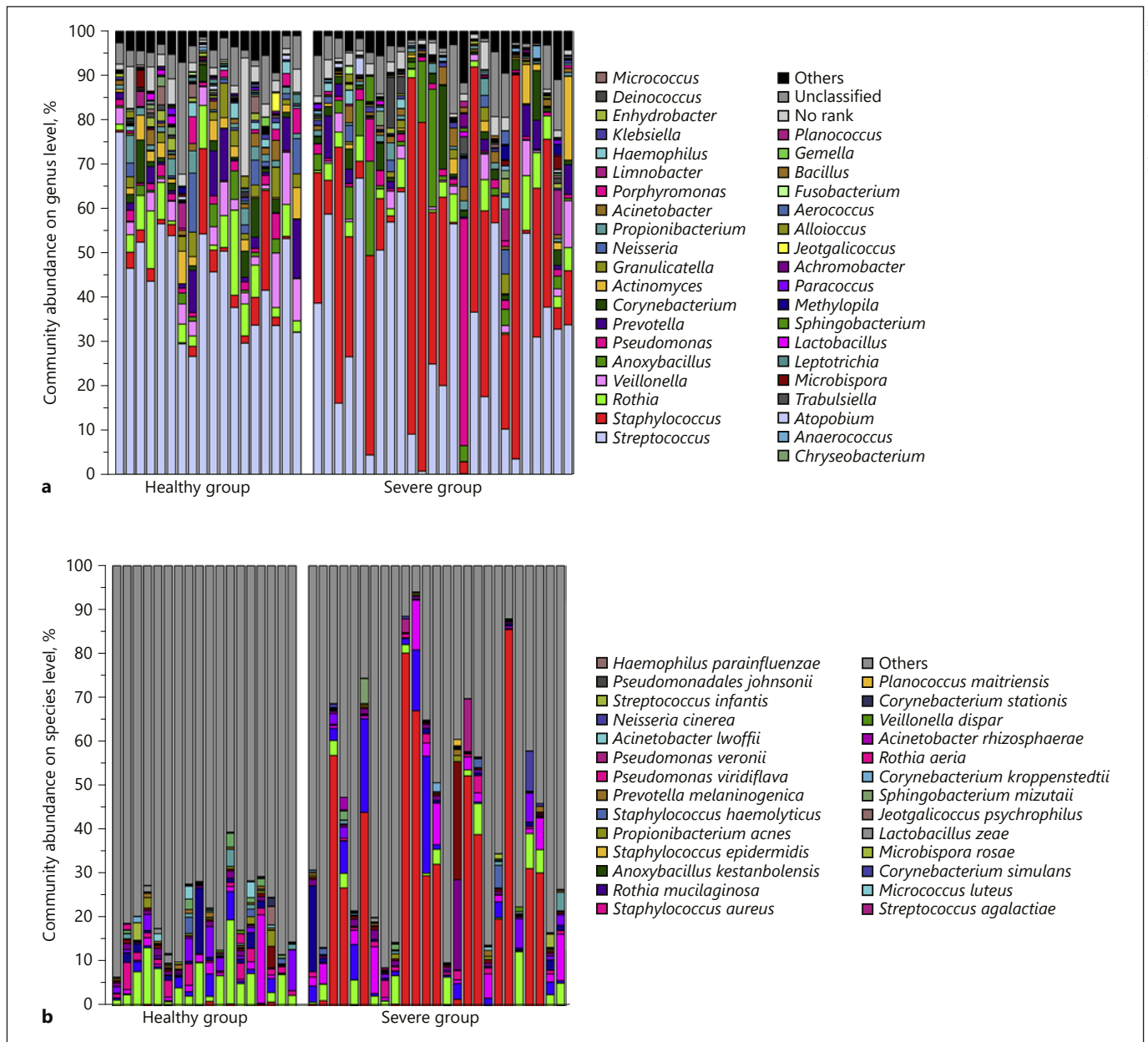


Fig. 3. Histogram of bacterial composition between the healthy and severe AD groups. **a** Genus compositions for every sample. **b** Species compositions for every sample.

Granulicatella, *Porphyromonas*, *Haemophilus*, *Microbisporea*, *Leptotrichia*, and *Jeotgalicoccus* ($p < 0.01$). The abundance of *Rothia* in the severe AD group was significantly lower than in the healthy group (3.27 ± 3.15 vs. $5.88 \pm 4.85\%$), as did *Prevotella*, *Propionibacterium*, *Neisseria*, and *Atopobium* ($p < 0.05$). A total of 9 different species were screened between the healthy group and the severe AD group by analysis of differences of species with relative abundance $>0.1\%$ (Table 2).

Effect of the Allergic History of Children with AD on the Skin Microbiome

We separated the severe AD group into 2 subgroups based on the presence or absence of a family history of allergy, and their bacterial distributions displayed clear separation (Fig. 2e). In children with a history of allergy, the abundance of *Streptococcus*, *Rothia*, and *Veillonella* decreased ($p < 0.05$), while *Pseudomonas* increased ($p < 0.05$). At the species level, there was a significant decrease

Table 2. Difference of bacteria between healthy and severe AD groups at species level (>0.1%)

Genera	Species	Healthy group, %	Severe AD group, %	p value
<i>Staphylococcus</i>	<i>S. aureus</i>	0.27±0.32	24.00±27.54***	0.0004
<i>Prevotella</i>	<i>P. melaninogenica</i>	1.86±2.73	0.94±1.88*	0.0249
<i>Propionibacterium</i>	<i>P. acnes</i>	1.89±1.71	0.94±1.06*	0.0153
<i>Haemophilus</i>	<i>H. parainfluenzae</i>	0.59±0.92	0.16±0.48**	0.0021
<i>Micrococcus</i>	<i>M. luteus</i>	0.58±1.06	0.08±0.14*	0.0423
<i>Microbispora</i>	<i>M. rosea</i>	0.28±0.92	0.18±0.62**	0.0041
<i>Jeotgalicoccus</i>	<i>J. psychrophilus</i>	0.24±0.99	0.01±0.03*	0.0284
<i>Rothia</i>	<i>R. aeria</i>	0.24±0.57	0.03±0.09*	0.0110
<i>Veillonella</i>	<i>V. dispar</i>	0.12±0.20	0.06±0.20**	0.0015

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

in *R. mucilaginosa* ($p < 0.01$), while *Pseudomonas veronii* increased ($p < 0.05$). The Chao1 and Shannon values with a history of allergy were 450.27 ± 107.35 and 2.46 ± 0.85 , respectively, and 497.07 ± 126.16 and 2.58 ± 0.60 , respectively, without a family history ($p > 0.05$). The results indicated that a family history of allergies can affect the microbiomes of infants with AD.

In vitro Antibacterial Activity of Skin Isolated Bacterial Culture Supernatants against *S. aureus*

We incubated culture supernatants from 4 types of skin isolated bacteria (*S. epidermidis*, *Klebsiella oxytoca*, *Micrococcus luteus*, and *Kocuria rhizophila* isolated from facial skin of a healthy person) with *S. aureus* to assess their effects on its growth (Fig. 4a–d). *S. epidermidis* did not profoundly affect *S. aureus* growth in vitro, but the difference was still statistically significant ($p < 0.05$), while *K. oxytoca*, *M. luteus*, and *K. rhizophila* showed strong inhibitory effects after 24 h ($p < 0.001$), indicating that they may produce active antimicrobial ingredients to inhibit *S. aureus* growth.

Inhibition of *S. aureus* Biofilm Formation by Skin Isolated Bacteria Supernatants

When *S. aureus* was incubated with each supernatant for 24 h, the inhibitory effects on membrane formation differed (Fig. 4e–h). A 50% concentration of *S. epidermidis* culture supernatant had an inhibitory effect on *S. aureus* biofilm formation, with no inhibition at other concentrations. *K. oxytoca* culture supernatants at 50 and 75% concentrations showed antibacterial activity. *K. rhizophila* supernatants between 50 and 90% inhibited *S. aureus* biofilm formation, and the effect was greatest at 50–75%. *M. luteus* showed no inhibitory activity in the concentration range of 25–90%. *K. rhizophila* had the greatest

effect on *S. aureus* biofilm formation, followed by *K. oxytoca* and then *S. epidermidis*.

Regulation of *S. aureus*-Induced HaCaT Cytokine Secretion by Skin Isolated Bacteria

To investigate whether the 4 skin bacteria can regulate the *S. aureus*-induced inflammatory response of HaCaT cells, we incubated the 4 skin bacterial culture supernatants and heat-inactivated *S. aureus* (1×10^6 CFU/mL) with HaCaT cells for 24 h. An enzyme-linked immunosorbent assay was used to detect interleukin (IL)-6 and IL-1 α secretion (Fig. 5). HaCaT cells upregulated IL-6 and IL-1 α expression ($p < 0.05$) after stimulation with *S. aureus*, while *S. epidermidis* and *K. rhizophila* significantly inhibited their expression ($p < 0.05$). *S. epidermidis* downregulated *S. aureus*-induced IL-6 from 496.2 ± 77.1 to 306.2 ± 120.5 pg/mL and IL-1 α from 18.7 ± 2.5 to 13.8 ± 4.9 pg/mL; *K. rhizophila* decreased *S. aureus*-induced IL-6 from 496.2 ± 77.1 to 387.2 ± 41.3 pg/mL and IL-1 α from 18.7 ± 2.5 to 12.2 ± 1.8 pg/mL. *K. oxytoca* had no effect on IL-6 expression, but reduced IL-1 α expression from 18.7 ± 2.5 to 13.00 ± 1.2 pg/mL ($p < 0.05$). Conversely, *M. luteus* increased *S. aureus*-induced IL-6 from 496.2 ± 77.1 to $559.5.2 \pm 41.2.5$ pg/mL and did not affect IL-1 α expression.

Discussion

With human growth, the skin also gradually develops, and the skin physiology of newborn infants and adults are very different [18]. In addition, the diversity of the skin microbiome undergoes dynamic changes [19]. We found that the skin microbiome of young children changed with age, with more pronounced changes after the first year of

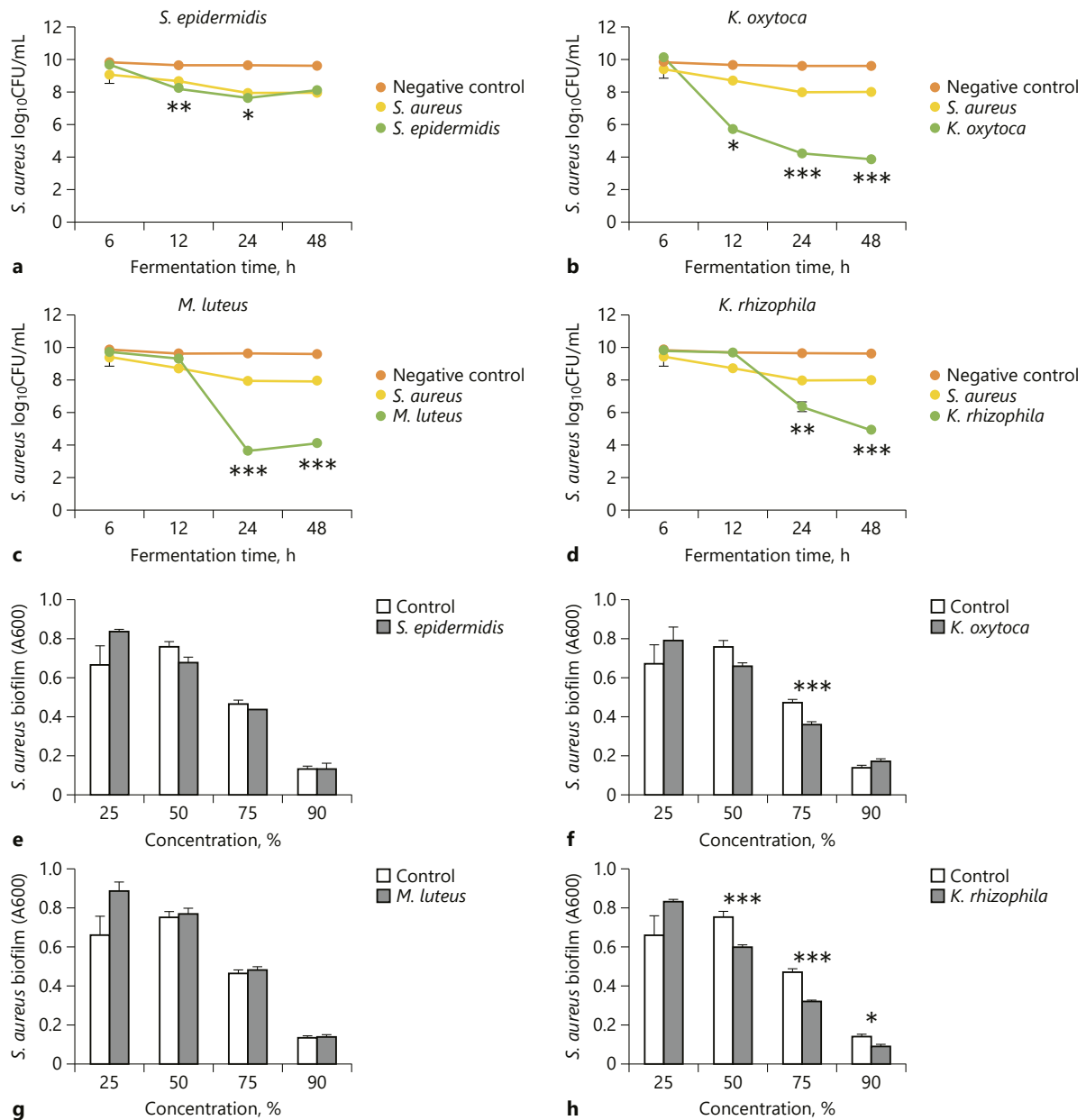


Fig. 4. Inhibition of *S. aureus* growth and biofilm formation in vitro by culture supernatants of skin bacteria. **a–d** Inhibition of *S. aureus* growth in vitro by culture supernatants of *S. epidermidis* (**a**), *K. oxytoca* (**b**), *M. luteus* (**c**), and *K. rhizophila* (**d**). **e–h** Inhibitory effects of different concentrations of *S. epidermidis* (**e**), *K. oxytoca* (**f**), *M. luteus* (**g**), and *K. rhizophila* (**h**) culture supernatants on *S. aureus*. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

life. The abundance of *Streptococcus* and *Rothia* decreased with age. *Streptococcus* is the predominant microorganism on the skin of infants and has a low abundance at birth, but its content significantly increases after birth [20]. Our data were consistent with this. *Streptococcus* is originally derived from the mother's mouth or breast milk

[21], and the higher water content of infant skin can be more suitable for its growth and stability. With age, skin development promotes the colonization of other bacteria. Several of the differential genera identified in this study are common oral bacteria, indicating that the formation of the infant skin microbiome involves oral microorganisms.

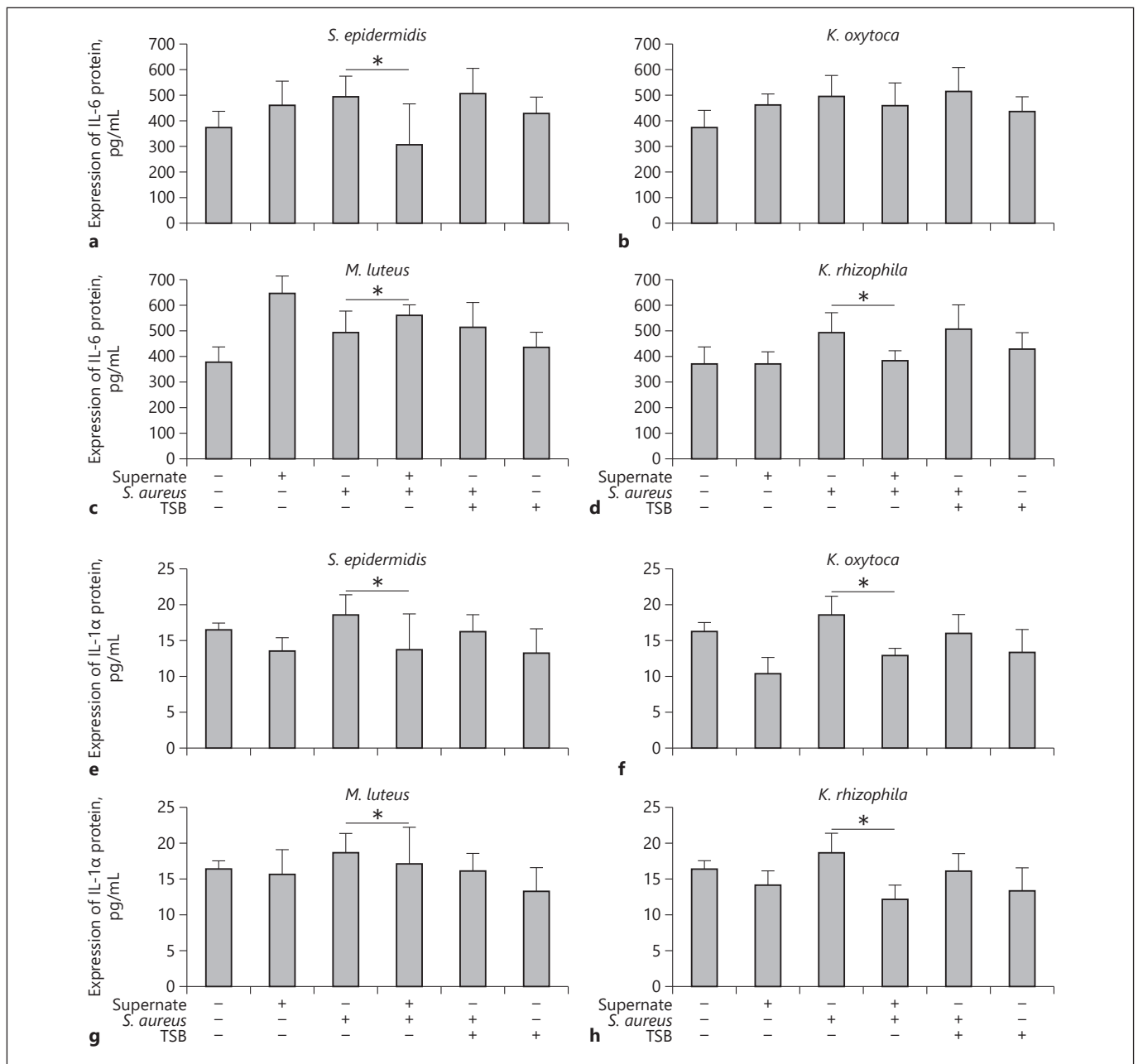


Fig. 5. Inhibition of *S. aureus*-induced IL-6 and IL-1α expression from HaCaT cells by skin bacterial culture supernatants. TSB, tryptic soy broth. **a–d** Inhibition of *S. aureus*-induced IL-6 expression from HaCaT cells by *S. epidermidis* (**a**), *K. oxytoca* (**b**), *M.*

luteus (**c**), and *K. rhizophila* (**d**) culture supernatants. **e–h** Inhibition of *S. aureus*-induced IL-1α expression from HaCaT cells by *S. epidermidis* (**e**), *K. oxytoca* (**f**), *M. luteus* (**g**), and *K. rhizophila* (**h**) culture supernatants. * $p < 0.05$.

The skin microbiome can significantly differ between infants with AD and healthy ones. Our results showed that bacterial diversity and richness in the cheeks of infants with AD were significantly decreased, and the abundance of *Staphylococcus* and *S. aureus* significantly increased, consistent with previous reports [22]. In addition,

many researchers have also reported a significant increase in *S. epidermidis* in AD lesions of older children [23, 24]. Our results also showed an increase, although not significantly. We also found that the abundance of *Finegoldia* and *Aerococcus* were significantly higher in the severe AD group compared to the healthy group. *Fine-*

goldia is an anaerobic gram-positive coccus and opportunistic pathogen which usually colonizes human skin and mucous membranes [25]. Dekio et al. [26] found *Finegoldia magnus* on the forehead of 5 healthy people. Another study found that this bacterium was also common in mixed infected skin [27]. The proportion of *Finegoldia* in infants with AD aged 0–6 months was significantly higher than in affected children aged 6–12 months. This may be due to the immune immaturity of very young babies. In addition, their skin is more sensitive, and their lesions often display serious exudation that may promote *Finegoldia* invasion. Several genera were decreased on the skin of infants with AD compared to healthy babies, suggesting that abnormal decreases in skin resident bacterial abundance may trigger imbalances in the skin microbiome. Changes in the physiological state of the skin may play a significant role in this.

Comparing the skin microbiomes of children with AD with or without a history of family allergy identified several genera that declined with a history of allergy, while no significant changes in diversity were observed. This suggests that a history of allergy may not affect the occurrence of AD by reducing the bacterial diversity in children, but by affecting the relative abundance of certain microorganisms. However, the sample size of this study is small and will require expansion for further analysis.

Interestingly, *Streptococcus* decreased in previous studies, especially in older children and adults with AD [20]. However, we found that the relative abundances of *Streptococcus* in infants with severe AD and healthy infants were not significantly different. In children with AD with a history of allergy, however, *Streptococcus* number was significantly lower than in children without a history of allergy. A history of allergies may be correlated with AD development. Many cases of AD are accompanied by an individual or family history of allergies, such as allergic rhinitis, asthma, and conjunctivitis, and often display increased IgE [28]. Most patients with AD display Th2-mediated immune dysfunction [29], and transcriptomic analysis of human samples has revealed different immune profiles in childhood and adult AD [30]. Therefore, determining whether children with AD can be divided into different classes, whether those with allergic histories show easier recurrence as older children or adults, whether decreased *Streptococcus* could be used as a marker to classify infant AD, and whether there are differences in the pathological mechanism of childhood AD depending on the presence of an allergic history warrant further study.

Skin resident bacteria often secrete bactericidal substances to inhibit the growth of foreign pathogens [31,

32]. For example, *S. epidermidis* can directly secrete antimicrobial peptides to inhibit *S. aureus* growth [16, 23]. To examine whether other skin isolated bacteria could inhibit *S. aureus* growth, we tested *S. epidermidis*, *M. luteus*, *K. oxytoca*, and *K. rhizophila* for in vitro effects on *S. aureus*. *S. epidermidis*, *K. oxytoca*, and *K. rhizophila* could inhibit *S. aureus* growth and biofilm formation, and reduced the production of pro-inflammatory cytokines by HaCaT cells, indicating complex interactions between the microorganisms. The results suggested that skin isolated bacteria or their fermentation products could be used to alter imbalanced skin microbiomes. A cream containing 5% nonpathogenic proteobacterium *Vitreoscilla filiformis* lysate has been shown to significantly improve AD severity and water loss [21, 33], providing a promising early example of the use of microorganisms in the treatment and prevention of childhood AD.

Key Message

There were complex interactions between skin isolated bacteria and *Staphylococcus aureus*.

Acknowledgments

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Statement of Ethics

This study has been approved by the Institutional Review Board of the Capital Institute of Pediatrics in Beijing. Written informed consent was obtained from each guardian before enrollment.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

As the first authors, L.S. and Q.W. contributed significantly to the experiment, data analysis, and manuscript preparation; Y.Z., L.M., Y.C., Y.G., S.C., and K.H. contributed to supplement some experiment contents, C.H. completed the overall design. All authors read and approved the final paper.

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