EAACI Guidelines on Allergen Immunotherapy: Hymenoptera venom allergy


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Abstract

Hymenoptera venom allergy is a potentially life-threatening allergic reaction following a honeybee, wasp or ant sting. Systemic allergic sting reactions have been reported in up to 7.5% of adults and up to 3.4% of children. They can be mild and restricted to the skin or moderate-to-severe with a risk of life-threatening anaphylaxis. Patients should carry an emergency kit containing an adrenaline auto-injector, H1-antihistamines, and corticosteroids depending on the severity of their previous sting reaction(s). The only treatment to prevent further systemic sting reactions is venom immunotherapy. This guideline has been prepared by the European Academy of Allergy and Clinical Immunology’s (EAACI) Taskforce on Venom Immunotherapy as part of the EAACI Guidelines on Allergen Immunotherapy initiative. The guideline aims to provide evidence-based recommendations for the use of venom immunotherapy, has been informed by a formal systematic review and meta-analysis and produced using the Appraisal of Guidelines for Research and Evaluation (AGREE II) approach. The process included representation from a range of stakeholders. Venom immunotherapy is indicated in venom allergic children and adults to prevent further moderate to severe systemic sting reactions. Venom immunotherapy is also recommended in adults with only generalized skin reactions as it results in significant improvements in quality of life compared to carrying an adrenaline auto-injector. This guideline aims to give practical advice on performing venom immunotherapy. Key sections cover general considerations before initiating venom immunotherapy, evidence-based clinical recommendations, risk factors for adverse events and for relapse of systemic sting reaction, and a summary of gaps in the evidence.

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Omalizumab pri bolnikih, ki imajo hude zaplete imunoterapije z žuželkami

**INTRODUCTION**
Specific immunotherapy is an established therapeutic option in patients with hymenoptera venom allergy, offering long-term protection from further generalized reactions. Vaccin-induced immunotherapy (VIT) may be associated with severe systemic reactions which compromise treatment tolerance. In the last years, some case reports appear to demonstrate that premedication with anti-IgE antibodies, Omalizumab, may be useful to prevent systemic adverse reactions related to VIT. However, this approach is still of label and not standardised, leading to different treatment schedules.

**AIM**
To report successful cases of tolerance to bee VIT after initiation of pre- and concurrent treatment with Omalizumab.

**METHOD**
Retrospective analysis of medical records clinical data diagnostic procedures or therapeutic interventions in patients with bee venom allergy and severe systemic reactions to VIT, which indicated Omalizumab or as a failed reaction to VIT tolerance. Omalizumab cases were calculated based on weight and total IgE levels.

**RESULTS**
We report the cases of 3 patients with bee venom allergy and severe systemic reactions to VIT. In all patients, patients first were administrated standardised extracts as an alternative pre-treatment.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Gender</th>
<th>Reaction</th>
<th>Symptoms</th>
<th>Omalizumab</th>
<th>Weight (kg)</th>
<th>Total IgE (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>45</td>
<td>female</td>
<td>anaphylaxis</td>
<td>30 min</td>
<td>150mg</td>
<td>70</td>
<td>3000</td>
</tr>
<tr>
<td>Patient 2</td>
<td>12</td>
<td>male</td>
<td>anaphylaxis</td>
<td>15 min</td>
<td>150mg</td>
<td>60</td>
<td>3000</td>
</tr>
<tr>
<td>Patient 3</td>
<td>18</td>
<td>female</td>
<td>anaphylaxis</td>
<td>20 min</td>
<td>150mg</td>
<td>50</td>
<td>3000</td>
</tr>
</tbody>
</table>

**Omalizumab and Omalizumab 300mg**

Patient 1 was treated with 150mg Omalizumab weekly and had no reaction after treatment. Patient 2 was treated with 150mg Omalizumab weekly and had no reaction after treatment. Patient 3 was treated with 150mg Omalizumab weekly and had no reaction after treatment.

**CONCLUSIONS**

**References**
Anafilaksija po pikih sršenov
#1233 - Is the skin prick test sufficient to diagnose vespid venom allergy?

4 of 51 allergic subjects (8%) were positive at the concentration of 10 µg/ml vespid venom extract, (65%) at 100 µg/ml and 45/51 (88%) at 300 µg/ml.

Adding serological testing for sIgE, all SPT negative subjects were positive for sIgE to vespid venom extract.

In the IDT positive results were obtained in 51/51 (100%) at 1 µg/ml.

In subjects with clinically irrelevant sensitization the IDT was positive in 86% of cases. In contrast, only 38% were positive in SPT.
Tryptase behaviour during venom immunotherapy associates with the risk of adverse reactions

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Allergy Service, Hospital Universitario de Guadalajara, Spain. "Manuel Valdés" Institute, Toledo, Spain
Salamanca University, Spain

Background
Tryptase levels have been associated with VIT severe adverse reactions. The decrease in tryptase level during VIT has been related to tolerance to insect stings and VIT efficacy.

We investigated the changes in serum tryptase during the build-up phase of VIT to analyze its relation to the presence of adverse systemic reactions (ASR) during VIT.

Results
150 venom immunotherapy = 150 patients.
136 men, 44 women, median age 44 years (IQR 35-56.5). Median tryptase 4.3 pg/ml (IQR 3.3-5.4, range 0.8-17.6 pg/ml).

Adverse Systemic Reactions (ASR) = 25 VIT (16.6%) Severe reactions grade 3-4 = 4 (25%)

Tryptase behaviour during the 1st day of VIT.

15.7% developed ASR with VIT. In 16 (64%) out of 25 patients who developed ASR, tryptase post-IT the first day of VIT was higher after the 4 doses, than tryptase pre-IT. Mean tryptase increase was 26.5%.

Conclusions
The increase of tryptase on the first day of IT is an independent variable strongly related to a high risk of suffering SAR with VIT. It is independent of the day of the SAR, the severity of the reaction, and regardless of the basal tryptase level.

In relation to this presentation, I declare that there are no conflicts of interest.
The kinetics of peanut allergen absorption using autologous serum in a human model of passive cutaneous anaphylaxis

**BACKGROUND**
Anaphylaxis is the result of a complex series of events. However, the anaphylactic reaction is rapid in onset and usually occurs within one hour of food intake. The rate of allergen absorption is most likely a key factor in the speed of onset. This study aimed to determine the kinetics of peanut protein absorption using autologous serum in a human model of passive cutaneous anaphylaxis.

**METHOD**
Healthy, non-atopic volunteers (n = 5) aged 25–66 years (median age 30 years) were used as recipients of a human serum obtained from a donor with a history of peanut allergy. The peanut protein was passively sensitized in the skin with a serum from a donor with a history of peanut allergy.

**RESULTS**
Samples were taken at various time points after peanut ingestion. One of the recipients showed a positive reaction with the serum sampled at 48 hours after peanut intake.

**CONCLUSION**
Ingested peanut protein is absorbed systemically and retains its immunoreactive capacity in non-atopic persons.

The gastrointestinal absorption of peanut proteins can occur very fast (≤3 minutes).

The concentration of peanut proteins in the blood peaks between 1 and 4 hours.

Peanut proteins can circulate in the blood up to 48 hours after oral intake.

**Graph 1**
The results of the autologous Prausnitz-Küstner test as a proxy for immunoreactive peanut protein absorption over a 48-hour period in 5 non-atopic volunteers passively sensitized in the skin with a serum from a donor with a history of peanut allergy.
Evaluation of a hypoallergenic wheat line IBS-18 lacking omega-5 gliadin

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1: Shimane University Faculty of Medicine, Shimane Japan
2: Hiroshima University, Hiroshima Japan
3: Ryukoku University, Kyoto Japan

ABSTRACT

Wheat-dependent exercise-induced anaphylaxis (WDEIA) is a distinct form of wheat allergy typically induced by exercise after the ingestion of wheat products. Prevalence of wheat allergy is estimated to be 0.1-3.0% among Europeans in a meta-analysis, and, in 0.21% among Japanese adults in a cross-sectional study of non-asthmatic adults in Japan [Shimane Current Study]. There is no established treatment for WDEIA; patients are forced to limit their intake of wheat products. As wheat is one of the dietary staple, patient’s quality of life is significantly suffered by this limitation. Among wheat allergens, α-5 gliadin is one of the dominant allergens affecting WDEIA patients. Possible explanations for the higher allergenicity of α-5 gliadin, the mesic-fertilization conditions or the increase in wheat in the regular diet is considered to be one of the physiological approaches against the sensitization to α-5 gliadin.

OBJECTIVES

We sought to evaluate hypoallergenic bread wheat that lack the genes encoding α-5 gliadin.

RESULTS

The deletion lines of bread wheat IBS-18 were selected among deletion line of Chinese spring, a well-established cultivar at wheat research field. Sensitization ability of gluten from deletion line IBS-18 was much less than that of gluten from commercially available wheat. Moreover, the practical feasibility of deletion line IBS-18 was low from the point of cost effectiveness. In addition, bread making property of IBS-18 whole-grain was low because of less expansion comparing with the one of commercially available whole-grain (both ca. 12cm of height, respectively).

METHODS

Selection of wheat strains

The α-5 gliadin gene is located on the short arm of chromosome 18 in wheat. We searched for candidate wheat lines among the deletion lines of common wheat on the website of the National Institute of Agro-Science (NARIP), WHEAT (https://wheat.pw.usda.gov) and obtained candidates deletion lines and other lines from NARIP (Table 1 and Table 2).

CONCLUSIONS

The use of the wheat products of the deletion line IBS-18 in daily life have possibility to provide a feasible solution for the onset of wheat allergy. Further study is needed to confirm the hypoallergenic ability of IBS-18. The bread making property of IBS-18 Chinese spring is low, repeated backcrossing of the IBS-18 line to elite commercial cultivars is desirable for better quality and practical feasibility.

COI: None

REFERENCES

Benefit from mepolizumab treatment in a patient with chronic spontaneous urticaria

Mägeri M, Terhorst D, Metz M, Altrichter S, Zuberbier T, Maurer M, Bergmann KC

Chronic spontaneous urticaria (CSU) is a common and debilitating disease that can be recurrent wheals, angioedema or both. Key features of the pathogenesis of CSU include skin mast cell activation, release of histamine and other mediators, subsequent vasodilatation, extravasation and nerve stimulation, and the recruitment of inflammatory cells including basophils and eosinophils. Antihistamine and oral corticosteroids are the only licensed CSU treatment options effective, but many patients do not respond to either or both of these treatments, and additional and better therapies are needed.

Mepolizumab is a humanized monoclonal antibody directed against IL-5, and is licensed for the treatment of severe asthma in patients aged ≥12 years (EU only adults) with an eosinophilic phenotype as an add-on treatment. Eosinophils are known to contribute to the pathogenesis of asthma. Eosinophils have also been suggested to contribute to the development of the signs and symptoms of CSU. Here, we report the case of a 27-year-old woman with both severe refractory eosinophilic asthma and CSU, who was treated successfully with 100 mg mepolizumab every 4 weeks. The asthma control test (ACT) score, at a score of <15 indicating uncontrolled disease, increased from 13 points at baseline to 23 points 4 weeks after the first injection of mepolizumab. FEV1 increased in the same period of time from 2.5 L (80% predictive) to 3.6 L (90% predictive). ACT scores improved further, to 25 points at 8 weeks later, indicating complete control of her asthma. The patient was maintained on mepolizumab for a total of 16 weeks, after which treatment had to be discontinued due to the occurrence of the signs and symptoms of an immune complex reaction. After discontinuation, the patient's asthma remained stable and well controlled with inhaled steroids (800 mcg/day) and long-acting beta-agonist (twice/day) treatment.

In addition to her asthma, our patient had long standing and difficult-to-treat CSU. Her CSU had started 5 years prior to mepolizumab treatment and was characterized by wheals and episodic angioedema, which were mostly appearing during phases of infections, most notably respiratory tract infections. Sleep and daily activities were then severely impaired, primarily due to the severe itch. The patient reported that her CSU symptoms were exacerbated by infections, the only known trigger for other causes, possibly with several other different allergens, all of which were managed doses, alone or in combination. Beclomethasone dipropionate had no result in CSU control. Over the course of the year, prior to mepolizumab treatment, her CSU symptoms led to several hospitalizations for at least two weeks. Finally, a poorly controlled CSU.

From the day the onset of treatment with mepolizumab, the patient reported a dramatic and sustained improvement of her urticarial symptoms, both the spontaneous wheals as well as the infection-triggered episodes. Four weeks after the first injection, the urticaria control test (UCT) was 12 (Figure 1). The UCT ranges from 0 (no control at all) to 10 (complete control), a score of 12 or higher indicates controlled disease. Another 8 weeks later, the UCT was 15, and the patient reported about an ongoing and complete absence of the urticarial lesions, despite several infectious episodes during the winter season. When we discontinued mepolizumab treatment, her CSU signs and symptoms returned during infectious episodes.

![Urticaria Control Test](image)

Figure 1: UCT values before and under treatment with Mepolizumab

To our knowledge, this is the first report of a therapeutic response to mepolizumab in a patient with CSU. The most likely explanation is that mepolizumab and its effects on IL-5 and eosinophils interfere with the pathogenic chain of events that leads to whealing and itch in CSU. It is unlikely that the CSU improved because of the effects of mepolizumab on asthma. Interestingly, the number of eosinophils in the skin of CSU patients has recently been reported to be higher than in healthy controls (Kay et al., 2011), and eosinophils have been proposed to contribute to the pathogenesis of CSU. Further studies are needed to the role of eosinophils in CSU. Our findings shed light on the role of IL-5 and eosinophils in chronic urticaria.
#0110 - Causal association between IgE anti-TPO and chronic urticaria. IgE anti-TPO expression in the three groups (CSU: 34%, ATD: 16.6%, healthy subjects 8.1%). Between those patients with positive IgE anti-TPO, flow cytometry showed CD203c induction with serial additions of TPO in 76.4% of CSU group and 40% ATD but not in healthy subjects.

#1321 - Increased risk of chronic spontaneous urticaria in patients with autoimmune thyroid diseases: a nationwide population-based study AITD group (N= 3,659), control group (N=18,295). Each subject was tracked for whether CSU occurs or not. Subjects with AITD had a significantly higher rate of CSU compared to the control group (HR, 1.46).
Presence and family distribution of SERPING1 mutations in Macedonian HAE type I patients

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AIM
Authors investigated presence and family distribution of SERPING1 mutations in Macedonian HAE type I patients.

RESULTS
Disease-causing mutations in SERPING1 were identified in all patients. In C1-INH-HAE type I, we identified 13 different mutations, and 2 large deletions. Two of the mutations (c.813_818delCAACAC>T and c.1188_T>G) are reported here for the first time. Depending on the type of SERPING1 gene mutation, patients were divided into two groups: group 1 (nonsense, frameshift, large deletions/insertions, splicing defect, and mutations at Arg444) or group 2 (missense, excluding mutations at Arg444).

METHODS
- C1-INH-HAE diagnosis was established based on clinical and anamnestic criteria in 23 patients from 15 families; 4 patients are silent carriers.
- Genetic studies were carried out using PCR and sequencing to detect SERPING1 mutations in promoter, noncoding exon 1, the 7 coding exons, and exon-intron boundaries.
- Multiplex ligation-dependent probe amplification was performed in order to search for large deletions/duplications in SERPING1 gene.

CONCLUSIONS
Authors have identified 13 different disease-causing mutations, including two novel mutations, contributing to the heterogeneity of mutations in the SERPING1 gene.
Are patients prone to using penicillin after testing negative for penicillin allergy at a specialist centre?

Of the 103 patients, 30 patients (29%) had taken penicillin since the investigation. Twenty nine patients (28%) were still hesitant to take penicillin. Eight patients (8%) answered that a doctor had hesitated to prescribe penicillin after the investigation.

Outpatient collaboration between allergist and pharmacists results in long-term increase in β-Lactam antibiotic prescriptions among patients with a history of penicillin allergy.

A cohort of PCN allergy patients were identified by a pharmacist at the local pharmacy. 27% of 496 pts underwent PCN skin test, 93% were negative. During 10 Y follow up among patients evaluated by an allergist compared to those who were not 56 (68%) were prescribed a β-Lactam antibiotic compared to 65 (25%; p < 0.0001);
Introduction
Idiopathic anaphylaxis is a rare disease with no discernible cause. It is due to mast cell activation. Idiopathic anaphylaxis accounted for approximately 10% of all cases of anaphylaxis. A large spectre of allergy tests and other diagnostic tests (basal tryptase, histamine intolerance, chromogranin, 5-HIAA) have to be done to exclude relevant allergen sensitization and diseases that could mimic it. According to guidelines patients with more than 6 episodes per year should be put on long term systemic glucocorticoid prophylaxis.

Objectives
Omalizumab is a monoclonal antibody, that binds to IgE and decrease mast cell reactivity. Therefore omalizumab might be helpful in prevention of the anaphylactic reactions.

Materials and Methods
We reviewed the medical files of 3 patients who started omalizumab treatment due to recurrent episodes of anaphylactic reactions with no discernible reason. Skin prick test were performed with a set of common respiratory allergens, common food allergens and fresh foods like nuts, peanuts, spices. Specific IgE against omega-5-gliadin, and alphi-3-gli were determined with ImmunoCAP system. Extended specter of sIgE sensitization was tested with ISAC microchip (Termo Fisher, Waltham, Massachusetts, USA).
Basal tryptase was determined. Serum chromogranin and diaminoxydase (D-HIT, Sciotec, Austria) determinations were ordered in routine diagnostic laboratories.

Results
Three women (56, 43 and 28 years) with recurrent spontaneous episodes of anaphylaxis (4-10 in year 2015), confirmed by tryptase elevation during episode. They were repeatedly treated with epinephrine at the emergency unit. Diagnostic workup didn’t reveal any relevant allergy, neither cofactor. Two patients have concomitant chronic urticaria. Because of frequent and severe episodes, patients were started off-label omalizumab 300 mg monthly and are without anaphylactic episodes since then (9-13 months). Table 1.

Table 1. Demographic and clinical data on 3 patients with idiopathic anaphylaxis.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Comorbidities</th>
<th>First episode</th>
<th>No. of episodes in 12 months</th>
<th>Tryptase during attack / basal</th>
<th>Symptoms</th>
<th>Positive diagnostic tests</th>
<th>Negative tests</th>
<th>Previous therapy</th>
<th>Outcome after omalizumab therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.G. 1988</td>
<td>Chronic urticaria</td>
<td>2015</td>
<td>³</td>
<td>18 &lt;br&gt; 10.4</td>
<td>Broncho spasm</td>
<td>IgE alpha-GAL; Dermographism</td>
<td>IgE against common allergens negative, DAO, ISAC</td>
<td>epinephrine</td>
<td>No systemic reactions</td>
</tr>
<tr>
<td>S.J. 1973</td>
<td>Chronic urticaria</td>
<td>2015</td>
<td>8</td>
<td>5,51/1.61</td>
<td>Broncho spasm, hypotension</td>
<td>IgE for inhalatory and food allergens (celery); low diaminoxydase, ISAC Ves v 3</td>
<td>ANA</td>
<td>epinephrine</td>
<td>2 mild systemic reaction (urticaria) 2 and 13 months after start of omalizumab</td>
</tr>
<tr>
<td>R.D. 1960</td>
<td>Hyperthyrosis, Mb Crohn</td>
<td>2014</td>
<td>4</td>
<td>135/10.9</td>
<td>Broncho spasm, hypotension</td>
<td>IgE: Bone marrow biopsy, Octreoscan, OPT phenacetin</td>
<td>epinephrine</td>
<td>No systemic reactions</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion
All three patients are in remission since the administration of omalizumab. Omalizumab seems an effective drug for prevention of recurrent episodes of idiopathic anaphylaxis.
Finski alergološki program

mag. Peter Kecelj, dr. med.
REMEDA d.o.o.

• program obvladovanja alergijskih bolezni na Finskem

• začetek programa 2008

• dogovor ekspertov (domači in gostujoči)

• finančna podpora finskega ministrstva za zdravje in njihovega nacinalnega inštituta za javno zdravje

• dolgoročni cilji
Načini delovanja v programu

- **ciljne skupine:**
  - splošna populacija
  - alergološki bolniki in njihove družine
  - nevladne organizacije in združenja bolnikov
  - zdravniki, zdravstveni delavci (posebni cilji)
  - zdravstvena politika (oblast)
Glavni poudarki programa

Endorse health, not allergy

Strengthen tolerance

Adopt a new attitude to allergy, and avoid allergens only if mandatory

Recognise and treat severe allergies early; prevent exacerbations

Improve air quality; stop smoking

European Respiratory Journal 2017
Organiziranost zdravstva na Finskem (5,5 milijonov prebivalcev)

- 21 bolnišničnih okrožij
- 5 univerzitetnih bolnišnic
- 250 centrov primarne oskrbe (22 000/center)
- 1000 izvajalcev medicine dela in športa (MDŠP)(5500/izvajalca)
Izvedba

- 20 000 zdravnikov in ostalih zdravstvenih delavcev se je udeležilo usmerjenih izobraževalnih programov

- ustvarili so mrežo posebej usposobljenih zdravnikov in med. sester (1500)

- 14 regionalnih strokovnih alergoloških skupin- koordinacija implementacije novih priporočil
**Primary prevention**

- Support breastfeeding, with solid foods from 4–6 months onwards

- Do not avoid exposure to environmental allergens (foods, pets), if not proven necessary

- Strengthen immunity by increasing contact with natural environments (e.g. by taking [regular physical exercise](#) and following a [healthy diet](#) such as a traditional Mediterranean or Baltic diet)

- **Antibiotics** should only be used in cases of [true need](#) (the majority of microbes are useful and build a healthy immune function)

- Probiotic bacteria in fermented food or other preparations may balance the immune function

- Do not smoke (parental smoking increases the risk of asthma in children)
- **Secondary and tertiary prevention:**

- Regular physical exercise is anti-inflammatory

- Healthy diets are anti-inflammatory (a traditional Mediterranean or Baltic diet may improve asthma control)

- Probiotic bacteria in fermented food or other preparations may be anti-inflammatory

- Respiratory/skin inflammation should be treated early and effectively; maintenance treatment titrated for long-term control

- To stop symptom exacerbations proactively, instructions for guided self-management are provided for 10 allergic conditions (available in both paper and electronic formats)
- **Allergen-specific immunotherapy** is recommended for more severe symptoms, *e.g.*:
  - allergens as such (for foods)
  - sublingual tablets or drops (sublingual immunotherapy, or SLIT) (for pollens)
  - subcutaneous injections (for pollens, pets, mites, insect stings)
  - Smoking should be strictly avoided (the effectiveness of asthma and allergy drugs is reduced in smokers)
Doseženi cilji po 5 letih programa

1) Prevent allergy
   - *Indicator*: asthma, rhinitis and atopic eczema prevalence reduced by 20%
   - *Outcome*: no information yet

2) Improve tolerance
   - *Indicator*: food allergy diets reduced by 50%
   - *Outcome*: allergy diets in day-care settings –40%

3) Improve allergy diagnostics
   - *Indicator*: skin prick testing practised in certified testing centres
   - *Outcome*: 30 hospitals and other centres educated, audited and certified
<table>
<thead>
<tr>
<th></th>
<th>4) Reduce work-related allergies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Indicator</em>: occupational allergies reduced by 50%</td>
</tr>
<tr>
<td></td>
<td><em>Outcome</em>: occupational allergies reduced by 40%</td>
</tr>
<tr>
<td></td>
<td>5) Focus on severe allergies and treat in time</td>
</tr>
<tr>
<td></td>
<td><em>Indicator</em>: effective allergy practice; asthma emergency visits reduced by 40%</td>
</tr>
<tr>
<td></td>
<td><em>Outcome</em>: emergency visits −46%; asthma hospital days −67%</td>
</tr>
<tr>
<td></td>
<td>6) Reduce allergy and asthma costs</td>
</tr>
<tr>
<td></td>
<td><em>Indicator</em>: allergy costs reduced by 20%</td>
</tr>
<tr>
<td></td>
<td><em>Outcome</em>: total costs in the 2000s −15%; in 2007–2013 −5%</td>
</tr>
</tbody>
</table>
Zdravstvena vzgoja na EAACI 2017

Perko Karmen
DMS
• Pacientovo vedenje o njegovi boleznih je pomemben del njegovega zdravljenja

• Največ gradiva oz. študij, ki so bile na kongresu predstavljene, so naredili na področju pacientov z diagnozo astme

• Zanimiva je študija o uporabi epipena pri pacientih z alergijo za hrano

• Sestrski protokol – sprejem otroka z alergijo za hrano na testiranje v bolnišnico – kratka primerjava z našim delom
Prilagajanje zdravstvene vzgoje pri starejših pacientih

- Saratov State Medical University, Russia

- Starejši se pogosto soočajo z težjimi oblikami poslabšanj, njihova zmožnost samokontrole je manjša kot pri mlajših.

- Namen je bil preveriti znanje o astmi, poiskati pomanjkljivosti in ugotoviti, na kakšen način pridobivajo znanje oz kako jim pomagati.

- Vključenih 50 pacientov z dg. astma, starejših od 64 let, zdravljenih v letih 2014 in 2015.
• Ugotovili so: 36% - pomanjkljivo znanje o bolezni
  : napačna pričakovanja - kar 56% jih je pričakovalo popolno ozdravitev
  : 56% - napačna tehnika jemanja th
  : neredno prejemanje th, strah pred stranskimi učinki, brez načrta samozdravljenja
• Ugotovili so, da so starejši manj prizadevni za izobraževanje, poiščejo si manj gradiva
• Večina bolnikov je dobila navodila od zdr. osebja, nekaj jih je obiskalo astma šolo, dobili so pisno gradivo – brošure. Samo 12 % se jih je poslužilo interneta.
* Več jih je obiskalo poljudne strani kot strokovno literaturo.
• Zaključek in povzetek študije je, da starejši še vedno potrebujejo zdravstveno vzgojo
• V primeru spletnega izobraževanja potrebujejo podporo in sodelovanje strokovnih delavcev, ki jim s svojim znanjem pomagajo.
Avtoinjektor in hrana – kdaj mladi nosijo s seboj zdravilo, kako dojemajo tveganje v različnih situacijah?

• Brighton&Sussex Medical schoolm Brightom, UK skupaj z LKC Medicinem Nanyang Tehnological University Singapore
• Najbolj uspešno je izogibanje alergenu. Včasih se zgodi, da pride do reakcije zaradi nenamerne izpostavljenosti alergenu.
• 188 mladostnikov starih med 13 in 23 let, ki so imeli potrjeno alergijo za hrano in predpisan epipen, 50% žensk
• Izvedeno na podlagi vprašalnika (ali nosijo avtoinjektor (AI) s seboj, ali se zavedajo tveganj za al. reakcijo)
• Poročajo o različnih navadah – večina, 90% nosi AI s seboj na potovanje. Ob športni aktivnosti ga ima pri sebi le 21% sodelujočih.
**Avtoinjektor in hrana – kdaj mladi nosijo s seboj zdravilo, kako dojemajo tveganje v različnih situacijah?**

- Kot najbolj tvegano dejanje so izpostavili poljub s partnerjem, ki je zaužil alergen, manj jih je skrbel pojav reakcije ob obisku šole;).
- Ženske so zaznale večje tveganje kot moški.
- Rezultate so primerjali z predhodno izvedeno študijo v Ameriki, bistvenih odstopanj niso opazili.

*Zaznali so, da so ženske predstavnice bolj dovzetne za izobraževanju o tveganih situacijah.*
Sestrski protokol sprejema otroka v dnevno bolnišnico (povzeto po Infanta Leonor University Hospital, Madrid Spain)

- Postavljen z željo po najboljši oskrbi ob sprejemu v bolnišnico
- Vpis pacienta in preverjanje podatkov - identifikacija
- Zagotoviti sodelovanje pacienta
- Zdravnik opravi intervju s pacientom in starši
- Natančno opredelijo, kaj in kako bo potekalo testiranje

- Podobno se ravnamo v alergološki enoti UKPA Golnik
- Administrativni sprejem
- Osebni kontakt z osebjem
- Zagotovimo intimo pri razgovoru
- Plan testiranja dogovorjen s pacientom
Sestriški protokol sprejema otroka v dnevno bolnišnico (povzeto po Infanta Leonor University Hospital, Madrid Spain)

• Identifikacija alergena
• Po testiranju opazovanje
• Ob zaključku podrobna navodila za doma

• Označimo katerikoli alergen z bolnikovimi podatki (napelka)
• Po testiranju opazovanje
• Ob zaključku odpustnica z navodili
**INTRODUCTION**

The nursing assistance to the children who attend to an Allergy daily hospital has as a main priority to provide the best care to the patients with specialized and well trained nurses.

**MATERIAL AND METHODS**

- **RECEPTION OF PATIENTS:**
  - Name/family name of patients are verified.
  - Confirmation of personal data of the children with the parents.
  - Introduction of the nursing staff.

- **IDENTIFICATION OF PATIENTS:**
  - Placement of a personal sticker with the name and the picture of the allergen in study (food or drug) on the back (if younger than 1 year old) or on the chest (if older than 1 year old).

- **CLINICAL ASPECTS:**
  - Interview concerning health problems within the previous 24 hours (fever, cough, rhinitis, diarrhoea, vomiting...) and any medication undertaken (vaccines, antibiotics, antihistamines, corticosteroids...).
  - Confirmation that the child has eaten before the procedure (children must not fast).

- **CONTROLLED ADMINISTRATION:**
  - Verification of the correct drug/food dose before each step and after every controlled administration.
  - Confirmation that the dose corresponds to the one prescribed by the allergist.
  - Avoidance of any contamination from other allergens (food/drug).

- **RECOMMENDATIONS:**
  - Parents/caregivers must keep the patient under surveillance over the next 6-8 hours after the discharge from the hospital.
  - A written information form is provided to the parents or caregivers with the guidelines to be followed at home.

**RESULTS**

With this nursing protocol we avoid any mistake that could occur during the oral controlled administration concerning allergen-dose, as well as we achieve a better compliance with the guidelines given to the children and their families.

**CONCLUSIONS**

This protocol ensure an appropriate nursing assistance as well as avoid any mistake during the oral challenge procedure.

---

**OBJECTIVES**

The aim of this work was to perform a nursing protocol which summarized all the steps to follow up and all the actions to perform in order to assess the best assistance to the children attended in our paediatric allergy daily hospital.
Pediatrična alergologija

Tina Vesel Tajnšek
Služba za alergologijo, revmatologijo in klinično imunologijo, Univerzitetna pediatrična klinika, Ljubljana

Golnik, EAACI po EAACI, 7.9.2017
Pristop k otroku z anafilaksijo in alergijo na hrano

1. Uporabnost opredelitve kvalitete življenja?

2. bulling- ustrahovanje?

3. preventiva?

DELOVNA SKUPINA PEDIATROV ALERGOLOGOV

VZROKI

ZDRAVLJENJE ANAFILAKSIJE

SAMOINJEKT OR ADRENALINA

OTROK, NJEGOVI BLIŽNJI

ZDRAVNIKI

ZORNI KOT:

IZOBRAŽEVANJE

IZOBRAŽEVANJE

OZAVEŠČANJE

ZAKONODAJA

PSIHOLOJIJA

www.imuno.si

www.klinika-golnik.si

OZAVEŠČANJE

IZOBRAŽEVANJE

Smernice za ukrepanje pri anafilaksiji otroka in mladostnika, Zdrav Vestn 2014

Dogovor o obravnavi anafilaksije
1. Ocena kvalitete življenja-QoL/HRQL otrok in mladostnikov z alergijo na hrano in anafilaksijo
Vprašalniki QoL- kazalec izida številnih bolezni:
- AD, astma, rinitis, urtikarija, piki kožekrilcev...
- alergija na hrano- ocena dobrega počutja bolnika?

Starši otrok z alergijo na hrano: višja QoL bolj poučeni, manj alergij, starejši
Knibb RC PAI 2016
Odrasli- Evropa: nižja QoL- prizadetost dihal/KVS, alergija na mleko, ribe, ženski spol
Otroci- Evropa: nižja QoL- alergija na arašide, sojo
Saleh-

Langenberg J, Allergy 2015

Provokacijski test s hrano: višja QoL
Na vsako vprašanje naj otrok odgovori s pomočjo naslednjih odgovorov z izbiro ENE možnosti:

ne                    komaj            malo                  kar                  precej          zelo        ekstremno

Koliko težav imaš ker...
1. moraš vedno biti pozoren na to kaj poješ?
2. lahko ješ manj stvari?
3. si omej en pri tem, da bi si kupil tisto, kar si želiš?
4. moraš brati o sestavi živil (deklaracije)?
5. moraš zavrniti hrano ko počneš stvari z drugimi?
6. manj pogosto lahko poješ obrok/ kosilo pri nekom?
7. lahko preskušaš manj stvari, ko ješ zunaj?
8. moraš vnaprej povedati, česa ne smeš jesti, ko ješ zunaj?
9. moraš sam preveriti ali lahko nekaj poješ zunaj?
10. oklevaš, da bi jedel, ko ne veš, če je zate določena hrana varna?
11. moraš biti previden, ko se dotikaš določene hrane?
12. ne dobiš ničesar, ko nekdo v šoli razdeli sladkarije?

Koliko te skrbi zaradi tvoje alergije na hrano...
13. se sestavine proizvodov spreminjajo?
14. na živilu piše »lahko vsebuje sledi«?
15. moraš drugim razlagati, da imaš alergijo na hrano?
16. drugi okrog tebe pozabijo da imaš alergijo na hrano?
17. ko si v družbi lahko drugi okrog tebe uživajo hrano, na katero si alergičen?
18. ne veš kakšnega okusa je hrana, ki je ne smeš jesti?

Koliko težav imaš zaradi alergije na hrano ker...
19. alergijska reakcija
20. da pomotoma zaužiješ napačno hrano?
21. poješ nekaj kar sploh še nisi?

Odgovori prosim še na naslednja vprašanja:
22. Koliko te skrbi, da se ne boš nikdar znebil svoje alergije?
23. Koliko si razočaran, ko drugi ne upoštevajo resno tvoje alergije?
24. Kako razočaran si, ker imaš svojo alergijo?
### Food Allergy Independent Measure – Child Form (8-12 years)

**FAIM- Ocena resnosti bolezni s strani bolnika**

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>never (0% chance)</td>
<td>very small chance</td>
<td>small chance</td>
<td>fair chance</td>
<td>big chance</td>
<td>very big chance</td>
<td>always (100% chance)</td>
</tr>
</tbody>
</table>

#### How big do you think the chance is that you...

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. will accidentally eat something to which you are allergic?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>b. will have a severe reaction if you accidentally eat something to which you are allergic?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>c. will die if you accidentally eat something to which you are allergic?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>d. can not do the right things for your allergic reaction should you accidentally eat something to which you are allergic?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>e. How many foods are you unable to eat because of your food allergy?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>f. Everyone does things with other people, such as; playing with friends, going to a birthday party, visiting, staying over with someone for a meal or eating out. How much does your food allergy affect things you do with others?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

- [ ] almost none
- [ ] very few
- [ ] a few
- [ ] some
- [ ] many
- [ ] very many
- [ ] almost all
- [ ] so little I don't actually notice it
- [ ] very little
- [ ] a little
- [ ] moderately
- [ ] a good deal
- [ ] a great deal
- [ ] a very great deal

Velde JL et al, Allergy 2010
IMPAIRED HEALTH-RELATED QUALITY OF LIFE IN FOOD ALLERGIC CHILDREN AND TEENAGERS IN SLOVENIA

Tina Vesel1, Mateja Sever1, Poredoš T2, Avčin T1
1Department of Allergology, Rheumatology and Clinical Immunology, University Children’s Hospital, University Medical Center, Ljubljana, Slovenia
2Department of Diethrotherapy and Hospital Nutrition, University Children’s Hospital, University Medical Center, Ljubljana, Slovenia

INTRODUCTION
- Food allergy may impair health-related quality of life (HRQL).
- Predictors of HRQL have been found in greater extent in adults than in children and teenagers. For children HRQL varied with perceived disease severity, peanut or soy allergy and country of origin (1).
- There are no data on HRQL of children and teenagers with food allergies in Slovenia.

AIMS:
- to identify HRQL of food allergic children and teenagers in Slovenia
- to examine clinical usefulness of HRQL and food allergy independent measure (FAIM)

METHOD
- 69 children were examined (Table 1). Eight adolescent completed Food Allergy Quality of Life Questionnaire (FAQQL)-Teenager Form, 20 children FAQQL-Child Form and 42 parents Parent Form of FAQQL.
- A new questionnaire assessing HRQL in kindergarten and school was also developed and applied.
- The FAQQL and FAIM scores were the sum of item scores divided by the number of completed items (ranging from 1- minimal impairment to 7- maximal impairment).

RESULTS

Table 1. Characteristics of 69 children

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number (%) of children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>21 (30)</td>
</tr>
<tr>
<td>Male</td>
<td>48 (70)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
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</thead>
<tbody>
<tr>
<td>0-3</td>
<td>4 (6)</td>
</tr>
<tr>
<td>4-6</td>
<td>22 (32)</td>
</tr>
<tr>
<td>7-12</td>
<td>35 (51)</td>
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<td>13-17</td>
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<th>Clinics</th>
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<td>Anaphylaxis/urticaria</td>
<td>17/18 (25/26)</td>
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<tr>
<td>Asthma</td>
<td>21 (30)</td>
</tr>
<tr>
<td>OAS</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Peanut allergy</td>
<td>52 (75)</td>
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<tr>
<td>Multiple food allergy</td>
<td>27 (40)</td>
</tr>
</tbody>
</table>

Legend: OAS- oral allergy syndrome

1. Total FAQQL score was worse when assessed by teenagers and children themselves (4.1 and 3.8, respectively), being most disturbed at the item of Social and dietary restrictions. Total FAQQL score was moderate low when assessed by the parents (2.7) (Table 2).

2. Experience of anaphylaxis and having multiple food allergies impaired HRQL according to FAQQL Parent Form (p<0.05). Sex, having prescribed an adrenaline autoinjector, experience of food provocation test, peanut allergy and FAIM did not contribute to different HRQL.

3. HRQL in kindergarten and schools were moderately diminished (2.6 in schools vs 2.2 in kindergartens) (p>0.05).

4. During FAIM 68% of participants reported at least some possibility of dying if child/teenager would accidentally eat a food allergen.

5. Clinical usefulness: After fulfilling FAQQL and FAIM questionnaires, all participants expressed satisfaction, ten children/teenagers decided to approach food provocation tests de novo, employees of children’s schools/kindergartens were encouraged in written invitations to assess anaphylaxis training programs and four families accepted additional psychological support.

CONCLUSIONS
- Food allergies impair HRQL in children and teenagers especially if asking children or teenagers. Social and dietary restrictions were most bothersome for children/teenagers.
- Allergy to multiple foods and experience of anaphylaxis were associated with more severe impairment of HRQL.
- Regarding FAIM: the perception of disease severity in food allergic children, teenagers and their parents is independently present, including in two thirds the tough of possibility of death.
- HRQLQ and FAIM are useful, additional tools to assess and discuss child’s/teenager’s/parent’s fears and obstacles because of food allergy and identify further needs of support.

REFERENCES

In relation to this presentation, we declare that there are no conflicts of interest.

CONTACT INFORMATION
tna.vesel@clj.si.
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5. Clinical usefulness: all participants expressed satisfaction, ten children/teenagers decided to approach food provocation tests de novo, four families accepted additional psychological support.

| Table 2. Health-related quality of life and food allergy independent measure in 69 children |
|-----------------------------------------------|-------------------|-------------------|---------------------|
|                                               | Children 8-12 years | Teenagers 13-17 years | Parents of 1-12 years old children |
| 1. FAQLQ (mean, SD)                           |                   |                   |                             |
| General emotional impact                      | 3.9± 1.6          | 4.1± 1.9          | 2.6± 1.1                  |
| Food anxiety                                  | 3.4± 1.2          | 3.9± 1.7          | 2.7± 1.5                  |
| Social and dietary restrictions              | 4.8 ± 1.6         | 4.8± 2.1          | 2.7± 1.5                  |
| Total score                                   | 3.9± 1.2          | 4.13± 1.8         | 2.7± 1.3                  |
| School/kindergarten domain                    | 2.4± 0.7          | 2.8± 1.4          | 2.4± 1.2                  |
| 2. FAIM (mean, SD)                            | 3.4± 1.0          | 3.6± 1.7          | 3.9± 1.2                  |
Pre-service teachers’ perception of allergic students’ quality of life

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¹ General and teaching hospital Izola, Department of pediatrics, Izola, Slovenia
² University of Ljubljana, Faculty of Education, Ljubljana, Slovenia
³ University Medical Center, University Children’s Hospital, Department of Allergology, Rheumatology and Clinical Immunology, Ljubljana, Slovenia

INTRODUCTION

- In management of allergic child in school, teacher’s knowledge but also perspective of child’s needs is important.
- The experience and perception of food allergy (FA) were lacking among caregivers of non-FA children (1).
- Health-related quality of life (HRQL) questionnaires have been applied with benefits in children with allergic diseases and in their families (2), but not in pre-service teachers or teachers.

PARTICIPANTS AND METHODS

- 137 pre-service primary and lower secondary school teachers (8% male; 91% female; average age 23.9 (SD=1.5) years participated in this study. 23% of students were allergic themselves.
- Participants fulfilled:
  1. Allergy Quality of Life Questionnaire (AQLQ) - Teacher’s Form which comprised 31 items about pre-service teachers’ perception of HRQL of an allergic student (HRQLS) (in Box 1 items about FA are presented) and
  2. 31 items about pre-service teachers’ own HRQL if they had to take care for an allergic student in school (HRQLT).
- The HRQL scores were the sum of item scores divided by the number of completed items (ranging from 0-minimal impairment to 6-maximal impairment).
- Cronbach Alpha: HRQLS 0.950; HRQLT 0.931
- Participants also answered edited Teachers’ Health Competences Development—Allergy Questionnaire (THCDAQ2), which comprised 9

AIM

The aim of our study was to assess:
- the knowledge of pre-service teachers about allergies
- pre-service teacher’s awareness of the impact of allergic child diseases on
  1. children’s and
  2. pre-service teacher’s quality of life.
RESULTS

- Female pre-service teachers ($M=18.01$ (51.5%); $SD=4.53$) showed higher knowledge about allergies than males ($M=14.73$ (42.1%); $SD=2.80$); $t(133)=-2.36; p=.020$. [Max. 35 points.]

- The total HRQLS score was quite low, but assessed significantly higher by female ($M=4.85; SD=.71$) than male pre-service teachers ($M=4.22; SD=.88$); $t(116)=-2.61; p=.010$. Among items on food allergy assessed HRQLS was lowest at the items of Social and dietary restrictions.

- The total HRQLT score was comparably low when assessed by males ($M=3.79; SD=1.39$) or females ($M=4.48; SD=1.10$); $t(116)=-1.85; p=.067$. Among items on food allergy assessed HRQLS was again the lowest at the items of Social and dietary restrictions.

- The level of pre-service teachers' knowledge about allergies did not contribute significantly to different average HRQLS or HRQLT scores ($p>0.05$).

CONCLUSIONS

- Pre-service teachers recognised reduced HRQL of allergic children and expressed also theirs lower HRQL when taking care for allergic child.

- There was no significant correlation between knowledge and HRQL assessment.

- HRQL issues should be included in recommendation for the management of allergic child in school besides training how to prevent, recognise and manage allergic reactions.

- Participants also answered edited Teachers' Health Competences Development--Allergy Questionnaire (THCDAQ2), which comprised 9 attitude items on managing children’s health issues, 3 items about their formal education about allergies and 33 alternative knowledge items on allergic disease.

REFERENCES


2. Ustrahovanje (bulling) otrok in mladostnikov z alergijo na hrano
Bullying in Australian children and adolescents with food allergies, EAACI 2017

Introduction
Recent international evidence suggests that food allergic children and adolescents experience an increased incidence of bullying compared to similar school-aged children, at rates of up to 30%. There have as yet been no studies to characterise this in Australian populations despite the high numbers of food allergic school children.

Objectives
Two survey tools were used; a questionnaire based on similar surveys done overseas, and the validated Food Allergy Quality of Life Questionnaire (FAQLQ).

Results
102 surveys have been collected at the time of writing of which 64 were answered by parents for young children. Overall, 44/97 (45%) reported bullying, with a higher portion in older children and adolescents (22/37; 59%). Of this group, 10/20 (50%) reported being bullied or teased because of their food allergies. From parental reports, 11/19 (57%) stated that their child had experienced bullying or teasing because of food allergies.
For those not bullied, parents mentioned that this may be due to their child having friends at school, being too young for bullying or because other children at school had a good understanding of the severity of allergies and were educated by teachers.

The most common location for bullying was “in the playground or sportsground” (36/39). The most common form of bullying involved being “teased, called names or someone has said mean things to me” (31/39). Whilst food allergens were involved in bullying in many cases (24/39), there were no reports of children being forced to eat food to which they are allergic. Of concern however, two adolescents reported experiencing an allergic reaction as a result of the bullying. The majority reported experiences of sadness from bullying (30/39) while seven stated that it had no effect.

Conclusions
Our current research shows that 45% of children and adolescents with food allergies experience bullying, and that 22% (21/97) experience bullying specifically because of their food allergies. This indicates a significant social problem that requires addressing to positively assist those children living with food allergies.
<table>
<thead>
<tr>
<th>Type of bullying</th>
<th>Status</th>
<th>Frequency (N = 120)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Never</td>
</tr>
<tr>
<td>Verbal (being called mean names, or</td>
<td>Allergic</td>
<td>59.17</td>
</tr>
<tr>
<td>teased in a hurtful way)</td>
<td></td>
<td>79.17</td>
</tr>
<tr>
<td>Relational (being target of rumors)</td>
<td>Allergic</td>
<td>70.83</td>
</tr>
<tr>
<td></td>
<td>Nonallergic</td>
<td>82.50</td>
</tr>
<tr>
<td>Social (being intentionally excluded</td>
<td>Allergic</td>
<td>75.83</td>
</tr>
<tr>
<td>or isolated)</td>
<td></td>
<td>81.67</td>
</tr>
<tr>
<td>Physical (being hit, kicked, or</td>
<td>Allergic</td>
<td>81.67</td>
</tr>
<tr>
<td>pushed)</td>
<td></td>
<td>88.33</td>
</tr>
</tbody>
</table>

45.4% of food allergic children and 36.3% of parents of food allergic children reported bullying—Shemesh E, Pediatrics 2013

Comparison of bullying of food-allergic versus healthy schoolchildren in Italy—Muraro A, JACI 2014: Food-allergic students have a probability of being bullied approximately 2 times higher than nonallergic peers.
IMPACT OF BULLYING IN FOOD ALLERGY

- 4.0% of incidents resulted in an allergic reaction
- 26.3% reported feeling sad/depressed,
- 20.2% reported loneliness/social withdrawal, low self-esteem,
- 20% reported nervousness/anxiety,
- 5% insomnia & fatigue
- 23% embarrassment/humiliation.

Qualitative reports include:
- Feeling angry, isolated, confused as to why they were targeted, vulnerable, and hesitant to eat at school after an incident
- Trying to hide their food allergies because of past bullying, teasing, or harassment

Muraro et. al Comparison of bullying of food-allergic versus healthy schoolchildren in Italy JACI. (2014) 134, 3
Koman, E; Raver E Adams Dunn Galvin, A. Living with food allergy : Bullying across 48 states in the US(submitted).
3. Preprečevanje alergijskih bolezni

**TO EAT OR NOT TO EAT?**

**PRIPOROČILA - ZGODOVINA**

60. leta
Večina dojenčkov uživa gostoto hrano pred 4. mesecem

70. leta
Priporočila za uvanjanje goste hrane po 4. mesecu

80. / 90. leta
**IZOBIRANJE ALEGENOM**
Teorija povezave preprečnosti in "nezrolosti" GI imunosti
Priporočila za kasnejše uvanjanje alegrene hrane za rizične (ZDA, UK, Australija...)
- izključno dojenje 6 mesecov
- KML po 12. mesecu
- jejce po 2. letu
- arašidi/oreščki/ribe po 3. letu

**EPIDEMIIJA ALEGIJE NA HRANO**

**PRIPOROČILA - ZGODOVINA**

**2008 (AAP*, ESPGHAN**, EAAC***)**

- uvanjanje goste hrane vključno s potencialnimi alegreni med 4. – 6. mesecem
- ni dokazov, da kasnejše uvanjanje zmanjša verjetnost alergije
- nobene diete za rizične nosečnice
- uvanjanje goste hrane še med dojenjem

**ALERGIJSKI PÔHOD**

**AKTIVNO PROMOVIRANJE ORALNE TOLERANCE**
ALERGIJA NA ARAŠIDE

• 1.4 – 3 % otrok v zahodnem svetu
• Najpogostejši vzrok anafilaksije in smrti zaradi alergije na hrano
• Velik vpliv na kvaliteto življenja
• Zgodaj se pojavi, redko izzveni
**UŽIVANJE ARAŠIDOV V IZRAELU IN VELIKI BRITANIJI**

<table>
<thead>
<tr>
<th></th>
<th>IZRAEL</th>
<th>VB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PREVALENCA ALERGIJE NA ARAŠIDE med šolarji</strong></td>
<td>0,17 %</td>
<td>1,85 %</td>
</tr>
<tr>
<td><strong>SREDNJA KOLIČINA MESEČNIH ZAUŽITIH BELJAKOVIN ARAŠIDOV med 8-14 mes</strong></td>
<td>7,1 g</td>
<td>0 g</td>
</tr>
<tr>
<td><strong>SREDNJE ŠTEVILO OBROKOV Z ARAŠIDI NA MESEC med 8-14 mes</strong></td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

Študija “LEAP”

randomizirana, odprta, kontrolirana intervencijska študija

**PRIMARNA PREVENTIVA**

4 – 11 mesečni dojenčki s težkim AD / alergijo na jajce

n = 640

**SEKUNDARNA PREVENTIVA**

n = 98

Redno uživanje arašidov

Izogibanje arašidom

Redno uživanje arašidov

Izogibanje arašidom

**PRIMARNI IZID: DELEŽ OTROK Z ALERGIJO NA ARAŠIDE PRI 5 LETIH (PROVOKACIJSKI TEST)**

LEAP študija

• arašidi
  • arašidovo maslo, Bamba, arašidova juha, z vsaj 3 x na teden, 6 g beljakovin/teden
  • dojenčki so jih zelo dobro sprejeli
  • rast in pridobivanje na teži enaka
Naslov: "LEAP" rezultati

Intervencija je bila varna in zelo učinkovita tako v namen primarne kot tudi sekundarne preventive alergije na arašide.

1° preventiva
86 % zmanjšano tveganje

2° preventiva
70 % zmanjšano tveganje

CONSENSUS COMMUNICATION ON EARLY PEANUT INTRODUCTION AND THE PREVENTION OF PEANUT ALLERGY IN HIGH-RISK INFANTS

• AAAAI, AAP, ACAAI, ASCIA, CSACI, EAACI, ISACI, JSA, SPD, WAO
• JACI, Allergy, Pediatrics, WAO Journal, Pediatric Dermatology, Allergy, Asthma and Clinical Immunology, Annals of Allergy, Asthma and Immunology

obstaja znanstven dokaz (level 1) v prid uvajanja arašidov “visoko rizičnim” dojenčkom zgodaj v življenju (4-11 mes) v državah kjer je alergija na arašide pogosta, saj je kasnejše uvajanje arašidov lahko povezano s povečanim tveganjem razvoja alergije na arašide

• alergolog slgE) KT, PROVOKACIJSKI TEST (ne svetujejo

• spodbujajo aktiven pristop pediatrov, alergologov in dermatologov za hitro implementacijo teh novih spoznanj
## ADDENDUM GUIDELINES FOR THE PREVENTION OF PEANUT ALLERGY IN THE UNITED STATES: REPORT OF THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES–SPONSORED EXPERT PANEL

(J Allergy Clin Immunol 2017;139:29-44.)

### TABLE I. Summary of addendum guidelines 1, 2, and 3

<table>
<thead>
<tr>
<th>Addendum guideline</th>
<th>Infant criteria</th>
<th>Recommendations</th>
<th>Earliest age of peanut introduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Severe eczema, egg allergy, or both</td>
<td>Strongly consider evaluation by sIgE measurement and/or SPT and, if necessary, an OFC. Based on test results, introduce peanut-containing foods.</td>
<td>4-6 months</td>
</tr>
<tr>
<td>2</td>
<td>Mild-to-moderate eczema</td>
<td>Introduce peanut-containing foods</td>
<td>Around 6 months</td>
</tr>
<tr>
<td>3</td>
<td>No eczema or any food allergy</td>
<td>Introduce peanut-containing foods</td>
<td>Age appropriate and in accordance with family preferences and cultural practices</td>
</tr>
</tbody>
</table>
Addendum Guidelines for the Prevention of Peanut Allergy in the United States: Summary of the National Institute of Allergy and Infectious Diseases—Sponsored Expert Panel

Table: Summary of addendum guidelines 1, 2, and 3

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<th>Earliest age of peanut introduction</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>Severe eczema, egg allergy, or both</td>
<td>Strongly consider evaluation by peanut-sIgE&lt;sup&gt;a&lt;/sup&gt; and/or SPT&lt;sup&gt;b&lt;/sup&gt; and, if necessary, an oral food challenge. Based on test results, introduce peanut-containing foods</td>
<td>4 to 6 months</td>
</tr>
<tr>
<td>2</td>
<td>Mild-to-moderate eczema</td>
<td>Introduce peanut-containing foods</td>
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<td>3</td>
<td>No eczema or any food allergy</td>
<td>Introduce peanut-containing foods</td>
<td>Age appropriate and in accordance with family preferences and cultural practices</td>
</tr>
</tbody>
</table>

Severe eczema or Egg allergy or Both

Peanut sIgE<sup>a</sup>

- <0.35
  - Risk of reaction low. Over 90% will have (-) SPT to peanut.
  - Options:
    a) Introduce peanut at home
    b) Supervised feeding in the office (based on provider/parental preference)

- ≥0.35
  - Refer to specialist for consultation/SPT protocol

Peanut Skin Prick Test

- 0-2 mm
  - Risk of reaction low (95% will not have peanut allergy).
  - Options:
    a) Introduce peanut at home
    b) Supervised feeding in the office (based on provider/parental preference)

- 3-7 mm
  - Risk of reaction varies from moderate to high.
  - Options:
    a) Supervised feeding in office
    b) Graded OFC in a specialized facility

- ≥8 mm
  - Infant probably allergic to peanut.
  - Continue evaluation and management by a specialist
Vprašanja?

• Ali lahko rezultate ekstrapoliramo na druge države oz populacije? Druga hrana?

• Kako pogosto je treba jesti arašide? Ali jih je treba jesti redno? Ali je to praktično izvedljivo? So arašidi zdrava hrana?

• Ali je tak pristop smiseln za splošno populacijo?

• Ali je tak pristop varen?
**PREDLOG ZA IZVAJANJE PRIPOROČIL**

<table>
<thead>
<tr>
<th>RAZPOREDITEV OTROKA GLEDE NA RIZIČNOST</th>
<th>PRIPOROČILA</th>
</tr>
</thead>
</table>
| težek AD alergija na jajce             | NAPOTITEV K SPECIALISTU ALERGOLOGU (SEKUNDARNI NIVO) za izvedbo alergoloških testov (KT, sIgE)  
  • neg testi → uvajanje doma  
  • nizko pozitivni testi → provokacija  
  • visoko pozitivni testi → dieta |
| blag - zmeren AD                       | PRIMARNI PEDIATRI  
  svetujejo uvajanje arašidov po 6. mesecu  
  BREZ ALERGOLOŠKEGA TESTIRANJA     |
| brez AD brez alergij                   | NOBENIH POSEBNIH NAVODIL |
Mastocitoza in preobčutljivost za strup kožekrilcev

Mihaela Zidarn
Definicija mastocitoze

- Heterogena skupina klonalnih motenj
- Značilna je proliferacija in akumulacija mastocitov v različnih tkivih (predvsem koži in kosteh)
- Sistemska mastocitoza: prizadetost enega ali več organov (ne samo koža)
- Večinoma je prisotna mutacija v kodonu 816 gena za kit receptor
- Simptomi:
  - Pruritus, urtikarija, angioedem, zardevanje, bruhanje, bolečina trebuhu, diareja, anafilaksija, osteoporoza
- Redko agresivna bolezen: hipersplenizem, patološke frakture, ascites, malabsorciija, citopenija
Table 1. WHO Diagnostic Criteria for Systemic Mastocytosis

A firm diagnosis of systemic mastocytosis is established when at least 1 major and 1 minor or at least 3 minor criteria are present.

<table>
<thead>
<tr>
<th>Major</th>
<th>Multifocal dense infiltrates of MCs in bone marrow sections or other extracutaneous organs (&gt;15 MCs in aggregate).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>a. MCs in bone marrow or other extracutaneous organs show an abnormal (spindle-shaped) morphology (&gt;25%).</td>
</tr>
<tr>
<td></td>
<td>b. Mutation at codon 816 of the KIT gene in extracutaneous organs. In most cases the mutation is D816V.</td>
</tr>
<tr>
<td></td>
<td>c. MCs in bone marrow express CD2 and/or CD25.</td>
</tr>
<tr>
<td></td>
<td>d. Serum tryptase &gt;20 ng/mL (not in patients with AHNMD-type disease).</td>
</tr>
<tr>
<td>B findings</td>
<td>a. Bone marrow biopsy showing &gt;30% infiltration by MCs (focal, dense aggregates) and/or serum tryptase level &gt;200 ng/mL.</td>
</tr>
<tr>
<td></td>
<td>b. Signs of dysplasia or myeloproliferation in non-MC lineages, but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm (AHNMD), with normal or slightly abnormal blood counts.</td>
</tr>
<tr>
<td></td>
<td>c. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging.</td>
</tr>
<tr>
<td>C findings</td>
<td>a. Bone marrow dysfunction manifesting as cytopenia (ANC &lt;1.0 x 10⁹/L, Hb &lt;10 g/dL, or platelets &lt;100 x 10⁹/L), but no obvious non-MC hematopoietic malignancy.</td>
</tr>
<tr>
<td></td>
<td>b. Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension.</td>
</tr>
<tr>
<td></td>
<td>c. Skeletal involvement with large osteolytic lesions and/or pathological fractures.</td>
</tr>
<tr>
<td></td>
<td>d. Palpable splenomegaly with hypersplenism.</td>
</tr>
<tr>
<td></td>
<td>e. Malabsorption with weight loss due to gastrointestinal mast cell infiltrates.</td>
</tr>
</tbody>
</table>

Abbreviations: AHNMD, associated clonal hematologic non-mast cell lineage disease; ANC, absolute neutrophil count; Hb, hemoglobin; MC, mast cell.

Diagnosis of:
(a) Indolent SM (ISM): meets criteria for SM. No C findings. No evidence of AHNMD.
(b) Smoldering SM: as ISM, but with 2 or more B findings and no C findings.
(c) Isolated bone marrow mastocytosis: as ISM with bone marrow involvement, but without skin involvement.
(d) Aggressive SM: meets criteria for SM. One or more C findings. No evidence of mast cell leukemia.
(e) Mast cell leukemia: meets criteria for SM. Bone marrow biopsy shows a diffuse infiltration, usually compact, by atypical, immature mast cells. Bone marrow aspirate smears show ≥20% mast cells. In typical mast cell leukemia, mast cells account for ≥10% of peripheral white blood cells.
Monoclonal mast cell activation syndrome (MMAS)

- Nepojasnjene ali ponavljajoče se anafilaksije
- Brez kožnih lezij
- Ne izpolnjujejo kriterijev za sistemsko mastocitozo
- Prisotni so markerji klonalnosti mastocitov
Sistemska mastocitoza in alergijske bolezni

• Sprožilci anafilaksije
  • Kožekrilci
  • Hrana
  • Zdravila
  • Redkeje: alkohol, napor, temperaturne spremembe
  • Kombinacija več dejavnikov
  • Idiopatska
**REMA kriteriji**

- >2 napove prisotnost klonalne motnje mastocitov pri bolnikih z anafilaksijo, ki nimajo kožne mastocitoze

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>+1</td>
</tr>
<tr>
<td>Female</td>
<td>-1</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td></td>
</tr>
<tr>
<td>Absence of urticaria and angioedema</td>
<td>+1</td>
</tr>
<tr>
<td>Urticaria and/or angioedema</td>
<td>-2</td>
</tr>
<tr>
<td>Presyncope and/or syncope</td>
<td>+3</td>
</tr>
<tr>
<td>Serum tryptase</td>
<td></td>
</tr>
<tr>
<td>&lt;15 ng/mL</td>
<td>-1</td>
</tr>
<tr>
<td>&gt;25 ng/mL</td>
<td>+2</td>
</tr>
</tbody>
</table>

*Table 2. REMA Scoring Model*

Abbreviation: REMA, Red Española de Mastocitosis (Spanish Network on Mastocytosis).

*Proposed as a screening method for the presence of clonal mast cells in patients presenting with anaphylaxis in the absence of cutaneous mastocytosis before a bone marrow study.*
Epidemiologija

• Prevalenca alergije za strup kožekrilcev v splošni populaciji je okoli 3%
• Med bolniki s katerokoli obliko mastocitoze pa 20-30%
  • Večje je tveganje težke reakcije
Prevalenca mastocitoze v splošni populaciji je 1-1,3 na 10.000, med bolniki z alergijo za strup kožekrilcev pa je bistveno višja.

Table 3. Prevalence of Clonal Mast Cell Disease in Patients With Systemic Reactions to Hymenoptera Venom Screened on the Basis of Elevated Tryptase

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Elevated Tryptase, No. %</th>
<th>Clonal Mast Cell Disease</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haeberli et al 2003a [69]</td>
<td>259</td>
<td>19 (7.3)</td>
<td>3 CM</td>
<td>1%</td>
</tr>
<tr>
<td>Dubois 2004b [47]</td>
<td>2375</td>
<td>32 (1.3)</td>
<td>22 SM</td>
<td>1%</td>
</tr>
<tr>
<td>Rueff et al 2006c [71]</td>
<td>1102</td>
<td>106 (9.6)</td>
<td>21 CM + 8 SM</td>
<td>2.6%</td>
</tr>
<tr>
<td>Bonadonna et al 2009 [24]</td>
<td>379</td>
<td>44 (11.6)</td>
<td>21 ISM + 9 MMAS</td>
<td>7.9%</td>
</tr>
<tr>
<td>Potier et al 2009c [72]</td>
<td>138</td>
<td>22 (15.9)</td>
<td>1 CM + 5 SM</td>
<td>4.4%</td>
</tr>
<tr>
<td>Guevara et al 2010c-d [73]</td>
<td>274</td>
<td>30 (10.9)</td>
<td>1 CM + 3 ISM</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

Abbreviations: CM, cutaneous mastocytosis; ISM, indolent systemic mastocytosis; MMAS, monoclonal MC activation syndrome; SM, systemic mastocytosis.

aBone marrow evaluation not performed.
bScreening with urinary histamine metabolite.
cEvaluation of CD25/CD2 mast cell coexpression and KIT mutation not performed or reported.
dBone marrow evaluation performed if serum tryptase >15 ng/mL.
Priporočila

• VIT
• Reakcija med imunoterapijo po piku na terenu: povišati dozo na 200
• Opremljeni z vsaj 2 avtoinjektorjema adrenalina tudi če prenašajo imunoterapijo
• Podaljšana, doživljenska VIT? Verjetno pri bolnikih z težko izvorno reakcijo
Dvojna senzibilizacija pri alergiji za strupe kožekrilcev

• Razširjen panel komercialno dostopnih rekombinantnih sIgE ima še vedno nižjo senzitivnost kot nativni alergen, dvojna pozitivnost pa se po pogostnosti približuje nativnim alergenom

• Če je indeks pri sIgE več kot 5 naj bi to nakazovalo na monosenzibilizacijo
The Allergy Diary was developed in collaboration between MACVIA-LR and ARIA.

MACVIA-LR (Contre les Maladies Chroniques pour un Vieillissement Actif en Languedoc-Roussillon, France) is a reference site of the European Innovation Partnership on Active and Healthy Ageing aimed at fighting chronic disease.

The ARIA (Allergic Rhinitis and its Impact on Asthma) initiative aims to educate and implement evidenced-based management of allergic rhinitis in conjunction with asthma.

First enter your profile

Entering your profile saves you time when using the app daily. To get started just enter your year of birth, gender and country. To continue using the app please complete your profile within 10 days.
Diagnostic value of T cell analysis and *in vitro* release of interleukins in patients with nonimmediate hypersensitivity to amoxicillin
Background

• Non immediate reactions caused by amoxicilin are most common drug hypersensitivities reactions in our practice
• The clinical picture is heterogeneous
• Diagnostic procedure is hampered by lack of practical \textit{in vitro} method

• CD69 is a marker of T cell activation
• Measurement of IL-2, IL-5, IL-13 and IFN-\(\gamma\) secretion in response to drugs were shown as potential \textit{in vitro} tool for detection of T-cell sensitization to drugs
Study protocol

- **Inclusion criteria**
  - Convincing history of nonimmediate reaction to amoxicilin: urticaria, maculopapular exanthema: more than one hour after last dose of amoxicilin and up to 2 weeks after starting of the antibiotic

- **Exclusion criteria**
  - Immediate reactions: anaphylaxis, urticaria less than 1 hour after antibiotic exposure
  - Unconvincing history (expected side effects)
  - Reactions in early childhood
  - Severe skin reactions: DRESS, SJS/TEN
  - Organ specific reactions: hepatitis, nephritis, pneumonitis
  - Typ II. or III. Reactions: blood disorders or serum sickness
  - Other uncontrolled diseases
Flow chart

20 patients with suspicion of amoxicillin allergy

ID and patch test
Provocation tests

13 positive
7 negative
5 exposed healthy controls
Positive patients = confirmed drug allergy

• 13 patients with confirmed amoxicillin hypersensitivity:
  • 6 with skin tests:
    • 1 immediate reading ID
    • 4 late reading ID
    • 1 patch test
  • 7 with drug provocation tests:
    • In one patient with positive late reading of intradermal skin test a provocation test was performed that was positive
    • No provocation test positive on the first day
**in vitro** tests

- **CD 69 upregulation** analyzed by flow cytometry
  - **absolute count** of CD69 upregulated CD3+, CD3+CD4+ and CD3+CD8+ after stimulation and incubation for 4 hours with 25µg/ml 100 µg/ml of **amoxicilin**
  - **absolute count** of CD69 upregulated CD3+, CD3+CD4+ and CD3+CD8+ after incubation with **culture media** alone

- Incubation of peripheral blood mononuclear cells (PBMC) for 48 hours, analysed by multiplex flow cytometry CBA Flex Array
  - **Concentration of IL-2, IL-5, IL-13 and IFN-γ in** supernatants after incubation with 25µg/ml 100 µg/ml of **amoxicilin**
  - **Concentration of IL-2, IL-5, IL-13 and IFN-γ in** supernatants after incubation with culture media alone
Result were considered positive for values that were higher than values for all negative patients and controls.

For all provocation test positive patients at least one in vitro test was positive.
Conclusion

• High number of positive patients 13/20 selected on the basis of clinical history

• Late reading of ID test is useful: 5/13 positive patients were confirmed with skin testing in one patient only patch test was positive

• All provocation tests were positive with prolonged provocation

• *In vitro* diagnostic tests are a potential possible surrogate for drug provocation test
THE ROLE OF BASOPHILS IN ACUTE ALLERGIC REACTIONS

Peter Korošec
Laboratorija za klinično imunologijo in molekularno genetiko
Univerzitetna Klinika za pljučne bolezni in alergijo
Golnik
Summary

IgE-mediated allergic reactions involve the activation of effector cells, predominantly through the high-affinity IgE receptor (FcεRI) on mast cells and basophils. Although the mast cell is considered the major effector cell during acute allergic reactions, more recent studies indicate a specific and potentially important role for basophils and their migration which occurs rapidly upon in vivo allergen challenge.
Basophils in mice display substantial differences in morphology, function and immunomodulatory roles in comparison to human basophils. This highlights major pitfalls in extrapolating from animal basophil models to acute allergic reactions in humans.

<table>
<thead>
<tr>
<th>Murine models</th>
<th>Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoglobulins</td>
<td>Monomeric IgA, 2 serotypes (IgA1, IgA2), IgA1 abundant in serum IgD, IgE, IgM IgG1, IgG2, IgG3, IgG4</td>
</tr>
<tr>
<td>High affinity IgE receptor (FcεRI) on mast cells and basophils</td>
<td>Yes</td>
</tr>
<tr>
<td>FcεRI receptor on antigen presenting cells</td>
<td>Yes</td>
</tr>
<tr>
<td>IgE-dependent anaphylaxis</td>
<td>Yes</td>
</tr>
<tr>
<td>IgG-dependent anaphylaxis</td>
<td>No evidence for IgG-mediated activation of human mast cells. If present, likely to require very high levels of antigen exposure</td>
</tr>
<tr>
<td>Allergen dose required through oral exposure to cause anaphylaxis</td>
<td>Very low doses (mgs) e.g. for peanut allergy, 10% of individuals react to 1/70 of a peanut</td>
</tr>
<tr>
<td>Sensitivity to histamine</td>
<td>++++</td>
</tr>
<tr>
<td>Anaphylaxis inhibited by H1-antihistamines</td>
<td>Little clinical evidence for this. Significant interspecies differences exist in histamine receptor pharmacology.</td>
</tr>
<tr>
<td>Basophils secrete Platelet Activating Factor (PAF)</td>
<td>Data inconsistent</td>
</tr>
</tbody>
</table>

OF MICE AND NOT MEN

Very high: in murine models of peanut allergy, dose/weight equivalent to a human eating of 1000 peanuts!

Allergen dose required through oral exposure to cause anaphylaxis

Very low doses (mgs) e.g. for peanut allergy, 10% of individuals react to 1/70 of a peanut

Very high affinity IgE receptor (FcεRI) on mast cells and basophils

FcεRI receptor on antigen presenting cells

IgE-dependent anaphylaxis

IgG-dependent anaphylaxis

Allergen dose required through oral exposure to cause anaphylaxis

Very low doses (mgs) e.g. for peanut allergy, 10% of individuals react to 1/70 of a peanut

Sensitivity to histamine

+++ +

Anaphylaxis inhibited by H1-antihistamines

Little clinical evidence for this. Significant interspecies differences exist in histamine receptor pharmacology.

Basophils secrete Platelet Activating Factor (PAF)

Data inconsistent
Histamine sensitivity

LD50 of histamine (thought to be an important mediator of anaphylaxis) in mice was greater than 20 mg/mouse – a sensitivity several orders of magnitude lower than that in humans. This may have contributed to the relative paucity of studies assessing the role of basophils in anaphylaxis, given that basophils are relatively uncommon in comparison to their tissue-fixed mast cell counterparts in both mice and humans. However, despite their relative rarity, human basophils are at least one order of magnitude more sensitive to IgE-mediated provoked than mast cells.

IgE versus IgG-mediated anaphylaxis

There are two major distinct pathways of anaphylaxis in mice: one is mediated by basophils, allergen-IgG- FcyRII-III receptor interactions and PAF release, whereas the other is mediated by mast cells, allergen-IgE-FcεRI receptor interactions and histamine release.

Antigen presentation

Human basophils are not able to present antigens.
Human experimental models of anaphylaxis

Controlled allergen challenge studies

Studies in the challenge setting do have the advantage of allowing comparison with pre-reaction samples, optimal sampling, and controlling potentially confounding factors (including acute treatment, where blood samples can often be taken prior to treatment. However, for safety reasons, in controlled allergen challenge studies, patients with previous severe reactions are often excluded from challenge studies due to the potential for life-threatening reactions. Furthermore, in the (oral food) challenge model, the reaction severity at challenge is also limited by the controlled nature of the challenge (allergen exposure is usually terminated at the onset of objective symptoms) and administration of pharmacologic interventions to treat the symptoms.
Emergency department-based studies

Patients with anaphylaxis are studied prospectively at the time of presentation to the ED, with sample collection typically occurring 1 to 2 hours after onset of symptoms, and usually after initial treatment and stabilisation. In the case of field-treatment of anaphylaxis, patients are very often treated with systemic corticosteroids and antihistamines as well. Corticosteroids have broad immunological effects, albeit much delayed compared to other anti-allergic therapies. With respect to basophils, corticosteroids inhibit their pro-allergic functions and this might be an important confounder.
FIG 1. Basophil CD63 activation (A); absolute basophil counts (B); whole-blood FCER1A (C), CPA3 (D) and HDC (E) expression; serum tryptase levels (F); and PMN (G) and lymphocyte (H) absolute counts in ED patients during acute anaphylactic reactions to Hymenoptera venom and 7 and 30 days after the anaphylactic episode. Horizontal lines represent median values with interquartile ranges.
FIG 2. Comparison of basophil CD63 activation (A), absolute basophil counts (B), whole-blood FCER1A gene expression (C), CCL2 serum concentrations (D), and serum tryptase levels (E) between patients with acute anaphylactic reactions to Hymenoptera venom on ED presentation and patients with venom allergy or healthy control subjects. Horizontal lines represent median values with interquartile ranges.
FIG 4. Serum CCL2 (A), CCL5 (B), CCL11 (C), IL-3 (D), and TSLP (E) levels in ED patients during acute anaphylactic reactions to Hymenoptera venom and 7 and 30 days after the anaphylactic episode. Horizontal lines represent median values with interquartile ranges.
FIG 3. Correlation between absolute basophil counts and whole-blood FCER1A (A), CPA3 (B), and HDC (C) gene expression and serum CCL2 concentrations (D) in patients with acute anaphylactic reactions presenting to the ED.
FIG 5. Absolute basophil counts (A) and whole-blood *FCER1A* gene expression (B) in patients with peanut allergy undergoing DBPCFCs to peanut. *Horizontal lines* represent median values with interquartile ranges.
Take-home messages

Basophil migration from the circulation might be one of the key events during anaphylaxis.

How can the understanding of the factors that regulate basophil trafficking and activation lead to new diagnostic and therapeutic strategies in anaphylaxis?
FIG E8. ROC curve analysis of basophil CD63 activation, absolute basophil counts, whole-blood FCER1A gene expression, CCL2 concentrations, and serum tryptase levels between patients with acute anaphylactic reactions to insect venoms on ED presentation and patients with venom allergy or healthy control subjects. *AUC*; Area under the curve.
FIG E4. Basophil CD63 activation (A), basophil absolute count (B), whole-blood FCER1A gene expression (C), and lymphocyte (D), and PMN (E) absolute counts in healthy control subjects 2.5 to 3, 5, and 24 hours after the single dose of oral methylprednisolone (64 mg). *Horizontal lines* represent median values with interquartile ranges.
**Figure E5.** Serum concentrations of CCL2 (A), CCL5 (B), CCL11 (C), and IL-3 (D) in healthy control subjects 2.5 to 3, 5, and 24 hours after the single dose of oral methylprednisolone (64 mg). *Horizontal lines* represent median values with interquartile ranges.
RESULTS – CCL2 measurements

Serial CCL2 measurements in 107 patients (P > 0,0001)

<table>
<thead>
<tr>
<th>CCL2</th>
<th>Anaphylaxis (pg/ml)</th>
<th>Basal (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>801,2</td>
<td>338,7</td>
</tr>
<tr>
<td>Range (min-max)</td>
<td>250,5 - 6661</td>
<td>74,8 - 3925</td>
</tr>
</tbody>
</table>

Descriptive statistics of CCL2 measurements.
Early and late asthmatic response

Inhalation of allergen leads to an early asthmatic response, which is associated with a decrease in lung function that occurs within 2 hours, caused by the release of histamine and cysteinyl leukotrienes from mast cells. In some patients, the early response is followed by a late asthmatic response, a decline in lung function that occurs during the subsequent 24 hours. The late response is caused by the continued release of mast-cell and/or basophil mediators, as well as by the infiltration of inflammatory cells (eosinophils), which produce cytokines and other mediators, resulting in prolonged swelling of the airway mucosa and aggravating of the airway obstruction.

Basophils are increased in induced sputum of asthmatic patients as well as in the sputum or bronchoalveolar lavage (BAL) fluid during exacerbation or after allergen challenge of asthma patients. Basophils were also observed in the lungs of patients with fatal asthma. This suggests that basophils infiltrate lung tissue in asthma patients. Basophils are increased in the sputum not only from allergic but also of non-allergic asthmatic patients.
The highest numbers of basophils were observed in the lungs of patients with eosinophilic asthma, and there is a strong positive correlation between sputum basophil and eosinophil counts.
Figure 1

Sputum → Flow Cytometry →

- Quantification
- Phenotyping
- Functional Analysis

- Eosinophilic Pneumonia
- Allergic Bronchopulmonary Mycosis
  - Allergic Asthma (adult)
  - Aspirin-Sensitive Asthma
  - Severe Late-Onset Hypereosinophilic Asthma

Fux Allergy 2017
**Take-home messages**

A rapid basophil infiltration in the airways and subsequent activation or immunomodulatory roles might be an important part of asthma pathogenesis and/or exacerbation.

Mast cells and basophils seem to collaborate to cause acute allergic reactions. Basophil migration occurs rapidly upon in vivo allergen challenge to target affected organs together with mast cells.
REKOMBINANTNI ALERGENI

dr. Julij Šelb dr.med.
Molekularna diagnostika
Vloga MD – splošni vidiki

• Razlikovanje med pristno (angl. ‘genuine‘) senzibilizacijo in navzkrižno reaktivnostjo – izboljšana identifikacija krivdnih alergenov, ki se uporabljajo pri IT

• Ocenjevanje tveganja (v izbranih primerih alergenov) za resnejšo obliko reakcije
  • Ara h 2, Cor a 9 – povezana z resnejšimi reakcijami
  • Ara h 8 – povezan z bolj blagimi reakcijami (saj je občutljiv na pH in temperaturo; za razliko od Ara h 2)
Pristna vs. navzkrižna reaktivnost

• Proteini znotraj iste družine so si podobni → osnova navzkrižne reaktivnosti

• Večina navzkrižne reaktivnosti je klinično nepomembne
  • Vloga MD pri identifikaciji primarnega senzibilizatorja (kurativni ukrepi)

• V določenih primerih lahko pride do klinično pomembne navzkrižne reaktivnosti
  • OAS po določenem sadju pri določenih bolnikih, ki so alergični na brezo (navzkrižna reaktivnost med PR-10 proteini npr. Bet v 1 [breza] in Mal d 1 [jabolko])
Pristna vs. navzkrižna reakcija na cvetni prah

- Osnovni diagnostični korak: anamneza (časovno orientirana) in dokaz IgE senzibilizacije (ekstrakti) → diagnoza in zdravljenje

- Problem:
  - Prekrivanje obdobjij cvetenja
  - Senzibilizacija na rastlinske pan-alergene
Pristna vs. navzkrižna reakcija na cvetni prah
do 30 % posameznikov, ki so senzibilizirani na aeroalergene, je senzibiliziranih na pan-alergene (predvsem profiline in polkalcine)
Pristna vs. navzkrižna reakcija na cvetni prah

- Dokaz IgE senzibilizacije na profiline (Phl p 12/Bet v 2)/polkalcine(Phl p 7/Bet v 4) → izguba diagnostične specifičnosti → nujna uporaba MD za dokaz specifičnih primarnih senzibilizatorjev → IT
  - Bet v 1 - pokrijemo bukovce (breza, leska, jelša, hrast, bukev, gaber in kostanj)
  - Ole e 1 – pokrijemo ustnatičevce kalina
  - Cup a 1 – pokrijemo cipreso
  - Phl p 1 in Phl p 5 – pokrijemo trave
  - Art v 1 – pokrijemo artemezijo (pelin)
  - Amb a 1 – pokrijemo ambrozijo
  - Par j 2 – pokrijemo krešino
Anafilaksa

• S kofaktorji povzročena anafilaksa (vadba, alkohol, zdravila ...):
  • WDEIA – dokaz senzibilizacije na w-5-gliadin
  • CEFA - IgE proti nsLTP (v mediteranskih državah [velikokrat tudi pri WDEIA-i in neg. w-5-gliadinu])- pokrijemo s Pru p 3 in Tri a 14
• Anafilaksa na rdeče meso (zakasnjena; 3-6 h po zaužitju mesa sesalcev):
  • IgE proti a-Gal – senzibilizacija s piki klopov; pametne so večkratne meritve, saj IgE odgovor s časom pada (nekateri bolniki prenašajo meso sesalcev, če jih 1-2 leti ni pičil klop)
• Idiopatska anafilaksa
  • W-5-gliadin, alergeni rakcev, lateksa, 'seed storage' proteini in nsLTP-ji
Ocena tveganja za težjo obliko reakcije pri alergiji na hrano

Table 1 High- versus low-risk molecules from foods giving rise to anaphylaxis

<table>
<thead>
<tr>
<th>Source</th>
<th>High risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>Ara h 1, 2, 3, 9</td>
<td>Ara h 8, profilin, CCD</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>Cor a 8, 9, 14</td>
<td>Profilin, CCD</td>
</tr>
<tr>
<td>Walnut</td>
<td>Jug r 1, 2, 3</td>
<td>Profilin, CCD</td>
</tr>
<tr>
<td>Soy</td>
<td>Gly m 5, 6, (4)</td>
<td>Profilin, CCD</td>
</tr>
<tr>
<td>Rosacea fruits</td>
<td>Pru p 3, Mal d 3</td>
<td>Pru p 1, Mal d 1, profilin, CCD</td>
</tr>
<tr>
<td>Wheat</td>
<td>Tri a 14, Tri a 19</td>
<td>Profilin, CCD</td>
</tr>
</tbody>
</table>

KEY: CCD = Cross-reactive Carbohydrate Determinant.

• Na temperaturo in pH odporni proteini načeloma povzročajo težje reakcije, dočim proteini, ki na temperaturo in pH niso odporni povzročajo blažje reakcije.
Navzkrižna alergija na hrano pri alergiji na aeroalergene

- Do 60 % alergij na hrano pri starejših otrocih, adolescentih in odraslih je povezanih z alergijo na aeroalergene
- Pri navzkrižni alergiji na hrano ob alergiji na aeroalergene, lahko do pride do alergične reakcije ob prvem zaužitju hrane.
- OAS je najpogostejša klinična manifestacija navzkrižne alergije na hrano, pri alergiji na aeroalergene, čeprav lahko pride tudi do resne prizadetosti (sistemska reakcija - najpogosteje generalizirane kožne manifestacije, lahko izolirane oz. v kombinaciji s prizadetostjo kakšnega drugega organskega sistema [izolirana prizadetost ostalih organskih sistemov, brez kožne prizadetosti, pri alergiji na hrano je redka]).
Navzkrižna alergija na hrano pri alergiji na aeroalergene

- Breza
  - Večinoma OAS, (soja, zelena, korenje - lahko resna anafilaktična reakcija)
  - Alergenost hrane ponavadi izgine po toplotni obdelavi (pazi visoko senzibilizirani)
- Večina posledica navzkrižne reaktivnosti z Bet v 1

**Table 3** Birch pollen (Bet v 1*)-associated food allergies

<table>
<thead>
<tr>
<th>Family</th>
<th>Food</th>
<th>Related food allergen</th>
<th>For in vitro testing available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosaceae</td>
<td>Apple</td>
<td>Mal d 1</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Cherry</td>
<td>Pru av 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pear</td>
<td>Pyr c 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peach</td>
<td>Pru p 1</td>
<td></td>
</tr>
<tr>
<td>Apiaceae</td>
<td>Celeriac</td>
<td>Api g 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carrot</td>
<td>Dau c 1</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Hazelnut</td>
<td>Cor a 1,04f</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Soybean</td>
<td>Gly m 4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mungbean</td>
<td>Vlg r 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>KiwiFruit</td>
<td>Act d 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peanut</td>
<td>Ara h 8</td>
<td></td>
</tr>
</tbody>
</table>

*Bet v 1 is a member of pathogenesis-related (PR) protein family and the major source of pollen-related food allergy in central Europe.
Hazelnut test is spiked with rCor a 1,04 in a commercial IgE test system.
MD pri alergiji na kožekrilce

• senzitivnost
  Vachova et al.; (84 % senzitivnost panela)
  Artz et al. (71.6% MS na ekstrakt; 92.7 % DS na ekstrakt)

• specifičnost
  Eberlin et al. JACI 2012; (95 % - DS)
  Frick et al. Allergy 2015; (75 % - 90 % DS)
  Michel et al. Allergy 2016; (75 % DS)
RECOMBINANT BASOPHIL ACTIVATION TEST (rBAT)

Mira Šilar
University Clinic for Respiratory and Allergic Diseases Golnik
BAT vs rBAT: different allergen
BAT vs rBAT: same technology

degranulation upon cross-linking of the sIgE bound on membrane-bound high affinity IgE-receptor by allergen exposure

Flow cytometer

Fluorochromes conjugated with different antigens exposed on the basophil surface can be used to identify basophils amongst leukocytes: CD123/HLA DR activation markers: CD63

The % of degranulated basophils was determined by FL1 (CD63)

(http://www.adr-ac.ch/en/diagnostics/bat)
Road map for the clinical application of the basophil activation test in food allergy

A. F. Santos¹ | W. G. Shreffler²

Summary

The diagnosis of IgE-mediated food allergy based solely on the clinical history and the documentation of specific IgE to whole allergen extract or single allergens is often ambiguous, requiring oral food challenges (OFCs), with the attendant risk and inconvenience to the patient, to confirm the diagnosis of food allergy. This is a considerable proportion of patients assessed in allergy clinics. The basophil activation test (BAT) has emerged as having superior specificity and comparable sensitivity to diagnose food allergy, when compared with skin prick test and specific IgE. BAT, therefore, may reduce the number of OFC required for accurate diagnosis, particularly positive OFC. BAT can also be used to monitor resolution of food allergy and the clinical response to immunomodulatory treatments. Given the practicalities involved in the performance of BAT, we propose that it can be applied for selected cases where the history, skin prick test and/or specific IgE are not definitive for the diagnosis of food allergy. In the cases that BAT is positive, food allergy is sufficiently confirmed without OFC; in the cases that BAT is negative or the patient has non-responder basophils, OFC may still be indicated. However, broad clinical application of BAT demands further standardization of the laboratory procedure and of the flow cytometry data analyses, as well as clinical validation of BAT as a diagnostic test for multiple target allergens and confirmation of its feasibility and cost-effectiveness in multiple settings.
6 | WHAT WOULD BE THE VALUE OF USING BAT IN CLINICAL PRACTICE?

Basophil activation test can be performed using single allergen components, which for some foods can be more accurate than using allergen extracts in the BAT (Table 2). For example, BAT to ovmucoid and BAT to Pru p 3 showed improved diagnostic accuracy compared to BAT to egg white and BAT to peach to diagnose egg allergy (both baked and raw egg allergies) and peach allergy, respectively. The use of single allergens has, however, the disadvantage of missing the contribution of minor allergens that are clinically relevant for some patients and of missing the combined effect of multiple allergens to which polysensitized patients produce IgE and which may increase the degree of basophil activation detected in the BAT.

---

**TABLE 2** Examples of studies assessing the utility of the basophil activation test to diagnose food allergy using whole allergen extracts or single allergens

<table>
<thead>
<tr>
<th>Food allergy</th>
<th>Food extract or allergen component</th>
<th>Study</th>
<th>Cut-offs</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow’s milk allergy</td>
<td>Cow’s milk extract</td>
<td>Rubio (2011)</td>
<td>≥5% CD63+</td>
<td>91%</td>
<td>90%</td>
</tr>
<tr>
<td>Egg allergy</td>
<td>Ovalbumin</td>
<td>Oomori (2009)</td>
<td>≥5% CD63+</td>
<td>77% for CD63</td>
<td>100% for CD63</td>
</tr>
<tr>
<td>Baked egg allergy</td>
<td>Egg white extract</td>
<td>Sato (2010)</td>
<td>SI C2D3b ≥2.4</td>
<td>74%</td>
<td>62%</td>
</tr>
<tr>
<td></td>
<td>Ovmucoid</td>
<td>Sato (2010)</td>
<td>SI C2D3b ≥2.4</td>
<td>88%</td>
<td>71%</td>
</tr>
<tr>
<td>Raw egg allergy</td>
<td>Egg white extract</td>
<td>Sato (2010)</td>
<td>SI C2D3b ≥1.7</td>
<td>88%</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td>Ovmucoid</td>
<td>Sato (2010)</td>
<td>SI C2D3b ≥1.7</td>
<td>88%</td>
<td>71%</td>
</tr>
<tr>
<td>Wheat allergy</td>
<td>Wheat extract</td>
<td>Tokuda (2009)</td>
<td>≥1.1% CD20c+</td>
<td>86%</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td>Omega-5 gliadin (14 a 19)</td>
<td>Tokuda (2009)</td>
<td>≥1.1% CD20c+</td>
<td>86%</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td>Omega-5 gliadin (F/r a 19)</td>
<td>Tokuda (2009)</td>
<td>≥1.1% CD20c+</td>
<td>86%</td>
<td>58%</td>
</tr>
<tr>
<td>Peanut allergy</td>
<td>Peanut extract</td>
<td>Santos (2014)</td>
<td>≥78% CD63+</td>
<td>98%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>Ara h 2</td>
<td>Glaumann (2012)</td>
<td>ND</td>
<td>92%</td>
<td>71%</td>
</tr>
<tr>
<td>Hazelnut allergy</td>
<td>Hazelnut extract</td>
<td>Brandtstrom (2010)</td>
<td>CD-sens &gt;1.7</td>
<td>100%</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td>Erdmann (2009)</td>
<td>SI C2D3b ≥1.7</td>
<td>86%</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Peach allergy</td>
<td>Peach extract</td>
<td>Gomara (2007)</td>
<td>≥20% CD63b-1 SI C2D3b ≥2</td>
<td>83%</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td>Pru p 3</td>
<td>Erdmann (2009)</td>
<td>SI C2D3b ≥1.7</td>
<td>77%</td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td>Erdmann (2009)</td>
<td>SI C2D3b ≥1.7</td>
<td>83%</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erdmann (2009)</td>
<td>SI C2D3b ≥1.7</td>
<td>83%</td>
<td>80%</td>
<td></td>
</tr>
</tbody>
</table>

SI, stimulation index; PFAS, pollen food syndrome; ND, not determined.

...it is necessary to achieve standardization of the laboratory procedure and data analyses and more rigorous validation.
Recombinant basophil activation test and "fingerprint" modeling of allergenic activity

Mira Šilar¹, Renato Eržen¹, Yvonne Resch², Susanne Vrtala², Mihaela Zidarn¹, Peter Kopač¹, Minja Zorc³, Tanja Kunej³, Edzard Spillner⁴, Rudolf Valenta², Mitja Košnik¹, Peter Korošec¹

1. University Clinic of Respiratory and Allergic Diseases Golnik, Golnik, Slovenia
2. Division of Immunopathology, Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna, Austria
3. Department of Animal Science, Biotechnical Faculty, University of Ljubljana, Slovenia
4. Immunological Engineering, Department of Engineering, Aarhus University, Aarhus, Denmark
The aim of this work:

To introduce a novel model of analysis of recombinant basophil activation test (rBAT), which allows displaying multi parameter features of allergenic activity of all major allergens of a specific allergen source on the level of individual patient.
Methods:

- 27 house dust mite (HDM) allergic patients
  3 healthy controls

- 30 patients with anaphylactic reactions to honey bee venom (HBV; n=24) or yellow jacket venom (YJV; n=6)
  4 healthy controls

Some HBV allergic patients were also followed during SIT
The protocol was performed in two steps:

1. **IgE reactivity** of recombinants was determined with dot blots or ELISA.

2. **Allergenic activity** was evaluated with basophil CD63 testing on heparinized whole blood with serial dilutions of:

   - **HDM**: nDer p 1, rDer p 2, rDer p 5, rDer p 7, rDer p 10, rDer p 21 and rDer p 23 allergens: $10^{-35}$ to 100 ng/ml
   - **HBV**: nApi m 1, rApi m 1, rApi m 2, rApi m 3, rApi m 5, rApi m 10, rApi m 11 allergens: 0.001–10 μg/ml
Results for HDM model:

1. IgE reactivity was determined in sera of all HDM allergic patients.

2. Positive recombinants were tested with BAT and quantified with CDsens.

Basophil sensitivity was determined as the allergen concentration giving a 50% of maximum CD63% up-regulation. CD-sens was calculated as the inverse value of this threshold allergen concentration multiplied by 100. The higher value for CD-sens represents higher basophil sensitivity.
CDsens results showed extremely wide range
(as such different allergens could not be combined and compared in individual patients)

<table>
<thead>
<tr>
<th></th>
<th>Der p 1</th>
<th>Der p 23</th>
</tr>
</thead>
<tbody>
<tr>
<td>mediana</td>
<td>1147</td>
<td>167293</td>
</tr>
<tr>
<td>range</td>
<td>$0.6 \times 10^{18}$</td>
<td>$31.3 \times 2.0 \times 10^{32}$</td>
</tr>
<tr>
<td>SD</td>
<td>$7.6 \times 10^{17}$</td>
<td>$4.7 \times 10^{31}$</td>
</tr>
</tbody>
</table>

High allergenic activity

Recombinants

CD sens

SD

Silar, EAACI 2017
Results for HBV model:

1. **IgE reactivity** was determined in sera of all HBV allergic patients

2. **All** recombinants were tested with BAT and quantified with AUC

BAT AUC (area under the curve) was calculated using the trapezoid rule on the data representing CD63% up-regulation with 4 consecutive bee venom concentrations (0.001 - 10 ug/ml)

---

**REACTIVITY**  ≠  **ALLERGENICITY**

Silar, EAACI 2017
Quantification of allergenic activity for single allergen with new developed 3D-plot of AUCs

- all patients, 24/24 (100%) were positive for nApi m 1
- nApi m 1 showed the highest AUC (geometric mean 123)
Allergenicity to rApi m 1 was detected in 22/23 (96%)
rApi m 2 in 12/24 (50%)
rApi m 3 in 11/24 (46%)
rApi m 5 in 11/24 (46%)
rApi m 10 in 10/24 (42%)
rApi m 11 in 3/16 (19%)
On the level of individual patient 3D-plot of AUCs represent multiparameter features of allergenic activity, including quantification for single allergen and summary for all tested allergens.

1 patient
7 rec BAT x 5 different conc. = 35 BAT
3D-plot of AUC:

a new tool for monitoring allergen immunotherapy

Silar, EAACI 2017
Highly positive for multiple HBV allergens.

A significant decrease of allergenic activity was evident for rApi m1, but not for rApi m2; less for rApi m3 and 5 and minor for rApi m10.
CONCLUSION

✓ Fingerprint modeling of allergenic activity pointing out the actual allergens from the offending allergen source that eliciting the allergic response in individual patients.

➢ This approach offers a new tool to address patient’s individual clinical reactivity at the molecular level and to monitor allergen immunotherapy.
Major basophil chemotactic factor CCL2 is increased in chronic urticaria patients and correlates with basopenia

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INTRODUCTION
Chronic urticaria (CU) is associated with basopenia, but the underlying mechanism for reduced basophil numbers remains unknown. Our recent study indicates substantial reduction in circulating basophils during acute allergic reaction, which correlates with a significant increase in the major basophil chemotactic factor CCR2 ligand CCL2. The aim of our current study was to investigate relationship between CCL2 level and basophil number in CU patients.

METHODS
Concentration of CCL2 and absolute basophil count were measured in 64 patients with CU and 24 healthy controls. CCL2 was determined with ELISA (R&D Systems, USA) and the absolute basophil count (CD123+ HLA-DR- cells) was determined with flow cytometry (BD, USA). Study was approved by Slovenian National Committee for Medical Ethics. Written informed consent was obtained from each participant before entering the study.

RESULTS
Basophil numbers in CU were reduced compared to controls (P<0.0001) (Figure 1). Serum CCL2 concentration was significantly increased (P=0.0002) in patients with CU (median 279 pg/ml) compared to healthy controls (median 191 pg/ml) (Figure 2). A significant negative correlation (r=-0.24, P=0.025) between serum CCL2 concentration and the absolute number of circulating basophils was demonstrated (Figure 3).

CONCLUSIONS
Our study indicates increase in the level of CCL2 in CU patients, which is associated with a decrease in the number of circulating basophils. CCL2-mediated migration may represent a mechanism for the selective migration of human basophils in CU. Additional studies will help clarify the importance of these observations.

CONFLICT OF INTEREST In relation to this presentation, I declare that there are no conflicts of interest.
Patient tailored omalizumab treatment in chronic urticaria – our experiences

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Background
Omalizumab is effective treatment in chronic spontaneous urticaria (CSU). There are reports that treatment schedules should not be uniformed, but patient tailored.

Method
We have analysed clinical response to omalizumab 300 mg/4 weeks in 52 CSU patients (41 females, median age 48 years). Treatment was started by 300 mg/4 weeks. Patients daily reported urticaria activity score (UAS) via a web based application. We analysed UAS7 at the beginning, 2 weeks (W2), 3 months (M3), and 12 (M12) months after first omalizumab application. The following definition of response to treatment were based on UAS7: complete response (UAS7=0), well controlled (UAS7=1-6), not well controlled (UAS7>6) and among last group significant improvement if reduction of UAS7 was 90-100%. In patients with complete response omalizumab dose was stepwise decreased and interval extended to the minimal dose/interval on which patients stayed symptom free.

Results
Complete response was achieved in 24/52 (46%) patients already at W2. In 11/52 (21%) patients at M3 and in 5/52 (10%) patients at M12. In 33/40 (82%) patients with complete response omalizumab treatment could be reduced to median 150mg/6 weeks. In 5 patients a remission was achieved after median 7 months of treatment (2-19 months) and were able to discontinue the treatment. In 4/52 (8%) patients CSU was well controlled at M12. 8/52 (15%) patients were not well controlled although in 4 patients significant improvement was achieved and patients continued with omalizumab 300 mg/4 weeks. In 4 patients with no significant improvement treatment was stopped after median 6 months (3-13 months).

Conclusion
Half of the patients with CSU completely respond to omalizumab very rapid and in these patients lower dose (150mg/6 weeks) is sufficient. In third of the patients complete response is achieved in several months and also in these patients less intensive treatment is needed. In patients with partial response, even after year of treatment, higher omalizumab dose is needed, while minority of patients did not respond to treatment and omalizumab was stopped.
Abstract Prize Winner

CCL2 MEASUREMENT IN SERA AS A NOVEL BIOMARKER OF ANAPHYLAXIS

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Currently, the most widely used laboratory test to confirm anaphylaxis is the **measurement of total tryptase** levels in serum or plasma.

**LIMITATION**: even when blood samples are optimally timed, tryptase levels are often within normal limits.

**CCL2** – major basophil chemotactic factor may be a useful biomarker of anaphylaxis.

WHY CCL2?

• Chemokine CCL2 is increased during acute anaphylactic reaction

• Induces strong basophil transendothelial migration to inflammatory tissue sites

• Reduction in circulating basophils correlates with increase in CCL2

• Therapy (corticosteroids) has no affect on CCL2
METHODS

- **107 patients** with clinical diagnosis of anaphylaxis and positive serial tryptase measurement (tryptase > 10 µg/l)

TIME POINTS:
Acute samples – reaction to 24h after
Basal samples – 24 h to 3 months after

- **98 healthy controls**

- Measurement of CCL2 - ELISA test: Quantikine Human MCP-1 Immunoassay
1. CCL2 levels are increased during anaphylaxis

2. There is a strong positive correlation between serum tryptase and CCL2 levels
3. During anaphylaxis is CCL2 significantly higher compared to healthy controls (4-fold increase).

P < 0.0001

4. The ROC curve analysis showed AUC of 0.98.

Cutoff > 385.7 pg/ml
Sensitivity 92%
Specificity 93%
CONCLUSION

• We showed that in patients with clinical diagnosis of anaphylaxis there is a **significant increase in CCL2 serum levels**

• CCL2 measurement in sera could lead to an **improved ability** to confirm the clinical diagnosis of anaphylaxis

• **... work in progress 😊**
  - testing of „tryptase negative" group with clinical diagnosis of anaphylaxis
  - correlation with severity
  - testing of specificity (other ED patients, local allergic reactions etc)