Bee Venom Allergy in Chinese Beekeepers and Patients Under Live Bee Apitherapy

Le Cui

Peking Union Medical College Hospital <https://orcid.org/0000-0002-1802-5981>

Ying-Yang Xu

Peking Union Medical College Hospital

Li-Sha Li

Peking Union Medical College Hospital

Zi-Xi Wang

Peking Union Medical College Hospital

Sai-Nan Bian

Peking Union Medical College Hospital

Qiao-Ju Han

Shijiazhuang Dazheng Hospital of TCM Apitherapy

Wan-Yao Li

Guangzhou University of Chinese Medicine

Yi Li

Chinese Academy of Agricultural Sciences Institute of Apiculture Research

Bobby Quentin Lanier

North Texas Institute for Clinical Trials

Christopher Chang

University of California Davis

Kai Guan (✉ dr_guankai@126.com)

Chinese Academy of Medical Sciences <https://orcid.org/0000-0003-0850-5874>

Research

Keywords: anaphylaxis, venom allergy, beekeepers, LBA population

Posted Date: May 26th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-511045/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Hymenoptera stings are one of the common causes of anaphylaxis. The prevalence of systemic allergic reactions seems to be higher in highly exposed populations such as beekeepers and individuals receiving live bee acupuncture (LBA). However, there are a very few of studies on venom allergy in these populations. We performed two observational studies to describe the characteristics and risk factors of venom allergy in beekeepers and the LBA population.

Methods: A total of 99 beekeepers and 127 individuals receiving live bee acupuncture were interviewed. Skin prick tests were performed on subjects with suspected bee venom allergy.

Results: The prevalence of bee venom allergy was 34.3% among beekeepers and 29.0% in the LBA population. Systemic reactions occurred in 11.3% of the LBA population, and 28.3% of beekeepers. For beekeepers with exposure to 2-4 stings per year and ≥ 5 stings per year, the risk for developing venom allergy increased to 6.745-fold (95% CI 2.139-21.266) and 42.297-fold (95% CI 7.060-253.399) respectively, compared to the ≤ 1 sting per year group. Conversely, in the LBA population, compared to frequency ≤ 2 LBA stings per week, the adjusted OR of venom allergy was 0.281 (95% CI 0.075-1.047) and 0.166 (95% CI 0.045-0.612) for frequency 3-6 LBA stings per week and ≥ 7 stings per week respectively. The knowledge of adrenaline and venom immunotherapy was limited in both beekeepers and traditional doctors.

Conclusion: The frequency of stings with high risk for bee venom allergy was >4 /year in beekeepers and <3 /week in the LBA population. The education on anaphylaxis management should be strengthened.

Background

In contrast to airborne allergens that have to cross mucosal barriers, venom allergens are injected directly into the skin and can rapidly enter the circulation. Non-allergic reactions to Hymenoptera stings include common local irritant reactions and, more rarely, toxic systemic reactions (seen after large numbers of simultaneous stings)¹. IgE-mediated allergic reactions triggered by Hymenoptera stings range from large local reactions (LLR) to systemic reactions, including urticaria, angioedema, asthma, or anaphylaxis, which may be life-threatening¹. The prevalence of LLR owing to Hymenoptera stings is estimated to be between 2.4% and 26.4%(2–4), whereas 0.4–8% may develop potentially life threatening systemic reactions after a Hymenoptera sting^{5–8}. In highly exposed populations such as beekeepers, forest rangers and gardeners, 6.9–26% experienced systemic reactions to stings^{9–12}. Since anaphylactic reactions owing to stings of Hymenoptera can cause a rapid death¹³, there is a significant component of anxiety in susceptible individuals and they experience significant impact on quality of life. A quality of life questionnaire was administered to venom-allergic patients in Spain. The results showed that people with venom allergy had a poor quality of life because of increased anxiety directed towards the risk of accidental exposure to Hymenoptera stings¹⁴. The essential therapeutic options for venom allergy are the

prescription of emergency medication (adrenaline/epinephrine auto-injector, anti-histamines, corticosteroids) or, as the only curative treatment, venom-specific immunotherapy¹⁵.

Bee venom therapy is delivered either through a live bee sting (also known as live bee acupuncture, LBA) or venom injection. In Asia, bee venom has been used to treat rheumatoid arthritis for decades¹⁶. Moreover, Bee venom therapy is also used to treat other conditions such as osteoarthritis, multiple sclerosis, asthma and cancer^{17–20}. Patients usually receive one or more live bee stings at each visit, with each sting delivering about 50 to 140 ug of bee venom²¹. LBA can also induce venom allergy. In 2018, a fatal case of after LBA was reported in Spain²². Additionally, Guan et al. reported that in northern China, 5.6% (3/54) of bee venom allergy cases were due to iatrogenic exposure²³. Therefore, bee venom allergy due to LBA is a significant problem warranting additional investigation.

There are a very few of studies on bee venom allergy in China, especially for the high-risk populations such as beekeepers. In this study, we analyzed bee venom allergy in two populations with high risk, beekeepers and individuals receiving LBA, to answer the following questions – 1) what are the prevalence and clinical features of bee venom allergy in Chinese populations who are at high risk, 2) what are the risk factors associated with bee venom allergy in China and 3) what is the management strategy used for venom allergy in these two populations.

Materials And Methods

Study design

We conducted two observational studies. The first focused on subjects receiving LBA from December 2017 to January 2018 in Shijiazhuang Dazheng Hospital of TCM Apitherapy in northern China, and First Hospital Affiliated to Guangzhou University of Chinese Medicine and Shenzhen Traditional Chinese Medicine Hospital in southern China. The second study focused on beekeepers from August to September 2018 in the Bee Institute of the Chinese Academy of Agricultural Sciences and Entomology department of China Agricultural University. Demographic information and characteristics of bee venom allergy were collected using a questionnaire. The features of allergic reactions including local reaction size, involvement of other systems, duration of symptoms, and prognosis were investigated in detail. Possible influencing factors such as working years or duration of LBA, frequency of bee stings, atopy history and family history were analyzed. We also collected the data regarding the management of venom allergy due to LBA and the education status about venom allergy management in beekeepers. To confirm the diagnosis, skin prick tests (SPT) were performed on subjects with suspected bee venom allergy. Serum venom-specific IgE (sIgE) was tested to a portion of beekeepers.

This study was approved by the ethics committee of Peking Union Medical College Hospital, and all participants provided written informed consents.

Diagnosis standard

Diagnostic standards of bee venom allergy included clinical history of allergic reactions post-LBA or bee sting, and positive results of SPT or serum sIgE to bee venom¹⁵. In this study, we performed SPT to confirm the diagnosis.

Classification of bee venom allergic reactions

LLR and systemic reactions were defined according to those described in a recent official guideline²⁴. LLRs are defined by edema, erythema and pruritus and have maximum diameters greater than 10 cm peaking at 1 to 2 d after the sting and resolving 3 to 10 d later. Systemic reactions involve two or more organ systems and usually begin 10 to 30 minutes after the sting, but can also arise faster (i.e. in patients with mast cell disorders) or slower (1–4 h). Severity of systemic reactions were then subcategorized into four grades according to Ring and Messmer²⁵.

SPT

SPT were conducted using standard honeybee extracts (100 ug/ml; ALK®, Denmark) together with positive (10 mg/ml histamine), and negative (saline) controls on the volar surface of the forearm. SPTs were regarded as positive when the wheal diameter was at least 3 mm greater than the wheal diameter of the negative control after 15 min²⁶.

Serum venom-sIgE tests

Serum venom-sIgE levels were measured using ImmunoCAP (Thermo Fisher Scientific, United States). sIgE values greater than or equal to 0.35 kU/L were considered positive.

Statistical analyses

Descriptive data for categorical and numerical variables are expressed as frequencies and means with standard deviations (SD) for normally distributed variables or as medians with interquartile ranges (IQR) in parentheses for the non-normally distributed variables. Group comparisons were established using ANOVA for numerical variables, rank-sum test for ranked variables and Fisher's exact test for categorical variables. Logistic regression without adjustment was applied to assess the odds ratio (OR) for comparisons of outcomes between exposure groups. Statistical analyses were performed with SPSS version 13 (SPSS Inc, Chicago, USA).

Results

i) Bee venom allergy in beekeepers

A total of 99 beekeepers ranging from 19 to 56 years old were surveyed. The median (quartile) of age was 28 (24-35) years old, and women accounting for 68.7%.

Prevalence and severity of bee venom allergy in beekeepers

Of the 99 beekeepers (Table 1), 34 (34.3%) reported having allergic reactions, including 6 (6.1%) with LLR and 28 (28.3%) with the systemic reactions. Among all the systemic reactions, the highest proportion was anaphylactic shock (10/28, 35.7%). Of the 28 patients with systemic reactions, 14 (50%) experienced LLR initially and then developed systemic reactions after being re-stung.

Table 1. Prevalence and severity of bee venom allergy in beekeepers

	BVA (n=99)	percentage (%)
LLR	6	6.1%
Systemic reactions	28	28.3%
Grade I	7	7.1%
Grade II	7	7.1%
Grade III	4	4.0%
Grade IV	10	10.1%
Total	34	34.3%

Risk factors of bee venom allergy in beekeepers

As shown in Table 2, there was a statistically significant difference in the frequency of bee stings between the bee venom allergy group and the non-allergic group ($P < 0.001$). Compared to the non-allergic group, the proportions of 2-4 stings per year and ≥ 5 stings per year in the allergic group were higher (44.1% vs. 26.2% and 32.4% vs. 3.1%). There was no significant difference in experience (years worked), history of atopy, and a family history of bee venom allergy between the two groups ($p > 0.05$).

In multi-factor analysis, after adjusting for the gender, length of service, family history of bee venom allergy, and history of atopy, compared to the ≤ 1 sting per year group, beekeepers with the exposure frequency of 2-4 stings per year and ≥ 5 stings per year had a 6.745-fold (95% CI 2.139-21.266) and 42.297-fold (95% CI 7.060-253.399) greater risk for developing bee venom allergy respectfully. As the number of working years increased, the risk of bee venom allergy increased, but there is no significance ($P = 0.083$).

Table 2. Risk factors of bee venom allergy in beekeepers

	Non-BVA ^a (n=65)	BVA (n=34)	P value	OR (95% CI) ^b
Female, n (%)	46 (70.8%)	22 (64.7%)	0.649	0.960 (0.311-2.969)
Working years, n (%)			0.459	2.987 (0.866-10.307)
<5 years	52 (80.0%)	25 (73.5%)		
≥5 years	13 (20.0%)	9 (26.5%)		
Bee stings in the past year, n (%)			<0.001	
≤1 sting per year	46 (70.8%)	8 (23.5%)		
2-4 stings per year	17 (26.2%)	15 (44.1%)		6.745 (2.139-21.266)
≥5 stings per year	2 (3.1%)	11 (32.4%)		42.297 (7.060-253.399)
Family history of BVA, n (%)	4 (6.2%)	1 (2.9%)	0.657	2.228 (0.181-27.354)
Atopy history, n (%)	20 (30.8%)	8 (23.5%)	0.490	0.608 (0.180-2.048)

^a bee venom allergy, ^b adjusted

Major sensitizing components in beekeepers and its relationship with exposure to bee stings

Serum was collected in 15 patients who had both allergic reactions after bee stings and positive SPTs. 13 patients (86.7%) were positive to bee venom (i1), and 9 patients (60%) were positive to Api m 1 (i208). Four patients (26.7%) were additionally positive to wasp venom (i3) but negative to Ves v 5 (i209). Serum from 15 participants without bee venom allergy were also collected as controls. Among these, 3 subjects (20.0%) were positive to i1 and 1 subject (6.67%) was weakly positive to i208.

The relationship between the frequency of bee stings and the specific IgE of i1 and i208 were further analyzed by non-parametric testing. The sIgE level of i1 (P=0.014) and i208 (P=0.006) were positively correlated to the frequency of bee stings.

Education about venom allergy management in beekeepers

For subjects with LLR, half of the subjects knew that epinephrine is needed for systemic reactions, but no one knew that venom-specific immunotherapy could be used to treat venom allergy (Table 3). Nearly two-thirds of patients with Grade 1-2 systemic reactions were aware of adrenaline injection and venom-specific immunotherapy.

Table 3. Education status of bee venom allergy management in beekeepers

	LLR (n=6)	Grade I (n=7)	Grade II-III (n=21)
Knowledge of use of antihistamines	33.3%	28.6%	28.6%
Knowledge of use of intramuscular adrenaline when SR occurs	50.0%	42.9%	61.9%
Knowledge of venom-specific immunotherapy	None	57.1%	61.9%

ii) Bee venom allergy in the population with LBA

During the study period, 127 participants (69.3% female) were surveyed. The median (quartile) of age was 54 (35-64) years, ranging from 18 to 78 years. Arthritis (57.5%) accounted for the majority of underlying diseases in patients receiving LBA. In northern China, people receive LBA more frequently ($P<0.001$), with the majority undergoing ≥ 7 LBA stings per week, compared to the majority that underwent 3-6 LBA stings per week in southern China.

Prevalence and clinical manifestations of bee venom allergy in the LBA population

Among the 127 participants (Table 4), 44 reported having experienced allergic reactions post-LBA and 41 out of them consequently underwent SPT. Of the 124 participants included in the statistical analysis, 36 (29.0%) were positive to SPT. Venom allergy occurred more frequently in healthy people who underwent LBA to improve their health (6/8, 75%).

Table 4. Prevalence of bee venom allergy in live bee acupuncture

	Shijiazhuang (n=77)	Shenzhen & Guangzhou (n=47)	Total (n=124)
Allergic reactions, n (%)			
LLR, n (%)	10 (13.0%)	12 (25.5%)	22 (17.7%)
SR, n (%)	6 (7.8%)	8 (17.1%)	14 (11.3%)
Grade I	1 (1.3%)	5 (10.6%)	6 (4.8%)
Grade II-III	5 (6.5%)	3 (6.4%)	8 (6.5%)

In subjects with systemic reactions (Table 4), 6 of 14 subjects presented only with skin symptoms and signs (i.e., pruritus, erythema, urticaria, and/or angioedema), which was widespread and involved areas that were not contiguous with the sting site. 8 of 14 subjects involved more than one organ system (respiratory or circulatory symptoms etc.). Four subjects involved anaphylactic shock. Of the 14 subjects

that had systemic reactions, 5 (35.7%) experienced LLR initially and then developed systemic reactions after being re-stung.

Risk factors of bee venom allergy in the LBA population

A comparison of baseline characteristics between the BVA and non-BVA groups is shown in Table 5. LBA frequency and living in the suburbs were significantly different between the BVA and non-BVA groups. In addition, there were strong cross-sectional associations between age at initiation of LBA ($p=0.002$).

After controlling for age at LBA initiation, gender, living in the suburbs and atopy history, in contrast to frequency ≤ 2 LBA stings per week, logistic regression showed that the adjusted OR of bee venom allergy was 0.281 (95% CI 0.075-1.047) and 0.166 (95% CI 0.045-0.612) for frequency 3-6 LBA stings per week and ≥ 7 stings per week respectively, indicating that as LBA treatment frequency increases, the risk of allergies due to LBA is reduced.

Table 5. Risk factors of bee venom allergy in LBA

	BVA ^a (n=36)	Non-BVA (n=88)	P value	OR (95% CI) ^b
Age at onset of LBA, year, mean (SD)	41.5 (17.7)	52.1 (15.6)	0.002	0.982 (0.954-1.011)
Female, n (%)	26 (72.2%)	59 (67.0%)	0.574	0.841 (0.321-2.209)
BVA frequency, n (%)			<0.001	
≤ 2 stings per week	13 (36.1%)	6 (6.8%)		
3-6 stings per week	11 (30.6%)	26 (29.5%)		0.281 (0.075-1.047)
≥ 7 stings per week	12 (33.3%)	56 (63.6%)		0.166 (0.045-0.612)
Living in the suburbs, n (%)	13 (36.1%)	12 (13.6%)	0.006	1.791 (0.606-5.297)
Family history of BVA, n (%)	3 (8.3%)	7 (8.0%)	0.944	1.204 (0.261-5.561)
Atopy history, n (%)	13 (36.1%)	25 (28.4%)	0.400	1.210 (0.483-3.028)

^a bee venom allergy, ^b adjusted

Management of bee venom allergy in the LBA population

Most LLR subjects continue with the same venom frequency (71.4%) or sting sites (81%) (Table 6). For 75% of subjects with Grade III-IV systemic reactions, the traditional medicine doctors adjusted their LBA frequency or sting sites. Moreover, the most commonly used drugs for bee venom allergy are oral or intramuscular antihistamines. Even in subjects with Grade III-IV systemic reactions, no adrenaline has been used and no one knew that venom-specific immunotherapy could be a possible curative treatment.

Table 6. Treatment choices for allergic reactions post-LBA

	LLR (n=21) ^a	Grade I (n=6)	Grade II-III (n=8)
Decreasing the frequency of LBA	28.6%	66.7%	75.0%
Changing the sting sites	19.0%	16.7%	75.0%
Administering oral antihistamines	4.8%	50.0%	75.0%
Administering intramuscular antihistamines	4.8%	16.7%	50.0%
Administering intramuscular adrenaline	None	None	None
Considering venom-specific immunotherapy	None	None	None

^a 5 people didn't answer these questions because of unclear memory

Discussion

In Europe, the prevalence of LLR due to Hymenoptera stings is estimated to range from 2.4–26.4% ^{2–4}, and the rate of systemic reactions varies between 0.4% and 8.0% ^{5–8}. The prevalence of systemic allergic reactions seems to be higher in highly exposed populations such as beekeepers, forest rangers and gardeners, systemic allergic reactions, varying between 6.9% and 26% ^{9–12}. Our study showed that a systemic reaction occurred in 28.3% of the beekeepers, which was not less frequent than the global data. The prevalence of systemic reactions in the LBA population was 11.3%, which was less than that of the beekeepers. One possible explanation for this apparent paradox may be that the studied subjects were being treated in hospitals. Patients who have BVA, especially those who experience severe reactions, may terminate LBA and thus were not included in the survey. We also thought the heterogeneity of patients and the number of stings could contribute to the different rate of systemic reactions in these two populations.

Our research shows that among beekeepers, as the frequency of bee sting increases, the risk of bee venom allergy increases. However, in the LBA population, the relationship between exposure and effect is inversely related. Bousquet et al. determined that the degree of sensitivity to bee venom is associated with the number of annual bee stings²⁷. At least 50 stings are required to develop natural protection against systemic reactions, and the risk of allergy is extremely low in individuals with more than 200 stings per year(27). In fact, beekeepers' exposure to bee stings is less than that of individuals who regularly receive LBA every week. In our study, among the beekeepers, the most prone to bee venom allergy are those who have been stung more than 4 stings per year (95%CI 6.842-250.964). But the risk of

bee venom allergy will begin to decrease when exposure to bee stings increases to more than 2 stings per week as seen in the population with LBA. This is similar to previous studies which showed that venom immunotherapy was demonstrated to be effective in more than 80% of treated patients and is considered as the ideal model for understanding the mechanisms of induction of immune tolerance produced by allergen specific immunotherapy²⁸. Despite the differences between the two study populations, it is especially important to be alert to bee venom allergy in high-risk groups who are exposed to more than 4 bee stings a year but less than 3 stings a week.

Guan et al. found that six patients with LLR developed systemic reactions between 1 and 12 months after having been stung²⁹. In this study, half of the beekeepers with systemic reactions initially showed an LLR. This ratio is also as high as 35.7% in the LBA population. Although LLR is not considered as a risk factor of anaphylaxis, in view of the situation that cardiorespiratory arrests can be observed in a median time of 15 min after the sting, the latest US guidelines recommend venom immunotherapy for patients with LLR²⁴. High risk populations such as beekeepers or individuals receiving LBA who exhibit LLR should receive close follow up and be given an emergency kit that includes epinephrine (intramuscular auto-injectors).

Our study found that the management of bee venom allergy and patient education were severely inadequate for both beekeeper and LBA populations. More than half of beekeepers with systemic reactions have awareness of using epinephrine to treat anaphylaxis. But beekeepers with LLR are less aware. Unfortunately, adrenaline auto-injector is still not available in mainland China. Traditional medicine doctors are usually unaware that the epinephrine is the first-line treatment for anaphylaxis, but also are unaware that venom immunotherapy can induce tolerance to venom in LBA patients. Beekeepers with LLR also have limited knowledge of venom immunotherapy.

Our study has several limitations. In this cross-sectional survey, patients may have inaccurate memory of relevant information. The occurrence and development of bee venom allergy cannot be accurately described. Therefore, prospective studies involving large study cohorts are needed to further examine the relationship between bee venom allergy and exposure to bee stings. Such studies may suggest the involvement of possible immunological or genetic factors.

Conclusions

In conclusion, our study is novel in that it is, to our knowledge, the first description of the prevalence of bee venom allergy in beekeepers and LBA populations in China. Beekeepers with an exposure of more than 4 stings per year, and LBA population with the exposure of less than 3 stings per week have high risk for bee venom allergy. It is very important for beekeepers and traditional medicine doctors to enhance education focused on anaphylaxis management.

Abbreviations

live bee acupuncture (LBA)

large local reactions (LLR)

skin prick tests (SPT)

specific IgE (sIgE)

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Peking Union Medical College Hospital, and all participants provided written informed consents.

Consent to publish

All the authors listed have approved the manuscript for publication and met the requirements for authorship. I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously, and not under consideration for publication elsewhere.

Availability of data and materials

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Not applicable

Funding

This study was supported by Beijing Natural Science Foundation Project (7172179); Public Welfare Industry Scientific Research Fund (201502012)

Youth Teacher Training Program of Peking Union Medical College (2015zlgc0726).

Authors' Contributions

Not applicable

Acknowledgements

Kai Guan and Le Cui made substantial contributions to conception and design, acquisition of data, analysis, and interpretation of data. Li-Sha Li, Zi-Xi Wang, Sai-Nan I participated in the field investigation. Le Cui and Ying-Yang Xu drafted the article. Qiao-Ju Han, Wan-Yao Li, Yi Li, Bobby Quentin Lanier and

Christopher Chang reviewed it critically for important intellectual content. Kai Guan given final approval of the version to be published and agrees to be accountable for all aspects of the work related to its accuracy or integrity.

References

1. Casale TB, Burks AW. Clinical practice. Hymenoptera-sting hypersensitivity. *N Engl J Med* 2014; 370:1432-9.
2. Bilo MB. Anaphylaxis caused by Hymenoptera stings: from epidemiology to treatment. *Allergy* 2011; 66 Suppl 95:35-7.
3. Fernandez J, Blanca M, Soriano V, Sanchez J, Juarez C. Epidemiological study of the prevalence of allergic reactions to Hymenoptera in a rural population in the Mediterranean area. *Clin Exp Allergy* 1999; 29:1069-74.
4. Romero-Gómez M, Suárez GE, Castro FM. Hymenoptera stings in conscripts. *Allergy* 1997; 52:680-1.
5. Bilo BM, Bonifazi F. Epidemiology of insect-venom anaphylaxis. *Curr Opin Allergy Clin Immunol* 2008; 8:330-7.
6. Golden DB, Marsh DG, Kagey-Sobotka A, Freidhoff L, Szklo M, Valentine MD, et al. Epidemiology of insect venom sensitivity. *JAMA* 1989; 262:240-4.
7. Bjornsson E, Janson C, Plaschke P, Norrman E, Sjoberg O. Venom allergy in adult Swedes: a population study. *Allergy* 1995; 50:800-5.
8. Graif Y, Romano-Zelekha O, Livne I, Green MS, Shohat T. Allergic reactions to insect stings: results from a national survey of 10,000 junior high school children in Israel. *J Allergy Clin Immunol* 2006; 117:1435-9.
9. Celiksoy MH, Sancak R, Sogut A, Guner SN, Korkmaz A. Characteristics of venom allergic reactions in Turkish beekeepers and alternative treatment modalities. *Int Forum Allergy Rhinol* 2014; 4:555-8.
10. Hayashih Y, Hirata H, Watanabe M, Yoshida N, Yokoyama T, Murayama Y, et al. Epidemiologic Investigation of Hornet and Paper Wasp Stings in Forest Workers and Electrical Facility Field Workers in Japan. *Allergology International* 2014; 63:21-6.
11. Annala IT, Karjalainen ES, Annala PA, Kuusisto PA. Bee and wasp sting reactions in current beekeepers. *Ann Allergy Asthma Immunol* 1996; 77:423-7.
12. Bonadonna P, Schiappoli M, Dama A, Olivieri M, Perbellini L, Senna G, et al. Is hymenoptera venom allergy an occupational disease? *Occup Environ Med* 2008; 65:217-8.
13. Cho H, Kim D, Choo Y, Park J, Choi J, Jang D, et al. Common causes of emergency department visits for anaphylaxis in Korean community hospitals: A cross-sectional study. *Medicine (Baltimore)* 2019; 98:e14114.
14. Armisen M, Guspi R, Alfaya T, Cruz S, Fernández S, Domínguez-Noche C, Alonso A, Dalmau G, Marqués L, Vega A. Cross-Sectional Validation of a Quality of Life Questionnaire in Spanish for

- Patients Allergic to Hymenoptera Venom. *J Investig Allergol Clin Immunol* 2015; 25(3):176-82. PMID: 26182683.
15. Golden DB, Demain J, Freeman T, Graft D, Tankersley M, Tracy J, et al. Stinging insect hypersensitivity: A practice parameter update 2016. *Ann Allergy Asthma Immunol* 2017; 118:28-54.
 16. Lee JA, Son MJ, Choi J, Jun JH, Kim JI, Lee MS. Bee venom acupuncture for rheumatoid arthritis: a systematic review of randomised clinical trials. *BMJ Open* 2014; 4:e6140.
 17. Roh DH, Kwon YB, Kim HW, Ham TW, Yoon SY, Kang SY, et al. Acupoint stimulation with diluted bee venom (Apipuncture) alleviates thermal hyperalgesia in a rodent neuropathic pain model: Involvement of spinal α -adrenoceptors. *Journal of Pain Official Journal of the American Pain Society* 2004; 5:297-303.
 18. Silva J, Mongefuentes V, Gomes F, Lopes K, Anjos LD, Campos G, et al. Pharmacological Alternatives for the Treatment of Neurodegenerative Disorders: Wasp and Bee Venoms and Their Components as New Neuroactive Tools. *Toxins* 2015; 7:3179-209.
 19. Choi MS, Park S, Choi T, Lee G, Haam KK, Hong MC, et al. Bee venom ameliorates ovalbumin induced allergic asthma via modulating CD4⁺CD25⁺ regulatory T cells in mice. *Cytokine* 2013; 61:256-65.
 20. Son D, Lee JY, Song H, Lee C, Hong J. Therapeutic application of anti-arthritis, pain-releasing, and anti-cancer effects of bee venom and its constituent compounds. *Pharmacology & Therapeutics* 2007; 115:246-70.
 21. Bilo BM, Rueff F, Mosbech H, Bonifazi F, Oude-Elberink JN. Diagnosis of Hymenoptera venom allergy. *Allergy* 2005; 60:1339-49.
 22. Vazquez-Revuelta P, Madrigal-Burgaleta R. Death due to Live Bee Acupuncture Apitherapy. *J Investig Allergol Clin Immunol* 2018; 28(1):45-46. doi: 10.18176/jiaci.0202. PMID: 29461208.
 23. Guan K, Li L, Wang R, Yin J. Clinical Characteristics of Anaphylaxis Induced by Honeybee Venom. [Chinese Journal of Allergy & Clinical Immunology](#) 2016; 10(3):197-201. doi: 10.3969/j.issn.1673-8705.2016.03.003.
 24. Alfaya AT, Soriano GV, Soto MT, Vega CA, Vega GJ, Alonso LA, et al. Key Issues in Hymenoptera Venom Allergy: An Update. *J Investig Allergol Clin Immunol* 2017; 27:19-31.
 25. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977; 1:466.
 26. Philipp A, Ferdman RM, Tam JS. Evaluation of venom allergy. *Ann Allergy Asthma Immunol* 2016; 117:344-7.
 27. Bousquet J, Menardo JL, Aznar R, Robinet-Levy M, Michel FB. Clinical and immunologic survey in beekeepers in relation to their sensitization. *J Allergy Clin Immunol* 1984; 73:332-40.
 28. Sturm GJ, Varga EM, Roberts G, Mosbech H, Bilo MB, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy. *Allergy* 2018; 73:744-64.
 29. Guan K, Li LS, Yin J. Use of sIgE/T-IgE in Predicting Systemic Reactions: Retrospective Analysis of 54 Honeybee Venom Allergy Cases in North China. *Chin Med J (Engl)* 2016; 129:2091-5.