

# Honey Bee Venom Re-Challenge During Specific Immunotherapy: Prolonged Cardio-Pulmonary Resuscitation Allowed Survival in a Case of Near Fatal Anaphylaxis

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## Case report

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# Abstract

**BACKGROUND** Specific immunotherapy for patients with honey bee hypersensitivity is commonly applied. Re-challenge with venom is performed to prove protection.

**CASE PRESENTATION** We report a case of near fatal anaphylaxis with asystolia for 24 minutes in a 35-years-old patient with mastocytosis after honey bee sting challenge despite 5-years of specific immunotherapy. Successful cardio-pulmonary resuscitation (CPR) was applied for 32 minutes.

**CONCLUSION** This intervention demonstrates, that in anaphylaxis with cardio-vascular arrest prolonged CPR for up to 40 minutes might be appropriate to overcome half time span of massively released histamine. Failure of specific immunotherapy was possibly due to sensitization to the allergen Api m10, probably underrepresented in commercial honey bee venom extracts. Also, molecular analyses might alert to potential unsuccessful outcome of venom specific immunotherapy especially in high-risk patients such as mastocytosis.

## Background

Hypersensitivity to insect venom is a quite common cause for severe partly even life-threatening anaphylaxis and affects up to 8.9% of the population.<sup>1</sup> Honey bees (*Apis mellifera*) or yellow jackets (*Vespula germanica* and *Vespula vulgaris*) lead to systemic anaphylactic sting reactions in the majority of cases.<sup>2</sup> Mastocytosis is a risk factor for very severe anaphylactic reactions in patients allergic to hymenoptera.<sup>3</sup> Venom immunotherapy (VIT) is highly effective in preventing further systemic anaphylactic sting reactions, however, 2.4–20.4% of those allergic to bee venom or yellow jacket venom were not protected by VIT.<sup>4</sup> Therefore, re-challenge is of importance to prove protection.<sup>5</sup>

## Case Presentation

We report on a 35 year old patient, who experienced a severe anaphylactic reaction after a honey bee sting in 2007 with hypotension and loss of consciousness (Grad IV reaction). Sensitization on bee venom (BV) was confirmed with specific IgE in serum (i1, 24 kU/l) and intradermal test (positive prick test at 0.01 ug/l), while no specific IgE against wasp (i3) were detectable. Thus, venom specific immunotherapy (VIT) with bee venom extract was initiated in June 2008 and performed according to international guidelines with 100'000 SQE every 4 weeks and was well tolerated by the patient.<sup>4,5</sup>

In January 2013 a follow-up control after almost 5 years of immunotherapy was performed. Specific IgE antibodies for bee venom (i1) decreased from 24 to 6 kU/l, while specific IgG were raised as expected after 5 years of VIT (see table 1). Unexpectedly serum tryptase level, in normal range in 2008 (3.3 ug/l) was now elevated to 21 ug/l.<sup>6,7</sup> Thus further investigations revealed some teleangiectasia on the trunk and swelling on mechanical pressure (positive Darier sign), a skin biopsy showed increased numbers of mast cells compatible with cutaneous mastocytosis.<sup>7</sup> Except of sporadic dizziness no symptoms compatible with systemic mastocytosis were reported by the patient; c-Kit mutation was not detectable.

However, a bone marrow aspirate showed two minor criteria of systemic mastocytosis (increased number of abnormal mast cells > 25%, expression of aberrant CD25 cells).<sup>8</sup>

**Table 1: Patient serum analysis on molecular sensitization patterns**

Patient serum analysis (time of sting provocation)

|                  | rApi m1 | rApi m2 | rApi m3 | rApi m4 | rApi m10 |
|------------------|---------|---------|---------|---------|----------|
| <b>IgE kU/l</b>  | 89.2    | >100    | 1.85    | 9.94    | 10.5     |
| <b>IgG4 ug/l</b> | >50000  | 7285    | 272     | >50000  | 241      |

Comparison data: serum of a protected patient

|                  | rApi m1 | rApi m2 | rApi m3 | rApi m4 | rApi m10 |
|------------------|---------|---------|---------|---------|----------|
| <b>IgE kU/l</b>  | 1.6     | 15.9    | 0.22    | 2.3     | 2.42     |
| <b>IgG4 ug/l</b> | >50000  | 15190   | 19320   | >50000  | 1800     |

Patient serum analysis (time of sting provocation; 1 month later; after 6 months of VIT)

|                  | rApi m1 | rApi m2 | rApi m3 | rApi m4 | rApi m5 | rApi m10 | Date**                   |
|------------------|---------|---------|---------|---------|---------|----------|--------------------------|
| <b>IgE kU/l</b>  | 89.2    | >100    | 1.85    | 9.94    | 9.9     | 10.5     | T + 3 days               |
| <b>IgG4 ug/l</b> | >50000  | 7285    | 272     | >50000  | 1890    | 241      | T + 3 days               |
| <b>IgG4 ug/l</b> | >50000  | 7692    | 339     | >50000  | 2470    | 533      | T + 28 days              |
| <b>IgG4 ug/l</b> | >50000  | 10640   | 1716    | >50000  | 3834    | <200     | T + 7 months *           |
| <b>IgG4 ug/l</b> |         |         |         |         |         | <200     | T + 4 years <sup>°</sup> |

(\*) 6 months after reaching triple VIP maintenance dose (100'000 SQE plus 300 mg HBV concomitant with Omalizumab)

(\*\*) T stands for day of sting challenge

<sup>°</sup> in between well tolerated 3years after sting challenge, under VIT mot Omalizumab and 200ug HBV

The patient was working as a gardener and therefore had a need to know his level of protection due to a high risk of re-stings – also knowing that patients with a tolerated sting challenge have a better quality of

life.<sup>9</sup> It is known that patients with mastocytosis are at higher risk for severe or even fatal anaphylaxis, after stopping or even during venom specific immunotherapy (VIT).<sup>10</sup>

Regarding the promising levels of decreased specific IgE and increased IgG4 against BV, we agreed finally on the patient will on a sting challenge with a honey bee, performed according to international guidelines for safety measurements to check whether protection by VIT was achieved and under ongoing VIT. Sting challenge was performed 10 days after last injection of maintenance dose. The patient was monitored with ECG, non-invasive blood pressure and pulse oximetry and intravenous access was established. The sting was performed on the patient's forearm; the stinger was left for 1 min in situ before being removed.

Four minutes later the patient reacted with a generalized flush and nausea, followed by cramps and vomiting. Despite immediately administered of two doses of 0.3 mg of adrenaline given intramuscularly and 250 mg of methylprednisolone as well as 2 mg of clemastine intravenously, the condition of the patient worsened. He developed within minutes severe emesis and dyspnea, followed by tachycardia and hypotension. Chest compressions were immediately started, and the CPR (cardio-pulmonary resuscitation) in-house alarm was triggered. Two minutes later the in-house CPR team arrived initiated advanced CRP treatment. At this moment the SpO<sub>2</sub> level was above 60%, the patient showed signs of central hypoxia, non-invasive blood pressure could not be measured and central carotid pulse was extremely weak. Assisted ventilation was started. Simultaneously the ECG showed 2nd degree AV block for about 30 seconds, followed by ventricular fibrillation. Defibrillator was attached and patient was endotracheal intubated. CPR was performed, strictly following international CPR guidelines.<sup>11,12</sup> The patient had to be external defibrillated (biphasic with 200 J) twice, followed by pulseless electric activity (PEA) for further 4 minutes. PEA limited and led to asystolia for a cumulative 24 minutes. Thereafter, ventricular fibrillation recurred, and patient was external defibrillated twice again. After a total of 32 minutes of CPR, intravenous administration of 10 mg adrenaline and 2000 ml isotonic fluid return of spontaneous circulation (ROSC) occurred. Amiodarone, fentanyl, rocuronium, propofol and midazolame was intravenously administrated and the patient was hemodynamically stabilized. The patient was transferred to the emergency department, where a central venous and an arterial catheter were inserted and a cumulative 1500 ml isotonic fluid administrated (results of initial and before discharge arterial analyzes are summarized in Table 2.). The patient was finally transferred to intensive care unit, where therapeutic hypothermia for 24 hours was initiated.

Table 2  
Pathophysiologic changes during and after CPR

|   | Initial analyze (time: 12:26) | Admission to ICU (time: 13:13) |
|---|-------------------------------|--------------------------------|
| pH  | 7.058                         | 7.197                          |
| pCO <sub>2</sub> (kPa)  | 5.93                          | 5.51                           |
| pO <sub>2</sub> (kPa)   | 26.1                          | 28.4                           |
| Hkt (%)   | 0.543 (*)                     | 0.548 (*)                      |
| Hb (mmol/l)   | 17.7                          | 17.9                           |
| Lactat(mg/dl)   | 11.2                          | 6.2                            |
| Glucose (mmol/l)  | 18                            | 15.1                           |
| HCO <sub>3</sub> (mmol/l)   | 11.9                          | 15.5                           |
| Base excess   | -19.5                         | -12.4                          |
| Total fluid administration  | 2000 ml                       | 3500 ml                        |
| (*) Demonstration of vasoplegia, as a direct consequence of anaphylactic shock. |                               |                                |

The patient recovered slowly, initially showing transitory signs of “posttraumatic” such as reduced fine motor skills and concentration. However, during a several months rehabilitation program these steadily improved so that finally no permanent sequelae remained and the patient has returned to his former work.

The treatment of the patient was continued with Omalizumab and 300 ug honey venom extract every 4 weeks. With this treatment he seems to be protected as 3 years after the reported anaphylactic event the patient got stung again several times. Once he was stung simultaneously by two honey bees during his work; all stings were well tolerated. Interestingly, levels of IgG4 against Api m10 remained low.

## Discussion And Conclusion

Duration of CPR theoretically partly corresponds to half-time of histamine to overcome circulation relevant effects.<sup>13,14</sup> Maximal amounts of histamine found 20 to 30 minutes after challenge and were shown to correlate very well with the severity of anaphylaxis.<sup>15,16</sup> Tryptase level two hours after sting challenge was measured and was excessively increased to around 1300 µg/l, confirming an extreme degranulation of mast cells.<sup>3</sup> This fulfills all criteria of mast cell activation (MCA) requiring a 20% increase from physiological baseline tryptase levels.<sup>3</sup> Four days after, tryptase level was fallen down to 10.4 ug/l, then increased again to 16ug/l.

Hymenoptera venoms typically contain a mixture of 3 to 4 major proteins as well as pharmacologically active peptides and other small molecules. There are common proteins but also significant differences amongst the various Hymenoptera species.<sup>17</sup> The possibility to measure specific IgE also on a molecular pattern has substantially contributed for a better understanding of allergologic mechanisms in recent years.<sup>18</sup> A detailed analysis of molecular sensitization patterns was performed and showed a relevant sensitization not only to major honey bee allergens Api m1 and Api m2, but among other proteins also to Api m3 and an even higher level to Api m10 (see table 1). Earlier studies demonstrated that commercial extracts seem to contain only very limited amounts of Api m10, in contrary to natural honey bee venom.<sup>19</sup> In the present case we retrospectively found that after the 5 years course of VIT the patient did show increased IgG to Api m1 and Api m2, but not to Api m10 reflecting possible insufficient immune response to Api m10. Thus, after near fatal sting challenge VIT was up-dosed to finally 300ug BV per session, using a part of 200 ug in aqueous solution of honey bee venom, which may contain higher amount of Api m10. In addition, the patient was put under preventive treatment with H1- and H2-blockers, ketotifen and omalizumab. After 6 months of VIT with a total dose of 300 ug honey bee venom every 4 weeks (always with Omalizumab) the patient showed an increase of IgG4 also to Api m3 and Api m5 but still almost no increase to Api m10 - while in comparison a sting-challenged and protected mastocytosis patient showed relevant titers of Api m10 specific IgG4 (see Table 2). Thus, mismatch between allergens such as Api m10 might explain severe anaphylaxis occurring after a bee sting in mastocytosis patients despite performed VIT. As recently suggested for food allergens <sup>20,21</sup>, and seen in this case, lack of allergens might only be partly compensated by dose escalation if, extracts are not truly “spiked” with the relevant lacking allergens. In the obvious absence of protective IgG 4 antibodies against Api m10 the question is whether Omalizumab is protecting the patient by modulating the IgE-dependent immune response or whether Api m10 was not playing an important role in the near fatal event after the sting challenge – as seen in other studies where patients with exclusively no IgG4 response to Api m10 also tolerated re-stings. Data from the use of Omalizumab as premedication for honey bee VIT with severe side effects underscore its potential therapeutic effect.<sup>22</sup> Additionally, Omalizumab is reported to be protective in patients with mastocytosis and anaphylaxis and bee keepers not protected by conventional VIT with HB.<sup>23,24</sup>

We conclude the following for the clinical application of VIT: re-challenges to hymenoptera venom should only be performed by a trained staff with all measures in place to start immediate CPR in case of severe anaphylaxis and all the resources to quickly escalate treatment to advanced CRP and ICU transfer; in case of anaphylaxis with cardio-vascular arrest prolonged CPR for up to 40 minutes might be appropriate to overcome half time span of released histamine and other cardio-vascular active mediators. In patients with bee venom allergy extensive molecular analyses might alert to potential unsuccessful outcome of SIT due to eventual allergen mismatch between bee venom and extract.<sup>25</sup> Omalizumab should be considered as an additional therapy in high risk patients even if honey bee VIT is performed.

## Declarations

**Ethics approval and consent to participate:** patient`s consent

**Consent for publication:** patient`s consent

**Availability of data and materials:** not applicable

**Competing interests:** not applicable

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