

Skin colonization by *Staphylococcus aureus* in patients with eczema and atopic dermatitis and relevant combined topical therapy: a double-blind multicentre randomized controlled trial

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Summary

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Key words

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Conflicts of interest

None declared.

Background *Staphylococcus aureus* has a peculiar ability to colonize the skin of patients with eczema and atopic dermatitis (AD), and is consistently found in eczematous skin lesions in these patients. A correlation between the severity of the eczema and colonization with *S. aureus* has been demonstrated, and it has been determined that bacterial colonization is an important factor aggravating skin lesions. Patients colonized with *S. aureus* have been treated with antibiotics in several open and double-blind placebo-controlled studies, with conflicting results.

Objectives To investigate the colonizing features of *S. aureus* in the lesional and non-lesional skin of patients with eczema and AD in China and to compare the therapeutic effect of mupirocin plus hydrocortisone butyrate with vehicle ointment plus hydrocortisone butyrate.

Methods A multicentre, double-blind randomized trial was conducted. Eczema Area and Severity Index (EASI) scores were evaluated before the start of the trial and on the 7th, 14th and 28th day of treatment. Swabs for bacterial isolation were taken from lesional skin before the start of the trial and on the 7th, 14th and 28th day of treatment, and from nonlesional skin only before the start of the trial. A combination topical therapy with mupirocin plus hydrocortisone butyrate ointment was used in the experimental group, with vehicle ointment plus hydrocortisone butyrate ointment as a control.

Results Of 327 patients enrolled in the study, 208 had eczema and 119 had AD. Bacteria were isolated from 70.2% of lesional and 32.7% of nonlesional skin samples from patients with eczema, of which *S. aureus* accounted for 47.3% and 27.9%, respectively. Bacteria were isolated from 74.8% of lesional and 34.5% of nonlesional skin samples from patients with AD, of which *S. aureus* accounted for 79.8% and 80.5%, respectively. The colonization density of *S. aureus* was markedly higher in lesional than in nonlesional skin, both in patients with eczema and with AD ($P < 0.01$, $P < 0.05$), and was positively correlated with lesion severity. Considering the EASI scores before and after treatment and the final effective rate, good therapeutic effects were obtained in both the combination experimental groups and the control groups ($P < 0.01$), and there were no differences in the global therapeutic effect between the two groups in patients with eczema and with AD ($P > 0.05$). However, in patients with eczema with a clinical score of > 8 or in patients with AD with a clinical score of > 7 , the therapeutic effect in

the experimental groups was superior to that in the control groups ($P < 0.05$) on the 7th day of treatment. There were no differences between the two groups on the 14th and 28th days of treatment ($P > 0.05$). Following the improvement of symptoms and signs of eczema and AD, the positive rates of bacteria and *S. aureus* were reduced on the 7th day of treatment.

Conclusions This study confirmed that lesional skin of patients with eczema and AD was more frequently colonized with *S. aureus* than was nonlesional skin. The more severe the eczema, the higher the colonization rate of *S. aureus*, and *S. aureus* was also more often present in lesional and nonlesional skin in patients with AD than in those with eczema. *Staphylococcus aureus* infection is related to the pathogenesis of eczema and AD. An antibiotic–corticosteroid combination and corticosteroid alone both gave good therapeutic effect in eczema and in AD, and both reduced colonization by *S. aureus*. Early combined topical therapy is beneficial to patients with moderate to severe eczema and AD, and it is unnecessary to use antibiotics at later stages of disease or in mild eczema or AD.

Eczema and atopic dermatitis (AD) are common inflammatory skin diseases that often begin in infancy and run a course of remission and exacerbation. Acute eczematous lesions are characterized by erythema, oozing and crusting, whereas chronic lesions show papules and lichenification. Pruritus is so prominent and constant that it has an effect on quality of life.¹

Staphylococcus aureus has a peculiar ability to colonize the skin of patients with eczema and AD and is consistently found in eczematous skin lesions in these patients. The skin lesions of 80–100% of patients with eczema and AD are colonized with *S. aureus*. In contrast, *S. aureus* can be isolated from the skin of only 5–30% of normal individuals, mainly from intertriginous areas.^{2–5} The colonization density of *S. aureus* can reach up to 10^7 colony-forming units cm^{-2} without clinical signs of infection in patients with AD. The density of *S. aureus* has been shown to correlate with cutaneous inflammation. A correlation between the severity of the eczema and colonization with *S. aureus* has been demonstrated, and it has been determined that bacterial colonization is an important mechanism aggravating skin lesions.^{4,6,7}

Several studies have investigated the effect of antimicrobial treatment on colonization by *S. aureus* and on severity of inflammation, with conflicting results. In several open or double-blind placebo-controlled trials, topical and systemic antimicrobials were able to reduce the colonization density and led to a partial improvement of skin lesions.^{3,8} On the other hand, treatment with oral antibiotics did not lead to a significant improvement in AD in two double-blind placebo-controlled studies.^{9,10} Topical corticosteroid is commonly used in the treatment of eczema and AD, and several studies have shown the impact of such treatment on bacterial skin flora. Therefore, a combination topical treatment with antibacterial and corticosteroid agents has been recommended.¹¹ A multicentre, double-blind randomized controlled trial was conducted to investigate the colonizing features of *S. aureus* in patients with eczema and AD in China and to compare the therapeutic

effect of mupirocin plus hydrocortisone butyrate with vehicle ointment plus hydrocortisone butyrate.

Patients and methods

Patients

All patients with eczema and AD who visited the department of dermatology of four different study units as outpatients from April 2002 to January 2003 were recruited for the study. There was no selection of patients by gender or by localization and severity of lesions. Patients were aged from 2 to 65 years, and agreed to implement the protocol of the study.

AD was diagnosed following the criteria of Hanifin and Rajka, which include pruritus, typical morphology and distribution of eczematous lesions, chronicity of the disease and personal or family history of atopy.¹² The clinical inclusion criteria for eczema were typical eczematous lesions and pruritus symptoms. Eczema was divided into two types according to the different localizations of skin lesions: localized (lesions limited to one location) and generalized (lesions at different parts of the body). Based on the different disease courses, eczema was further divided into three types: acute, subacute and chronic.

Exclusion criteria included patients with severe fungal infection or other skin diseases which might disturb the diagnosis and treatment; the concomitant presence of other severe systemic infection; pregnant or lactating women; severe heart, liver or kidney diseases and mental diseases; diseases affecting immune function, such as diabetes, AIDS, malignant tumours and autoimmune diseases; treatment with systemic corticosteroids or immune-suppressive agents in the last 4 weeks, treatment with topical antibiotics in the last 2 weeks or with systemic antibiotics in the last 4 weeks; allergy to components of the study drugs; and enrolment in another clinical study either currently or in the last 4 weeks.

Dropout criteria included patients with other diseases during treatment which might affect the evaluation of therapeutic

effect and adverse reactions; irregular visits or no follow-up; not keeping the treatment scheme; needing systemic therapy due to the disease becoming more severe; and dropout because of adverse reactions.

Methods

A randomized, double-blind and multicentre clinical study was undertaken, precautions being taken to preserve the 'blinding' of both patients and observers. All drugs were packaged to maintain randomization and blinding. Mupirocin ointment and vehicle ointment were identical in appearance and packaging. To aid in achieving uniformity in diagnosis and in grading of response to treatment, all investigators were trained, and each patient was followed by the same investigator at each visit. Enrolled patients were randomized into the experimental group and the control group. The experimental group applied topical mupirocin ointment (Bactroban®; Tianjing Smith Kline & French Labs Ltd, Tianjing, China) and hydrocortisone butyrate ointment (Pandel®; Tianjing Yaoye Jituan Co., Ltd, Tianjing, China). The control group applied topical mupirocin ointment base and hydrocortisone butyrate ointment. Mupirocin ointment was applied topically once every morning between 08.00 and 09.00 hours, followed by hydrocortisone butyrate ointment once between 10.00 and 11.00 hours. The time was flexible for the patient using the drugs, but the sequence could not be changed. The time interval between the two drugs had to be 2–3 h. If the skin lesion was acute with severe exudation, it was first treated with topical zinc oxide oil for 3 days, and then enrolled into the study after remission of exudation. The duration of treatment was 28 days. Follow-up visits were scheduled for the 7th, 14th and 28th day of treatment.

Scoring system and clinical index

The severity of skin lesions of eczema and AD was based on Eczema Area and Severity Index (EASI) scoring,¹³ which includes an assessment of skin lesions involved in four body regions: head and neck, lower limbs, upper limbs and trunk. Clinical index included erythema, papules/oedema, excoriation, fissuring, exudation/crusting, lichenification and itching. Skin lesions and itching were scored on the selection day, and on the 7th, 14th and 28th day of treatment, on a four-point scale: 0, none; 1, mild; 2, moderate; 3, severe.

Isolation and identification of bacteria

Swabs were taken from the target skin lesion (the most severe lesion) before the start of the trial and on the 7th, 14th and 28th day of treatment, and from the nonlesional skin (symmetrically to the target skin lesion or 5 cm away from the target skin lesion) only before the start of the trial. Bacterial cultures were performed. The swabs were plated on to blood agar. Colonies were grown for 24 h at 37 °C. *Staphylococcus aureus* was identified by testing typical colonies for coagulase activity.

Finally, the colony numbers were calculated and the strains were conserved.

Assessment of therapeutic effect

The clinical curative effect was assessed by scores of symptoms and signs at each observation during treatment, as excellent, good, fair and poor, where 'excellent' reflected a change in clinical score of $\geq 75\%$, 'good' a change of 50–74%, 'fair' a change of 25–49% and 'poor' a change of $< 25\%$. Improvement in symptoms and signs was defined as [(total scores before treatment – total scores after treatment)/total scores before treatment] $\times 100\%$.

Statistical analysis

We used a paired t-test for comparison of measurement data, and a χ^2 test for comparison of enumeration data. Analyses were made on an intent-to-treat (ITT) basis and on a per-protocol (PP) basis.

Results

Distribution of patients with eczema and atopic dermatitis

In total, 337 patients were enrolled in the ITT analyses. There were 10 dropouts, and thus there were 327 patients in the PP analyses: 177 males and 150 females, 75 of whom were aged under 10 years, 48 between 10 and 18 years, and 204 above 18 years. The sex distribution of patients with eczema and AD in every age group was similar, without significant difference ($P > 0.05$). There were 81 patients with localized eczema, 127 with generalized eczema, and 119 with AD. The distribution of subtypes of eczema and AD in the different age groups is shown in Table 1. One hundred and sixty patients were treated with mupirocin plus hydrocortisone butyrate, and 167 patients received vehicle ointment plus hydrocortisone butyrate.

Distribution of flora in lesional and nonlesional skin

Of the 208 patients with eczema, 146 (70.2%) yielded bacteria in lesional skin upon culture: 69 strains of *S. aureus* (47.3%), 56 strains of *S. epidermidis* (38.4%), six strains of haemolytic *Streptococcus* (4.1%), two strains of *Staphylococcus lugdunensis* (1.4%), one strain of *S. capitis* (0.7%), two strains of *Micrococcus tetragenus* (1.4%), five strains of *Escherichia coli* (3.4%) and five other bacterial strains (3.4%). Sixty-eight patients (32.7%) yielded bacteria in nonlesional skin: 19 strains of *S. aureus* (27.9%), 42 strains of *S. epidermidis* (61.8%), four strains of haemolytic *Streptococcus* (5.9%), one strain of *E. coli* (1.5%), one strain of *Enterobacter cloacae* (1.5%) and one other bacterial strain (1.5%).

Of the 119 patients with AD, 89 (74.8%) yielded bacteria in lesional skin upon culture: 71 strains of *S. aureus* (79.8%), 14 strains of *S. epidermidis* (15.7%), one strain of haemolytic *Streptococcus* (1.1%), one strain of *E. coli* (1.1%), one strain of

Table 1 Numbers of patients with eczema and its subtypes and with atopic dermatitis (AD)

Age group (years)	Localized eczema				Generalized eczema				AD
	Acute	Subacute	Chronic	Total	Acute	Subacute	Chronic	Total	
< 10	1	5	1	7	3	7	3	13	55
10–18	1	0	2	3	2	6	5	13	32
> 18	9	35	27	71	17	40	44	101	32
Total	11	40	30	81	22	53	52	127	119

Proteus (1.1%) and one other bacterial strain (1.1%). Forty-one patients (34.5%) yielded bacteria in nonlesional skin: 33 strains of *S. aureus* (80.5%), six strains of *S. epidermidis* (14.6%), one strain of *Proteus* (2.4%) and one strain of *E. coli* (2.4%). Results are shown in Table 2.

After comparative analyses, we found that the colonization rate of bacteria and the positive rate of *S. aureus* in lesional skin of the eczema group were distinctly higher than in nonlesional skin of the same group ($\chi^2 = 55.21$, $P < 0.01$; $\chi^2 = 35.677$, $P < 0.01$), and the differences were highly significant. The colonization rate of bacteria and the positive rate of *S. aureus* in lesional skin of the AD group were distinctly higher than in nonlesional skin of the same group ($\chi^2 = 39.459$, $P < 0.01$; $\chi^2 = 24.824$, $P < 0.01$), and the differences also were highly significant. However, there was no significant difference in the constituent ratio of *S. aureus* between lesional skin and nonlesional skin in the AD group ($P > 0.05$). The positive rates of *S. aureus* in lesional skin and nonlesional skin were distinctly higher in the AD group than in the eczema group ($P < 0.01$). The differences were highly significant. By comparing bacterial species and constituent ratios in different regions of China, we found that *S. aureus* was the main colonization bacterium in patients from Nanjing (*S. aureus*/*S. epidermidis* 65/17) and Guangzhou (*S. aureus*/*S. epidermidis* 40/15). However, the proportions of *S. aureus* and *S. epidermidis* in patients from Chongqing (*S. aureus*/*S. epidermidis* 35/38) were similar. These results showed that there are differences in the bacterial species composition in different parts of China.

The colonization density of *Staphylococcus aureus* in lesional and nonlesional skin

In total, 140 patients had *S. aureus* in lesional skin, and 52 had *S. aureus* in nonlesional skin. The colonization density of *S. aureus* was markedly higher in lesional than in nonlesional skin of patients with eczema ($\chi^2 = 9.907$, $P < 0.01$), and the difference was highly significant. The colonization density of *S. aureus* was also higher in lesional than in nonlesional skin in patients with AD ($\chi^2 = 5.781$, $P < 0.05$), and the difference was significant. Statistical analyses showed a positive correlation between the colonization density of *S. aureus* and the severity of eczema and AD. The more severe the eczema, the higher the colonization rate of *S. aureus*. There was no significant difference in colonization density between different age groups ($P > 0.05$).

Therapeutic effect

Global therapeutic effect

The final therapeutic effect was evaluated at the end of treatment (28th day). In patients with eczema the effective rate

Table 2 Distribution of flora in lesional and nonlesional skin of patients with eczema and atopic dermatitis (AD)

	Eczema								AD	
	Lesional skin				Nonlesional skin				Lesional skin	Nonlesional skin
	Acute	Subacute	Chronic	Total	Acute	Subacute	Chronic	Total		
Total (n)	33	93	82	208	33	93	82	208	119	119
Positive (n)	22	69	55	146	8	31	29	68	89	41
<i>Staphylococcus aureus</i>	16	30	23	69	4	8	7	19	71	33
<i>Staphylococcus epidermidis</i>	4	28	24	56	3	20	19	42	14	6
Haemolytic <i>Streptococcus</i>		5	1	6		3	1	4	1	
<i>Staphylococcus lugdunensis</i>	1	1		2						
<i>Staphylococcus capitis</i>		1		1						
<i>Micrococcus tetragenus</i>		2		2						
<i>Escherichia coli</i>	1	1	3	5			1	1	1	1
<i>Enterobacter cloacae</i>							1	1		
<i>Proteus</i>									1	1
Other bacteria		1	4	5	1			1	1	

(including excellent and good) was 79% and 80%, respectively, in the experimental group and the control group. In patients with AD the corresponding figures were 95% and 89%, respectively. The combination experimental groups and the control groups all showed good therapeutic effects (Table 3).

Comparison of severity scores in each group before and after treatment

The mean EASI scores all decreased after treatment ($P < 0.01$) in both experimental groups and control groups (including patients with eczema and with AD). All groups showed a good therapeutic effect ($P < 0.01$). The changes in EASI scores in each group during treatment are shown in Tables 4 and 5. The improvement in symptoms and signs is shown in Table 6.

Comparison of therapeutic effect between experimental groups and control groups after treatment

By repeated-measures analysis of variance, there were no significant differences in the global therapeutic effect between combination therapy groups and control groups in patients with eczema and AD after treatment ($P > 0.05$). However, by comparison of the score changes, we found that in the

Table 6 Improvement in symptoms and signs in each group during treatment (%)

Group	n	7th day	14th day	28th day
Eczema				
Control group	106	54.9	73.1	84.0
Experimental group	102	45.7	68.8	82.5
Atopic dermatitis				
Control group	61	48.7	76.2	81.7
Experimental group	58	61.3	80.6	89.8

patients with eczema with clinical score > 8 , the therapeutic effect in the experimental group was superior to that in the control group ($P < 0.05$) on the 7th day of treatment. There were no differences between the two groups on the 14th and 28th day of treatment ($P > 0.05$). In the patients with eczema with clinical score ≤ 8 , there was no significant difference between the two groups on the 7th, 14th and 28th day of treatment ($P > 0.05$).

In the patients with AD with clinical score > 7 , the therapeutic effect in the experimental group was superior to that in the control group ($P < 0.05$) on the 7th day of treatment. There were no differences between the two groups on the 14th and 28th day of treatment ($P > 0.05$). In the patients with AD with clinical score ≤ 7 , there was no significant dif-

Group	n	Excellent (%)	Good (%)	Fair (%)	Poor (%)
Eczema					
Control group	106	49 (46)	36 (34)	8 (8)	13 (12)
Experimental group	102	48 (47)	33 (32)	6 (6)	15 (15)
Atopic dermatitis					
Control group	61	35 (57)	19 (31)	1 (2)	6 (10)
Experimental group	58	35 (60)	20 (34)	0	3 (5)
Total	327	167 (51)	108 (33)	15 (5)	37 (11)

Table 3 The therapeutic effect at the investigator's final evaluations

Table 4 Total Eczema Area and Severity Index score comparison in different types of eczema before and during treatment (mean \pm SD)

Group	Eczema type	n	Before treatment	7th day	14th day	28th day
Control group	Localized	45	4.062 \pm 4.691	1.958 \pm 2.026	1.180 \pm 1.359	0.480 \pm 0.730
	Generalized	61	7.734 \pm 4.146	3.395 \pm 2.577	2.225 \pm 2.148	1.360 \pm 2.120
	Total	106	6.175 \pm 4.730	2.785 \pm 2.454	1.781 \pm 1.918	0.990 \pm 1.720
Experimental group	Localized	36	5.156 \pm 5.087	2.642 \pm 3.231	1.664 \pm 2.315	1.290 \pm 3.120
	Generalized	66	6.814 \pm 5.455	3.795 \pm 3.402	2.098 \pm 2.207	0.980 \pm 1.470
	Total	102	6.223 \pm 5.035	3.382 \pm 3.372	1.944 \pm 2.244	1.090 \pm 2.200

Table 5 Total Eczema Area and Severity Index score comparison in atopic dermatitis before and during treatment (mean \pm SD)

Group	n	Before treatment	7th day	14th day	28th day
Control group	61	13.607 \pm 8.492	6.977 \pm 8.196	3.238 \pm 4.501	2.493 \pm 5.179
Experimental group	58	13.918 \pm 8.484	5.388 \pm 4.923	2.702 \pm 2.917	1.414 \pm 2.317

Table 7 Therapeutic effect in generalized eczema with score > 8 (mean ± SD)

Group	n	Before treatment	7th day	14th day	28th day
Control group	26	11.74 ± 2.77	4.91 ± 2.97	3.11 ± 2.61	2.05 ± 2.98
Experimental group	19	13.14 ± 6.19	7.31 ± 4.22	3.85 ± 3.18	1.66 ± 2.21
P-value		> 0.05	< 0.05	> 0.05	> 0.05

Table 8 Therapeutic effect in atopic dermatitis with score > 7 (mean ± SD)

Group	n	Before treatment	7th day	14th day	28th day
Control group	49	15.81 ± 8.03	8.34 ± 8.60	3.87 ± 4.80	3.02 ± 5.66
Experimental group	42	17.24 ± 7.38	6.42 ± 5.31	3.09 ± 3.24	1.67 ± 2.61
P-value		> 0.05	< 0.05	> 0.05	> 0.05

ference between the two groups on the 7th, 14th and 28th day of treatment ($P > 0.05$) (Tables 7 and 8).

Changes in the positive rate of *Staphylococcus aureus* with clinical improvement

We found that the positive rates of all bacteria and of *S. aureus* in patients with eczema and AD were distinctly decreased on the 7th day of treatment (Table 9). There were no significant differences between the experimental groups and control groups in patients with eczema or AD. The changes in the positive rate of *S. aureus* were in accord with the improvement in symptoms and signs in patients with eczema and AD. The changes in *S. aureus* in relation to clinical improvement are shown in Figures 1 and 2.

Table 9 Positive rates of bacteria before and on the 7th day of treatment

	Before treatment (%)	After treatment (%)
Eczema (n = 208)		
All bacteria	70.2	34.1
<i>Staphylococcus aureus</i>	47.3	25.3
Atopic dermatitis (n = 119)		
All bacteria	74.8	36.7
<i>Staphylococcus aureus</i>	79.8	40.2

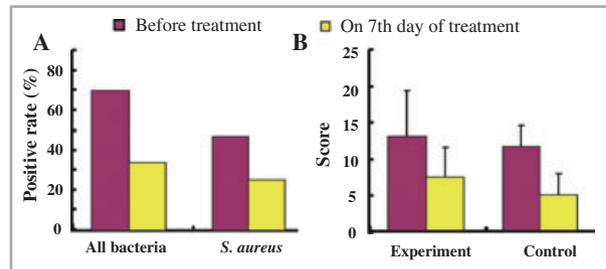


Fig 2. Positive rates of bacteria and scores of patients with eczema before and on the 7th day of treatment (mean ± SD). *S. aureus*, *Staphylococcus aureus*.

Discussion

The high prevalence of *S. aureus* in the lesional skin in patients with eczema and AD, and a correlation between colonization and eczema severity as confirmed in our study, are in accordance with the findings of others in eczema and AD. Goh *et al.*⁴ isolated *S. aureus* in 69.7% of eczematous lesions and in 42.4% of noneczematous skin samples in patients with AD. *Staphylococcus aureus* was isolated in 53% of patients with mild eczema, and in 100% with moderate and severe eczema. The colonization density of *S. aureus* was 14×10^6 colonies cm^{-2} in lesional skin, which was distinctly higher than in nonlesional skin (10^3 colonies cm^{-2}). Leung *et al.*¹⁴ found that *S. aureus* isolated from the lesional skin of more than half of their patients with AD could secrete toxin with the characteristics of superantigen. Therefore, it was considered that *S. aureus* infection can aggravate AD and eczema, and may play an important role in the outbreak and continuation of skin inflammation. A recent study showed that *S. aureus* was present in 22% of nasal swabs from Chinese children with AD. The anterior nares are an important reservoir for *S. aureus*, and significant nasal *S. aureus* colonization was clinically associated with more extensive lesions and the presence of oozing or crusting.¹⁵

In our study, 235 bacterial strains were isolated from lesional skin of 327 patients with eczema and AD. Among them there were 213 strains of *Staphylococcus*, including 140 strains of *S. aureus*, 70 strains of *S. epidermidis*, two strains of

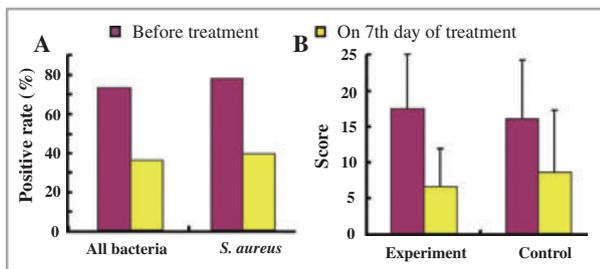


Fig 1. Positive rates of bacteria and scores of patients with atopic dermatitis before and on the 7th day of treatment (mean ± SD). *S. aureus*, *Staphylococcus aureus*.

S. lugdunensis and one strain of *S. capitis*. One hundred and nine bacterial strains were isolated from nonlesional skin, of which *S. aureus* (52 strains) and *S. epidermidis* (48 strains) accounted for 90%. By comparing the flora distribution and constituent ratio in different regions of China, we found that *S. aureus* was the main colonization bacterium in patients from Nanjing (*S. aureus/S. epidermidis* 65/17) and Guangzhou (*S. aureus/S. epidermidis* 40/15), while similar numbers of *S. aureus* and *S. epidermidis* were found in patients from Chongqing (*S. aureus/S. epidermidis* 35/38). Our study showed that bacteria were isolated from 72% of the eczematous lesions of patients with eczema and AD in China, of which *S. aureus* accounted for 60%. Although the positive rate of *S. aureus* is lower than in other countries, the infection rate of *Staphylococcus* was as high as 91%, which is the same as the result of Lin *et al.*¹⁶ This shows that infection with *Staphylococcus* species other than *S. aureus* may play an important role in the pathogenesis of eczema and AD in China. The bacterial species distribution differs between different parts of China.

On the whole, the colonization rate of bacteria and the positive rate of *S. aureus* were distinctly higher in lesional than in nonlesional skin of patients with eczema and AD. The differences were highly significant. There were positive correlations between the bacterial colonization density and the severity of eczema and AD. By comparing the flora distribution and constituent ratio in patients with eczema and AD, we found that the positive rate of *S. aureus* in the AD group was distinctly higher than in the eczema group, not only in lesional skin but also in nonlesional skin. This shows that *S. aureus* infection plays a more important role in the pathogenesis of AD. Following improvement of skin lesions, the positive rates of *S. aureus* in patients with eczema and AD were distinctly decreased in both groups. The improvement in symptoms and signs was correlated with the reduction of *S. aureus*. We consider that the antibiotic action of mupirocin and the anti-inflammatory effect of corticosteroid both play important roles in reducing *S. aureus* and improving patients' symptoms and signs.

The susceptibility of the eczematous skin to colonization with *S. aureus* may be related to adherence of *S. aureus*, skin surface damage and immunological factors.^{17,18} Due to the skin protective function that is damaged in AD, the disturbance of the quantity and quality of lipids of the stratum corneum is one reason for the increasing degree of skin colonization with *S. aureus*.⁵ One study indicated that the reduction of antimicrobial peptides in sweat of patients with AD may contribute to the high susceptibility of these patients to skin infections and altered skin colonization.¹⁹

Staphylococcus aureus is able to secrete exotoxins with superantigenic properties. The staphylococcal enterotoxins A–D (SEA–D) and the toxic shock syndrome toxin-1 have been found to be produced by *S. aureus* strains isolated from the skin of up to 65% of patients with AD who are colonized with this microorganism.²⁰ Our researches have also shown that the positive rate of superantigen produced by *S. aureus* colonizing the lesional skin was 55.4% in patients with eczema and AD, and was related to clinical severity.²¹ The levels of SEB-specific IgM were

significantly increased in patients with both AD and eczema, those of SEB-specific IgE were significantly increased in patients with AD, and those of SEB-specific IgM were decreased after treatment.²² Our study also found that serum levels of interleukin (IL)-4 and interferon- γ were significantly higher in patients with AD and eczema than in normal controls, and the level of IL-4 decreased after treatment. This shows that cytokines are involved in the pathogenesis of eczema and AD.

Corticosteroid is commonly used in treatment of eczema and AD. However, when steroid is stopped the diseases easily relapse, and when it is used for a long time it may lead to a number of adverse effects such as skin atrophy and secondary infection. A recent study showed that microbial superantigens can induce corticosteroid insensitivity.²³ Therefore, the eradication of *S. aureus* may lead to a steroid-saving effect. Leyden *et al.*²⁴ first showed that the therapeutic effect of antibiotics combined with steroid was better than that of steroid monotherapy. David and Cambridge²⁵ found that the clinical symptoms of infection were not diagnostic for AD aggravated by bacterial infection. However, if treated with antibiotics, the symptoms and signs of AD were markedly remitted. Breuer *et al.*³ found that the SCORAD of patients dropped after antibiotic therapy, and the therapeutic effect was correlated with disease severity. The effect was more pronounced in patients with an initial SCORAD over 50, and the bacterial colonization in lesional skin was decreased. Our study indicated that a antibiotic–corticosteroid combination and corticosteroid alone both gave good therapeutic effect, and there were no significant differences in the global therapeutic effect between the two groups, either in patients with eczema or in those with AD. When comparing the relation of scores to therapeutic effect, we found that in the patients with eczema with clinical score > 8 or in the patients with AD with clinical score > 7, the therapeutic effect of the combination experimental group was superior to that of the control group ($P < 0.05$) on the 7th day of treatment. There were no differences between the two groups on the 14th day. This shows that earlier administration of the antibiotic–corticosteroid combination is beneficial in patients with moderate to severe eczema and AD, because we found that, at early stages of disease, the more severe the skin lesions, the better the therapeutic effect of the combination therapy. Therefore, we consider it unnecessary to use antibiotics at later stages of disease or in patients with mild eczema or AD. However, we cannot completely exclude the possibility that other factors may impact on the evaluation of therapeutic effect, such as patient selection criteria: for example, there was a tremendous difference in EASI scores between enrolled patients, as no limits were placed on lesion area or severity. In addition, the moisture contained in the vehicle ointment may possibly improve the symptoms and signs of AD and eczema.

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