Disclosures of Potential Conflicts of Interest:

**Speakers Bureau**
- Genentech / Novartis
- Mylan / Dey

**Research / Clinical Trials**
- Genentech / Novartis
- Siemens

**Consultant**
- Stallergenes
- Sanofi-Aventis

**Learning Objectives**

Upon completion of this session, participants should be able to:

1. Recognize the indications for, and interpretation of, diagnostic tests for venom allergy.

2. Describe the advantages and limitations of new diagnostic materials and methods.
Diagnostic Tests for Venom – IgE

- Venom-IgE (skin test or serum) is positive in 15%-25% of asymptomatic (history-neg) adults.
- History-pos / IgE-pos patients have no reaction to sting in 30% - 70% of cases.
- Presence of venom-IgE is not necessarily predictive of clinical reactivity or severity.

Risk of Systemic Reaction Depends on Severity of Previous Reactions and Insect Species

(Golden et al - JACI 2006)

Risk of Sting Reaction Related to Venom Skin Test

(Golden et al - JACI 2006)
Diagnostic Evaluation of Patients With History of Systemic Reaction to Stings


<table>
<thead>
<tr>
<th>Test Result</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin test positive</td>
<td>68%</td>
</tr>
<tr>
<td>ST negative / RAST positive</td>
<td>14%</td>
</tr>
<tr>
<td>ST neg / RAST neg</td>
<td></td>
</tr>
<tr>
<td>sting challenge negative</td>
<td>17%</td>
</tr>
<tr>
<td>sting challenge positive</td>
<td>1%</td>
</tr>
</tbody>
</table>

Correlation of Dialyzed and Undialyzed Venom Skin Tests


Natural History of Insect Allergy: Risk Based on Severity of Previous Reactions

<table>
<thead>
<tr>
<th>Previous Sting Reaction</th>
<th>Chance of Future Systemic Sting Reaction:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>50 - 75%</td>
</tr>
<tr>
<td>Moderate Systemic</td>
<td>30 - 50%</td>
</tr>
<tr>
<td>Cutaneous Systemic</td>
<td></td>
</tr>
<tr>
<td>– child</td>
<td>1 - 10%</td>
</tr>
<tr>
<td>– adult</td>
<td>10 - 20%</td>
</tr>
<tr>
<td>Large Local</td>
<td>5 - 10%</td>
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</tbody>
</table>
Advances in Diagnostic Materials and Methods in Insect Sting Allergy

Recombinant venom allergens
Diagnostic accuracy
Cross-reactivity

Basophil Activation Tests
Diagnostic accuracy
Predicting systemic reactions

Recombinant Allergens for Diagnosis of Hymenoptera Venom Allergy
Muller 2009 – Sensitivity (by ADVIA-Siemens)
96% for rApi m 1; 87% for rVes v 5
Hofmann 2011 – found 79% for rApi m 1 by ImmunoCAP
Korosec 2011 – Sensitivity 57% for rApi m 1;
91% for nApi m 1; 100% for HBV
Mitterman 2010 – “Use of rApi m 1, rApi m 2 and rVes v 5 allows identification of patients with HB and YJ allergy.”
Sturm 2011 – Using rApi m 1 and rVes v 5 is insufficient, will miss genuine sensitization to other major allergens
Korosec 2012 – Sensitivity 92% for rVes v 5 or rVes v 1 (84% Vv5, 8% Vv1); 100% for YJV

Low sensitivity of commercial rApi m 1 for diagnosis of HB venom allergy. (Korosec et al. JACI 2011;128:671)
High sensitivity of CAP-FEIA rVes v 5 and rVes v 1 for diagnosis of Vespula venom allergy.
(Korosec et al. JACI 2012;129: 1406)

Basophil Activation Tests: Reporting Results

Ratio of “positive” activation to 1.0 vs 0.1 mcg/ml venom (Kosnik 2005)

Proportion of basophils showing increased CD63 expression in response to allergen (cut-off: 15% – Korosec 2009, Kucera 2010; Zitnik 2011; 10% Eberlein 2012; unclear – Peternelj 2008)

CD-sens = 100 / conc for 50% maximal CD63 response (Nopp and Johansson 2009) – Zitnik 2011, Eberlein 2012

Basophil responsiveness in patients with negative venom-IgE and skin prick tests.
Basophil Sensitivity Ratio Predicts Systemic Reactions to VIT

Basophil sensitivity in patients not responding to VIT.

Monitoring HB VIT in children with the basophil activation test. (Zirnik et al. Ped Allergy Immunol 2012;23:186)
Basophil activation predicts sting reaction after VIT

Basophil Activation / Sensitivity Tests in Insect Sting Allergy

Kosnik 2005 – BAT predicts systemic reactions to VIT
Peternelj 2008 – Basophil CD63 expression higher in patients not responding to VIT
Korosec 2009 – CD63 expression more sensitive (92%) than ID skin tests (62%) in patients with negative serum IgE and negative venom prick tests.
Kucera 2010 – BAT a helpful tool in predicting clinical sensitivity to HB after VIT
Zitnik 2011 – Basophil activation test reflects protective immune response to HB VIT in children.

Diagnostic Tests for Insect Sting Allergy

<table>
<thead>
<tr>
<th>Reason for test</th>
<th>Hx</th>
<th>ST</th>
<th>sigE</th>
<th>BAT</th>
<th>Recomb allergen</th>
<th>RAST Inhib</th>
<th>Tryptase baseline</th>
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<tbody>
<tr>
<td>Diagnosis</td>
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<td>Mld SR</td>
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<tr>
<td>Ana</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>Predict ana</td>
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<td>X</td>
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<tr>
<td>using VIT</td>
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<tr>
<td>Cross-reactivity</td>
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<td></td>
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<td>X</td>
<td>X</td>
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<tr>
<td>(HB / YJ)</td>
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<tr>
<td>Stop VIT</td>
<td>X</td>
<td></td>
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<td>X</td>
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</tr>
</tbody>
</table>

Reason Hx ST sIgE BAT Recomb RAST Tryptase
for test allergen Inhib baseline

No rxn X
LLR X
Mld SR X X X
Ana X X X X X X
Predict ana X X X
using VIT
Cross-reactivity X X
(HB / YJ)
Stop VIT X X X

Diagnostic Tests for Insect Sting Allergy
REFERENCES 1


REFERENCES 2


