**Objective:** To study the prevalence of *Staphylococcus aureus* colonization in close contacts of patients with atopic dermatitis (AD) and the influence on AD severity.

**Design:** Prospective case-control study.

**Setting:** Pediatric dermatology clinic in a Hong Kong university hospital.

**Patients:** We recruited 211 subjects prospectively, including 50 AD patients, 50 non-AD control subjects, 60 close contacts of AD patients, and 51 close contacts of controls.

**Intervention:** Nasal swabs and skin swabs were taken. Severity of AD was assessed using the SCORAD (Scoring Atopic Dermatitis) index.

**Main Outcome Measures:** The prevalence of *S aureus* colonization in the close contacts of AD patients was compared with that of the close contacts of non-AD controls. Between-group differences were assessed, where appropriate, by unpaired t test or Pearson χ² test. Multivariate logistic regression using the forward stepwise method was performed to identify independent predictors of severe AD. A probability value of *P* < .05 was considered statistically significant.

**Results:** Significantly more nasal carriers of *S aureus* were found among the close contacts of AD patients (14 of 60 [23%]) than among the close contacts of non-AD controls (4 of 51 [8%] [ *P* = .03]). The difference was still significant after the exclusion of the AD patients’ close contacts who also had AD (24% vs 8% [ *P* = .03]). By multivariate analysis, only skin colonization of *S aureus* was independently associated with severe AD (odds ratio, 17.0; 95% confidence interval, 1.60-181.1 [ *P* = .02]).

**Conclusions:** Anterior nares of close contacts of AD patients are reservoirs of *S aureus*. The presence of *S aureus* carriers among close contacts does not predict AD severity. Skin colonization is associated with severe AD.

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**METHODS**

**STUDY DESIGN AND STUDY SUBJECTS**

In a prospective case-control study, a total of 211 subjects were recruited from a pediatric dermatology clinic at a tertiary university hospital (the Prince of Wales Hospital) from November 1, 2007, through August 31, 2008. These consisted of 4 groups of subjects: 50 AD patients younger than 21 years; 60 close contacts of AD patients; 50 age- and sex-matched non-AD controls; and 51 close contacts of the non-AD controls. We defined cases of AD according to the UK Working Party’s Diagnostic Criteria for AD. We proposed that close contacts of AD patients may be important reservoirs of *S aureus*. We compared the prevalence of *S aureus* colonization in the anterior nares of close contacts of AD patients and that of non-AD patients and determined the clinical correlation of *S aureus* colonization in close contacts and of AD severity.

**STUDY DESIGN**

In a prospective case-control study, a total of 211 subjects were recruited from a pediatric dermatology clinic at a tertiary university hospital (the Prince of Wales Hospital) from November 1, 2007, through August 31, 2008. These consisted of 4 groups of subjects: 50 AD patients younger than 21 years; 60 close contacts of AD patients; 50 age- and sex-matched non-AD controls; and 51 close contacts of the non-AD controls. We defined cases of AD according to the UK Working Party’s Diagnostic Criteria for AD. We proposed that close contacts of AD patients may be important reservoirs of *S aureus*. We compared the prevalence of *S aureus* colonization in the anterior nares of close contacts of AD patients and that of non-AD patients and determined the clinical correlation of *S aureus* colonization in close contacts and of AD severity.
Atopic Dermatitis. Non-AD controls were recruited from the pediatric dermatology clinic and were followed up for non-AD dermatological conditions, including nevi, hemangiomas, viral warts, alopecia, vitiligo, nail problems, and pigmentation. Close contacts were defined as people who lived together and spent a significant amount of time (>12 h/d) with the AD index case in the past 3 months. These people included parents, grandparents, household members, domestic helpers, and siblings. Exclusion criteria of the study included recent admission to the hospital, recent residency in institutions, and recent exposure to antibiotics in the past 4 weeks. This study was reviewed and approved by the Joint Chinese University of Hong Kong and New Territories East Cluster Clinical Research Ethics Committee.

CLINICAL EVALUATION

Severity of AD was assessed by a single investigator (L.S.C.) using the SCORAD (Scoring Atopic Dermatitis) index. Moderate disease was defined as an objective SCORAD index of at least 15, and severe disease was defined as an objective SCORAD index of at least 40. Clinical and demographic data of all subjects, including age, sex, and history of allergic rhinitis and asthma, were recorded. Written informed consent was obtained from all subjects or their legal guardians and their close contacts.

SAMPLE COLLECTION

Nasal swabs were obtained from AD patients, non-AD controls, and the close contacts of both groups. A sterile cotton-tipped swab was used to collect the specimen by approaching upward toward the top of both nares followed by a 360° twist to cover the whole vestibule. In addition, skin swabs were taken from the AD patients by rolling a sterile cotton-tipped swab stick over their worst affected skin area twice for at least 5 seconds. All samples were sent within the same day to the laboratory of the Department of Microbiology in the Prince of Wales Hospital for analysis.

LABORATORY ANALYSIS OF S aureus ISOLATES

Bacterial cultures of the nasal and skin swabs were performed using standard laboratory techniques. The identity of S aureus was confirmed by colony morphologic features, coagulation of citrated rabbit plasma with EDTA, and production of clumping factor and protein A. Bacterial growth was classified as scanty (<10^4 colony-forming units [CFU]/mL), moderate (10^4 to 10^5 CFU/mL), or heavy (>10^5 CFU/mL).

STATISTICAL ANALYSIS

Data were analyzed using statistical software (SPSS for Windows, version 11.5.1: SPSS Inc, Chicago, Illinois). Normality of continuous data was analyzed using the Kolmogorov-Smirnov test. All continuous variables were normally distributed. Results are expressed as mean (SD) or number (percentage) of patients as appropriate. Between-group differences were assessed, where appropriate, by the unpaired t test or the Pearson χ^2 test. Correlations between normally distributed variables were tested by the Pearson coefficient. Multivariate logistic regression using the forward stepwise method was performed to identify independent predictors of severe AD. The predictors tested were age, sex, asthma, allergic rhinitis, nasal or skin colonization of S aureus in AD patients, and nasal colonization of S aureus in the close contacts of AD patients. A probability value of P<.05 was considered statistically significant.

### Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AD Patients (n=50)</th>
<th>Non-AD Controls (n=50)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>7.0 (5.5)</td>
<td>9.0 (5.1)</td>
<td>.61</td>
</tr>
<tr>
<td>Male sex</td>
<td>31 (62)</td>
<td>27 (54)</td>
<td>.54</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>17 (34)</td>
<td>15 (30)</td>
<td>.83</td>
</tr>
<tr>
<td>Asthma</td>
<td>8 (16)</td>
<td>9 (18)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

Abbreviations: AD, atopic dermatitis; NA, not applicable; SCORAD, Scoring Atopic Dermatitis.

a Unless otherwise indicated, data are expressed as number (percentage) of subjects.

b Indicates 100% in patients with severe AD.

c Indicates 90% in patients with severe AD.

RESULTS

CHARACTERISTICS OF STUDY PARTICIPANTS

The age of 50 AD patients ranged from 4 months to 20 years. The mean objective and total SCORAD index values of the AD patients were 25.2 (15.6) (range, 0.2-63.7) and 35.1 (18.7) (range, 5.5-78.7), respectively. Among the 50 AD patients, 10 (20%) had severe AD, 23 (46%) had moderate AD, and 17 (34%) had mild AD. The age of the 50 controls ranged from 3 months to 17 years. The characteristics of the AD patients and the non-AD controls were similar, with details summarized in Table 1.

Sixty close contacts of AD patients and 51 close contacts of non-AD control subjects were recruited. The age of close contacts of AD patients ranged from 8 to 70 years, whereas that of close contacts of non-AD controls ranged from 7 to 70 years. There was a significantly higher prevalence of AD among the close contacts of AD patients compared with those of non-AD controls (11 of 60 [18%] vs 1 of 51 [2%] [P=.01]). The characteristics of close con-
contacts of AD patients and non-AD controls are compared in Table 2.

### S aureus COLONIZATION

Twenty-six AD patients (52%) were colonized by _S aureus_ in the nose and 22 (44%) on the skin. Nasal colonization of _S aureus_ was significantly more common (_P_ = .04) among AD patients (26 of 50 [52%]) than among non-AD controls (16 of 50 [32%]). Notably, skin colonization of _S aureus_ was present in all 10 patients with severe AD as opposed to only 12 of 40 (30%) among those with mild to moderate disease (_P_ < .001) Table 3. There were significantly more nasal carriers of _S aureus_ among the close contacts of AD patients (14 of 60 [23%]) than among the close contacts of non-AD controls (4 of 51 [8%] [ _P_ = .03]). The difference was still significant after the exclusion of the AD patients’ close contacts who also had AD (12 of 49 [24%] vs 4 of 50 [8%] [ _P_ = .03]). The microbiological findings among AD patients, non-AD controls, and their respective close contacts are summarized in Tables 1 and 2.

### COLONIZATION OF OTHER MICROBIALS

Apart from _S aureus_, cultures from the skin and nasal swabs yielded other microbials. _Streptococcus pneumoniae_ was cultured from anterior nares of 1 AD patient (2%) and 1 non-AD control subject (2%). One AD patient had diphtheroid bacterium (2%) and 1 had group _G_ streptococcus (2%) isolated from the anterior nares. _Moraxella catarrhalis_ was cultured from the anterior nares of 2 AD patients (4%). _Serratia_ species were found in the nasal culture of 1 AD patient (2%). Diphtheroid bacteria were found on the skin of 3 AD patients (6%), and _Streptococcus agalactiae_ was found on the skin of 1 AD patient (2%). None of the microbials had a significant association with AD severity.

### DETERMINING FACTORS OF AD SEVERITY

Among the 50 AD patients studied, the total SCORAD index of patients with skin colonization of _S aureus_ was significantly higher than for those without skin colonization (48.3 [16.8] vs 24.6 [12.5] [ _P_ < .001]). The total SCORAD index of AD patients with _S aureus_ nasal colonization (42.5 [18.8]) was also significantly higher than that of patients without nasal colonization (26.9 [15.0] [ _P_ = .002]). The density of growth of _S aureus_ from the nasal and skin swabs was not associated with AD severity. Patient age, sex, and history of asthma or allergic rhinitis also did not predict AD severity. The presence of close contacts with _S aureus_ colonization was not related to an increase in AD severity.

By multivariate analysis, only skin colonization of _S aureus_ was independently associated with severe AD (odds ratio, 17.0; 95% confidence interval, 1.60-181.1 [ _P_ = .02]). Comparisons of clinical and microbiological findings between AD patients with severe and those with mild to moderate disease are summarized in Table 3.

### COMMENT

We found a higher rate of _S aureus_ nasal colonization in the close contacts of AD patients than in those of non-AD controls. The finding still held true after exclusion of the AD patients’ close contacts who also had AD. The higher colonization rate, therefore, cannot be explained only by the higher prevalence of AD among close contacts of AD patients. We believe that the anterior nares of close contacts of AD patients serve as reservoirs of _S aureus_ and contribute to the transmission of _S aureus_ between AD patients and their close contacts. A recently published study in Singapore showed a high concordance of _S aureus_ isolates in AD patients and their close contacts, which supports our hypothesis of intrafamilial transmission of _S aureus_. The next question is whether _S aureus_ colonization among close contacts affects AD severity. Leung et al reported that a high burden of environmental _S aureus_ was associated with an increase in AD severity. They collected dust from the bed, bedroom floor, and vacuum bag and extracted _S aureus_ DNA from the dust particles. They found that AD severity correlated with the amount of _S aureus_ DNA from bed and bedroom floor dust. Simi-
larly, close contacts of AD patients who have *S. aureus* nasal colonization may contribute to a high burden of environmental *S. aureus*. However, we were unable to demonstrate any association between *S. aureus* colonization in close contacts and AD severity in our study, possibly because of the small sample size. The importance of *S. aureus* colonization in the close contacts of AD patients needs to be further clarified. Additional studies are needed to investigate whether decolonization of *S. aureus* from the close contacts influences AD disease control, which may affect the management of AD in the future.

Our study demonstrated a higher prevalence of *S. aureus* colonization on the skin and in the nose among AD patients than among the non-AD controls. However, the overall nasal and skin colonization rates of AD patients (52% and 44%, respectively) were lower than those in previous studies. The lower colonization rate can be explained by the fact that about one-third (34%) of our AD patients had mild disease only, and it is known that *S. aureus* colonization correlates with AD severity. The colonization rate was higher in those with severe AD, with a nasal colonization rate of 90% and skin colonization rate of 100%. Our finding was very similar to that of the study by Goh et al in Singapore. In that study, the skin colonization rate was only 53% in those with mild disease but reached 100% in patients with severe disease. Their overall nasal colonization rate in AD patients was 55%. Two major factors have been found to be responsible for the increased carriage of *S. aureus* in AD patients, namely, a defective skin barrier function and a compromised innate skin immunity. The stratum corneum of healthy skin is an important, functionally active cell layer that serves as a major barrier to soluble environmental substances and provides water-retaining properties. There is a decreased level of ceramides in the stratum corneum of AD skin. Ceramides are major water-retaining molecules in the stratum corneum. A reduction of ceramides leads to an increase in transepidermal water loss and ultimately results in dry, cracked skin. In addition, the expression of barrier proteins such as filaggrin, loricrin, and involucrin are reduced in AD patients, resulting in a defective skin barrier. Inducible antimicrobial peptides are produced by keratinocytes and include β-defensins and cathelicidins. They have antimicrobial activities against viruses, fungi, and bacteria, including *S. aureus*. Levels of both cathelicidin LL-37 and human β-defensin 2 are reduced in AD patients. The compromised innate skin immunity, together with the defective skin barrier, makes skin with AD highly susceptible to *S. aureus*.

Nasal and skin colonization of *S. aureus* were both found to be associated with AD severity in terms of a higher SCORAD index in our study. Similar findings have been reported in other studies. However, we found that only skin colonization was independently associated with severe AD on multivariate analysis. *Staphylococcus aureus* colonized on the skin can produce superantigens that contribute to the increased cutaneous inflammation in AD via several mechanisms. First, they directly interact with the major histocompatibility complex class II molecules and the β chain of the T-cell receptor to induce T-cell proliferation and activation of the inflammatory cascade, without the need for antigen-presenting cells. Second, superantigens upregulate the expression of cutaneous lymphocyte-associated antigen on T cells and the production of several keratinocyte-derived chemokines that increase T-cell recruitment into the skin. Finally, superantigens have been found to contribute to the development of resistance to local corticosteroid treatment by causing the upregulation of the β-isofrom of the glucocorticoid receptor in mononuclear cells, which does not bind to corticosteroids. We believe that *S. aureus* can be transmitted from the skin to the anterior nares or vice versa in AD patients through autoinoculation. The rate of *S. aureus* skin colonization is expected to parallel that of nasal colonization, and the latter is therefore indirectly associated with AD severity.

Our study had several limitations. First, we recruited controls from the pediatric clinic. It would be a better representation of the normal healthy population if we could have recruited non-AD healthy controls from the community. Second, we were unable to recruit all the close contacts of AD patients because some of them were not available at the time of the study. The sample size was therefore smaller than expected. Third, we took swabs only from the noses of the close contacts. Other areas, such as the hands and flexural and intertriginous areas, might also be involved in the transmission of *S. aureus*. The overall colonization rate might therefore be underestimated.

In conclusion, the anterior nares of close contacts of AD patients are important reservoirs of *S. aureus*. Nasal colonization of *S. aureus* among close contacts of AD patients is not associated with AD severity. Skin colonization is the only factor independently associated with severe AD.

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**Correspondence:** Lai Shan Chiu, MBChB, MRCP, Department of Medicine and Therapeutics, Ninth Floor, Clinical Science Building, Prince of Wales Hospital, Shatin, NT, Hong Kong SAR (monachi@gmail.com).

**Author Contributions:** Drs Chiu, Chow, and Ling had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. **Study concept and design:** Chiu and Hon. **Acquisition of data:** Chiu, Chow, and Ling. **Analysis and interpretation of data:** Chiu and Ling. **Drafting of the manuscript:** Chiu. **Critical revision of the manuscript for important intellectual content:** Chiu, Chow, and Hon. **Statistical analysis:** Chiu. **Obtained funding:** Chow and Ling. **Administrative, technical, and material support:** Chiu, Chow, and Ling. **Study supervision:** Chiu and Hon.

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**REFERENCES**

Announcement

Volunteering With Health Volunteers Overseas

The American Academy of Dermatology partnered with Health Volunteers Overseas (HVO) in 2004 to match interested dermatologists with overseas volunteer opportunities. Through HVO programs, volunteer dermatologists train local health care providers, giving them the knowledge and skills to make a difference in their own communities.

The major goal of the HVO dermatology programs is to build capacity through training local health care providers (ranging from dermatology residents to primary care health workers) in clinical dermatology.

Sites with volunteer opportunities for dermatologists include Costa Rica, Palau, India, Peru, Uganda, Cambodia, and Saint Lucia. Volunteers generally serve for 2 to 4 weeks, although shorter and longer assignments are possible.

A private, nonprofit membership organization, HVO was founded in 1986 to improve global health through education. HVO designs and implements clinical education programs across the spectrum of health specialties. To learn more about volunteering with HVO, visit the Web site (www hvousa org) or contact the HVO Program Department at (202) 296-0928.