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## Letter to the Editor

## Specific IgE sensitization to honey bee venom and auto-injector adrenaline prescriptions for Japanese beekeepers



Dear Editor,

Honey bee stings are an occupational hazard for beekeepers and often lead to allergic reactions. Furthermore, approximately 40% of Japanese forestry workers have specific (s) immunoglobulin (Ig) E to Hymenoptera venom.<sup>1</sup> Recently, we reported that around 6–33% of Japanese outdoor workers (forestry workers, building contractors, and electrical facility field workers) with sIgE positivity to Hymenoptera venom received prescriptions for adrenaline auto-injectors.<sup>2</sup> Only 23–57% of such workers who had experienced systemic reactions to a Hymenoptera sting with a positive result of sIgE to Hymenoptera venom had been prescribed adrenaline auto-injectors.<sup>2</sup> However, honey bee stings and the prescribing of adrenaline auto-injectors for affected workers have not been surveyed in occupational settings. In this study, we conducted a survey of beekeepers in Japan to examine the presence of sIgE to honey bee venom and the number of adrenaline auto-injectors prescribed.

The participants included 113 beekeepers (104 men, 9 women; [Table 1](#)) who were almost all staff members of private apiaries based in Tochigi, Gunma, and Saitama prefectures, Japan. The main work of the beekeepers is to collect honey and maintain the breeding colonies; consequently, workers are at high risk of honey bee stings. All participants completed questionnaires and underwent peripheral blood tests on the same day between December 2015 and February 2016. Fifteen volunteers who had never experienced a honeybee sting were enrolled as controls. The study was approved by the Dokkyo Medical University Koshigaya Hospital Research Ethics Committee, authorization numbers No. 1525 and No. 1526. Written, informed consent was obtained from all participants prior to enrollment.

The questionnaire was administered by an allergist and included the following items: age, sex, experience of a honey bee sting (yes or no), systemic reaction to a honey bee sting according to Mueller grading system<sup>3</sup> (grades I to IV) (yes or no), adrenaline auto-injector prescription given (yes, no, unknown), and adrenaline auto-injector carried (usually, sometimes, rarely). An adrenaline auto-injectors were prescribed to 3 subjects with Mueller grade I (14 subjects total), 0 in grade II (2 subjects total), 2 in grade III (3 subjects total), and 5 in grade IV (16 subjects total).

A 10-mL peripheral blood sample was collected from each participant. Serum was immediately extracted, and sIgE antibody (Ab) to honey bee venom was measured by Sanritsu Corporation, Chiba, Japan. Detection of sIgE Ab by AlaSTAT 3g Allergy (AlaSTAT), a chemiluminescent enzyme immunoassay (CLEIA), was expressed

in quantitative units (IU<sub>A</sub>/mL), with a working range of 0.1–500 IU<sub>A</sub>/mL. Positive results for AlaSTAT were defined as values  $\geq 0.1$  IU<sub>A</sub>/mL, as described previously.<sup>2,4</sup> Data are presented as means  $\pm$  standard deviation (S.D.).

[Table 1](#) summarizes the characteristics of the beekeepers. The quantity of sIgE to honey bee venom was  $\geq 0.1$  IU<sub>A</sub>/mL in 88 (77.9%) participants. Each of the 15 controls was negative for sIgE. Since hornets hunt honey bees, beekeepers are also frequently exposed to hornet stings, and we found sIgE ( $\geq 0.1$  IU<sub>A</sub>/mL) to hornet venom in 41 participants (36.3%) (data not shown). Furthermore, antigenic cross-reactivity between honeybees and *Vespa* venom is limited and largely confined to hyaluronidase.<sup>5</sup> Beekeepers therefore also need to be aware of systemic reactions to hornet stings. We found that adrenaline auto-injectors were prescribed for 12 (10.6%) beekeepers. However, in a UK report, 18% of British beekeepers had received prescriptions.<sup>6</sup> Hence, compared with British beekeepers, adrenaline auto-injectors are less frequently prescribed to Japanese beekeepers. Among our subjects, 110 (97.3%) had experienced a honeybee sting, and a systemic reaction to or positivity for honeybee venom-sIgE was seen in 35 (31.8%) and 87 (79.1%) beekeepers, respectively. Similarly, other investigators have reported that 14–35% of beekeepers have had at least one episode of systemic allergic reaction after a bee sting.<sup>7</sup> Moreover, 30–60% of beekeepers show honey bee venom-sIgE positivity.<sup>8</sup> Compared with Japanese outdoor workers, 18.6% forestry workers had experienced systemic reactions, and 62.8% showed venom-sIgE positivity after a Hymenoptera sting.<sup>2</sup> These results indicate that systemic reactions and sIgE positivity to Hymenoptera venom occur more frequently in beekeepers than in Japanese forestry workers.

[Figure 1A](#) shows the occupations of the participants and the number of auto-injector prescriptions given. Prescriptions were given to 11 of 88 (12.5%) beekeepers with sIgE Ab to honey bee venom, regardless of the presence or absence of systemic reactions, while 4 out of 11 (36.4%) beekeepers usually carried auto-injectors. In comparison, 71 of 214 (33.2%) Japanese forestry workers with sIgE Ab to Hymenoptera venom were given prescriptions, and 37 of 71 (52.1%) usually carry auto-injectors.<sup>2</sup> These results indicate that the number of prescriptions given and the number of adrenaline auto-injectors carried among workers with sIgE to Hymenoptera venom in Japan are lower in beekeepers than in forestry workers.

[Figure 1B](#) shows that 35 beekeepers had experienced a systemic reaction to a honey bee sting and adrenaline auto-injector prescriptions were given to 9 out of 31 (29.0%) beekeepers who showed sIgE to honey bee venom. In contrast, prescriptions were given to 28 of

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**Table 1**  
Subject characteristics (n = 113).

Beekeepers (n)	113
Sex (n)	
Male (%)	104 (92.0)
Female (%)	9 (8.0)
Age (years)	
10–19	1 (0.9)
20–29	1 (0.9)
30–39	13 (11.5)
40–49	11 (9.7)
50–59	14 (12.4)
60–69	44 (38.9)
≥70	29 (25.7)
Honey bee-sIgE (mean ± SD, n)	4.2 ± 11.1
Negative (%)	25 (22.1)
Positive (%)	88 (77.9)
Prescription of adrenaline (n)	
Yes (%)	12 (10.6)
No (%)	89 (78.8)
Unknown (%)	12 (10.6)
Experience of a honey bee sting (n)	
Yes (%)	110 (97.3)
No (%)	3 (2.7)
Out of beekeepers who had experienced a honey bee sting	
Systemic reaction (n)	
Yes (%)	35/110 (31.8)
No (%)	75/110 (68.2)
Honey bee venom-sIgE (n)	
Negative (%)	23/110 (20.9)
Positive (%)	87/110 (79.1)

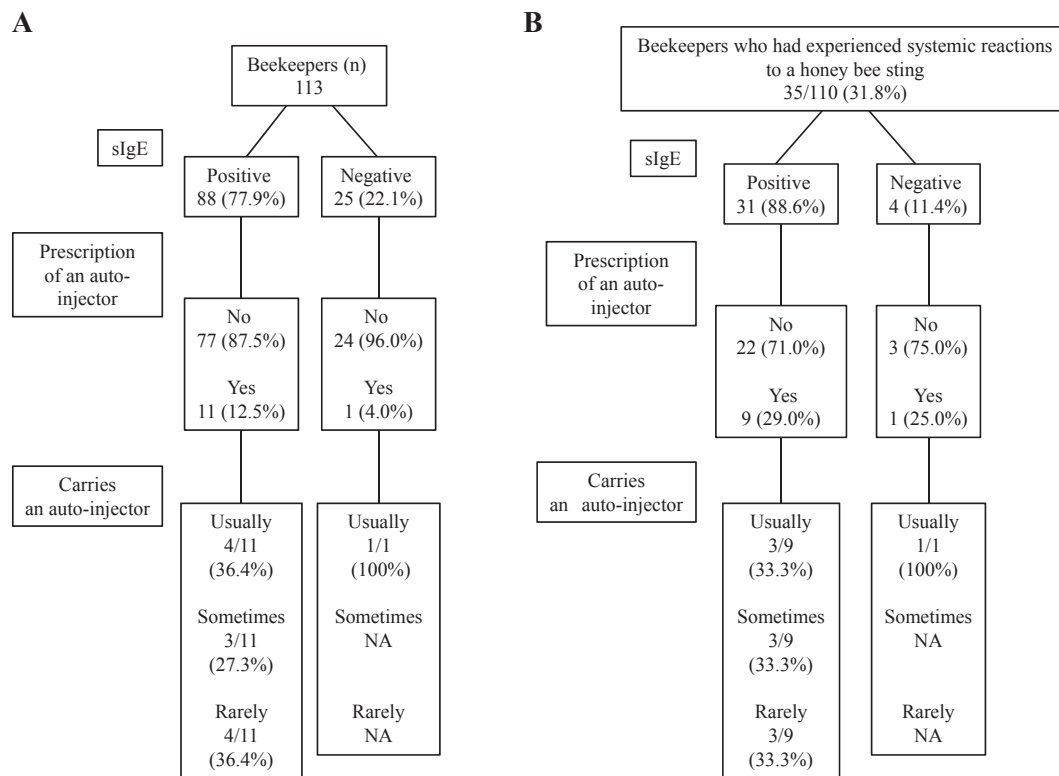
n, numbers; sIgE, specific IgE.

Levels of sIgE (IU<sub>A</sub>/mL) are presented as mean ± standard deviation (SD).

Interpretations of positive results are based on values ≥ 0.1 IU<sub>A</sub>/mL.

49 (57.1%) Japanese forestry workers who had systemic reactions to Hymenoptera stings and had sIgE to Hymenoptera venom.<sup>2</sup> These results indicate that among subjects who have had systemic reactions and showed sIgE to Hymenoptera venom in Japan, beekeepers are less likely to be prescribed auto-injectors than forestry workers. In addition, only 3 of 9 (33.3%) beekeepers given prescriptions usually carry auto-injectors. Although Japanese beekeepers experience frequent Hymenoptera stings, and often subsequent systemic reactions, there appears to be a lack of awareness of potential anaphylaxis resulting from honey bee stings. These findings indicate that few adrenaline auto-injectors are prescribed to Japanese beekeepers, and even then, auto-injectors are not usually carried. On the other hand, the absence of sIgE to honey bee venom was found in 4 of the 35 (11.4%) beekeepers who had experienced systemic reactions to a honey bee sting. Indeed, sIgE levels decline over several years if there are no further Hymenoptera stings and are thought to disappear immediately after a sting.<sup>3,10</sup> Thus, if sIgE to Hymenoptera venom is negative immediately after a sting, the test should be repeated after a few weeks.

Although this was not investigated in the present study, Richter *et al.* presented the first study in the UK of bee venom allergy in beekeepers, one of the largest to date.<sup>6</sup> Interestingly, this study identified that a number of factors, including having a family member with bee venom allergy, female sex, over 2 years of beekeeping, and premedication with antihistamines, were associated with development of systemic reactions.<sup>6</sup> The study also noted that attendance at emergency departments and subsequent review by allergy specialist was low, which is a likely explanation that only a low proportion of beekeepers received venom immunotherapy after a systemic reaction. As a countermeasure to anaphylaxis,



**Fig. 1. A.** Numbers of prescriptions given and adrenaline auto-injectors carried by beekeepers with sIgE to honey bee venom in this study. **B.** Numbers of prescriptions given and adrenaline auto-injectors carried by beekeepers following systemic reactions to a honey bee sting combined with the presence of sIgE to honey bee venom in this study. NA, not applicable.

beekeepers with sIgE Ab to honey bee venom, with or without experience of a systemic reaction, should be prescribed adrenaline auto-injectors.<sup>2</sup> Furthermore, beekeepers who have indeed experienced a systemic reaction to a honey bee sting with sIgE Ab should receive venom immunotherapy.<sup>11</sup> Subjects who have experienced an anaphylactic reaction due to honey bee stings, with negative results of sIgE to honey bee venom, also should be prescribed adrenaline auto-injectors.

In conclusion, we found that approximately 11% of Japanese beekeepers with sIgE to honey bee venom and 29% who had experienced systemic reactions to a honey bee sting and showed sIgE to the venom were prescribed adrenaline auto-injectors. Moreover, approximately 35% of beekeepers usually carry auto-injectors during work, regardless of the presence or absence of systemic reactions to honey bee stings. This study suggests that the owners of the cooperative should consider obtaining adrenaline auto-injector prescriptions for beekeepers who have sIgE Ab to honey bee and/or hornet venom. In addition, beekeepers should be educated about regularly carrying adrenalin auto-injectors.

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### Conflict of interest

DS is an employee of Pfizer Japan. The rest of the authors have no conflict of interest.

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