Component-resolved Diagnosis

Are We Just Scratching the Surface?

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Linda Cox, MD Disclosure

Allergist: solo private practice
Associate Clinical Professor of Medicine Nova Southeastern University
Medical advisory board/consultant: Stallergenes, Genentech
Safety Data Monitoring/Adjudication Committee: Circassia, Novartis
Organizational interests:
• FDA Allergenic Products Advisory Committee: consultant
• AAAAI: President
• ABAI Board of Directors -member
Sublingual Immunotherapy to Aeroallergens
Learning Objectives

• At the end of the session attendees will be able to discuss:
  – Serum specific IgE testing diagnostic utility, difference amongst assays
  – Component-resolved diagnostic testing-predictive value in food allergy evaluation
  – Component-resolved diagnostic testing utility in selecting allergens for allergy immunotherapy
Current Allergy Diagnostic Assays-are not RAST but Allergen-Specific IgE Antibody Assays

Features of Current IgE Antibody Autoanalyzers

*Basic reagents and chemistries are similar*

- The antibody binds to the allergen on the solid phase
- Enzyme anti-IgE detects bound IgE
- All assays report in similar units (kUa/L) with comparable analytical sensitivities of 0.1 kUa/L
- All assays primarily use allergens from extracts

<table>
<thead>
<tr>
<th>Name</th>
<th>Company*</th>
<th>Solid Phase Matrix</th>
<th>Enzyme-labeled Detection Antibody</th>
<th>Substrate**</th>
<th>Calibration System</th>
<th>Analytical Sensitivity***</th>
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</thead>
<tbody>
<tr>
<td>HYTEC-288</td>
<td>Hycor-Agilent</td>
<td>Paper disc</td>
<td>Alkaline phosphatase labeled anti-IgE</td>
<td>p-nitrophenyl phosphate</td>
<td>Total IgE system</td>
<td>0.1 kUa/L</td>
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<tr>
<td>ImmunoCAP</td>
<td>Thermo-fisher</td>
<td>Cellulose sponge</td>
<td>B-galactosidase labeled anti-IgE</td>
<td>4-methyl-umbelliferyl β-D galactoside</td>
<td>Total IgE system</td>
<td>0.1 kUa/L</td>
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<tr>
<td>Immulite</td>
<td>Siemens</td>
<td>Biotinylated-allergen &amp; avidin particle</td>
<td>Alkaline phosphatase labeled anti-IgE</td>
<td>4-methoxy-4-(3-phosphatephenyl)-spiro-1,2 dioxetane-3,2'- adamantine</td>
<td>Total IgE system</td>
<td>0.1 kUa/L</td>
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<tr>
<td>Immuno Solid phase Allergen Chip ( ISAC¶)</td>
<td>Thermo-Fisher</td>
<td>Biochip</td>
<td>B-galactosidase labeled anti-IgE</td>
<td>4-methyl-umbelliferyl β-D galactoside</td>
<td>Positive controls</td>
<td>Semi-quantitative</td>
</tr>
</tbody>
</table>

Chip Based IgE Antibody Multiplex Assay
Molecular Allergy

- Serum (20 µl) is pipetted onto a small area on a washed glass slide with >100 individual aeroallergen and food allergen components bound to the chip, each in triplicate spots.
- Slide is washed with buffer and 20 ml of fluorescent label-conjugated anti-IgE is pipetted onto the slide.
- Following a 1 hr incubation, the slide is washed and bound fluorescent label is detected in a dot matrix scanner.
- Fluorescence interpolated from a calibration curve into semi-quantitative IgE antibody units; IgE anti-component levels >0.3 ISU are reported as positive and an indication of sensitization to that allergen specificity.
Multiplexed Assays using Component-Allergen Chip

- Chemically modified glass as substrate
- Hundreds of molecules or molecular fragments attached to the glass

**Procedure:**
1. Prepare serum
2. Incubate sample
3. Stain with SAb
4. Scan biochip
5. Analyse images
6. Create report

**Duration:**
- 3 hours
- 10 minutes

Modified from Pearls and Pitfalls of Allergy Diagnostic Testing on www.aaaai.org
How Are Allergy Laboratory Tests Approved?

FDA Clearance

• FDA requires that the manufacturer provide data per CLSI: data on 35 or more “clinically defined” positive sera along with 100 non-atopic, healthy donors showing that there is no non-specific binding to the allergen/solid phase.
• General assay and each allergen-containing reagent must also be separately FDA-cleared.
• A lack of FDA clearance means that the assay cannot be sold across state lines.
• Analyte-specific reagents: not cleared-will be phased out in next few years.
Molecular Allergy is the measurement of specific IgE to individual proteins from within whole allergen extract.

Understanding the nature of cross-reactivity

Two different patients with 2 different clinical profiles but same SPT and sIgE results to timothy extract: 7 mm wheal/20mm erythema and 8 kUa/L
Components and risk assessment

Labile protein

*Increasing risk to cause severe symptoms and reactions*

Stable protein

**Risk**

**Profilin**
- OAS
- Bet v 2, Phl p 12

**PR-10**
- OAS, some food SR
- Bet v 1 & Bet v 1 homologues
- Cor a 1, Mal d 1, Act d 8, Pru p 1

**LTP**
- Severe SR, OAS
- Cor a 8, Pru p 3, Art v 3

**Storage Proteins**
- Ara h 1
- Ara h 2
- Ara h 3

**Severe SR Wheat-anaphylaxis**
- Cor a 9, Tri a 19

Predictive Value of Component Testing in Peanut Sensitivity

- Population-based birth cohort, 933 assessed for peanut sensitization by SPT & sIgE at age 8 years.
- Sensitization defined as: SPT ≥ 3mm, sIgE ≥ 0.2 kUa/L
- Peanut allergy vs tolerance determined by OFC but not if convincing history and wheal ≥ 8,mm and/or ≥15 kUa/L
- Components tested: peanut (Ara h 1-3 and 8), grass (Phl p 1, 4, 5b, 7, and 12) and Bet v 1, Pru p 3, and CCD
- 110 (11.8%) children were peanut sensitized
  - 79 oral food challenges: 22% positive
  - 2% of general population clinically allergic

Nicolaou et al. JACI 2010 Jan;125(1):191-7 e1-13
Predictive Value of Component Testing in Peanut Sensitivity

• Allergic ‘misclassification’ rate for sIgE of 15 kUa/L was 17.3% and 15% for SPT ≥ 8 mm,
  Tolerant: 55% had sIgE and 61% had SPT > 95% prediction value

• Component recognition clearly differed between peanut allergy and peanut-tolerant subjects
  – **Tolerant**: higher Phl p 1, Phl p 4, and Phl p 5
  – **Allergic**: higher Ara h 1 to 3,
  – **No difference**: Bet v 1, Ara 8

**Clinical Implications**: Measurement of IgE response to major peanut allergen Ara h 2 is more useful in predicting clinical allergy than currently used skin or blood tests

Nicolaou et al, JACI 2010;125(1):191-7
Ara h 1, Ara h 2, Ara h 3
Predictors of Respiratory Reactions

• A birth-cohort study of 4089 children that assessed peanut allergy through questionnaires.
• Different peanut/birch sensitization phenotypes were defined among 200 selected children using microarray technique to measure peanut and pollen allergen components.
• **Results**: 87% of the peanut allergic patients had IgE reactivity to Ara h 1, 2 or 3 but not Ara h 8, which is the Bet v 1 homologue.
• More reactions with respiratory symptoms were reported in children sensitized to Ara h 2 plus Ara h 1 or 3 versus Ara h 2 alone.

Asarnoj A et al Allergy 2010;65:1189-95
Peanut component Ara h 8, a Bet v 1 homologue sensitization and tolerance to peanut

- **Methods:** 144 children in a clinical center database & birth cohort sensitized to Ara h 8 but not to Ara h 1, Ara h 2, or Ara h 3
  - Sensitization defined by cutoff: 0.35 kU(A)/L
- Oral challenge in those not regularly eating (62)
  - Open: 46 no symptoms, 14 OAS
  - DBPC: 1 no symptoms but reacted during open challenge during birch season, 1 SR in pt with Ara h 6 level 0.45

**Clinical implications:** Isolated Ara h 8 sensitization seems to indicate peanut tolerance. Peanuts can be carefully introduced at home in children with such sensitization. However, as yet unidentified determinants can rarely induce sensitization and symptoms.

CRD: Identifying Specific Allergen Sensitivity
Milk & Egg Allergy: Higher Negative-Predictive Value

• Clinical performance of microarray in children with challenge-proven/excluded CM or egg allergy
• 105 children  mean age 4.9 (0.7-15.1 yrs) with suspected CM or HE  IgE-mediated hypersensitivity were studied: SPT, ImmunoCAP, microarray and FCT.
   – Bos d 8: PPV of 96% and NPV of 78%
   – Gal d 1: PPV of 94% and an NPV of 79%
   – Both had higher NPV than ImmunoCAP (CM 57% and HE 59%).

D’Urbano et al, Clin Exp Allergy. 2010;40(10):1561-70
Sequential use of the two tests
No further improvement in performance in HE, slight in CM

D’Urbano et al, Clin Exp Allergy. 2010;40(10):1561-70
Ovomucoids IgE (Gal d 1) is a better marker than egg white-specific IgE to diagnose boiled egg allergy

- 100 children (median age 17 months) no prior egg exposure
- Compared results OFC with boiled egg, sIgE to EW and OVM
  - OVM had better predictive value than EW
- **Results of OFC in Negative OVM**:
  - 88% (21 of 24) likelihood of a negative challenge regardless of the EW level
  - 3 individuals with positive OFC showed only mild cutaneous reaction
- Authors: “a new predictive marker for application in conjunction with a restricted patient background..”

Haneda et al JACI 2012;129:1681-2
Component-resolved diagnosis of pollen allergy based on SPT with profilin, polcalcin and LTP pan-allergens

• **Principle objective**: evaluate a new diagnostic strategy - SPTs specific for 3 pan-allergens, together with an appropriate and complete panel of allergenic molecules.

• **Study**: 1329 pts with previous 2-year history of pollinosis, tested by vitro method to 13 purified allergen including pan-allergens & SPT to major allergens and pan-allergens.

• **For SPT:**
  – peach commercial extract adjusted to 30 mg/mL of Pru p 3, which is a LTP
  – date palm extract: natural profilin, Pho d 2 adjusted to 50 mg/mL & procalin
Peach allergy in China: A dominant role for mugwort pollen lipid transfer protein as a primary sensitizer

- 70 pts with a convincing history of mugwort, peach or both allergy tested to rPru p 1, rPru p 3, rPru p 4, nArt v 1, and nArt v 3)
- Two IgE molecular recognition patterns: peach allergy with primary sensitization to pollen Art v 3 and a smaller group with primary sensitization to Pru p 3.
- Mugwort only pts had lower mugwort-sIgE titers than mugwort/peach but more had Art v 1
- Study suggest that in China- peach LTP allergy originates from primary sensitization to pollen LTP (Art v 3)

CRD with commercially available DPT, Der p 1, Der p 2, and Der p 10: relevant markers for HDM allergy

• 123 HDM allergic patients tested Der p 1, Der p 2, Der p 10 and MUXF3.
• DPT-sIgE strongly correlated with Der p 1 and Der p 2 IgE but not Der p 10 and MUXF3
• Der p 10-sgE prevalence and levels suggest different patterns in food and mite-related tropomyosin sensitization

Bronnert et al, Clin Exp Allergy 2012 ahead of print
Improvement of shrimp allergy after sublingual immunotherapy for house dust mites: a case report

- 15 year-old with mild persistent asthma and rhinitis due to mites, and concomitant shrimp-anaphylactic: urticaria, glottis oedema, asthma, & enteritis
- HDM SLIT – daily maintenance 2x usual SLIT give in 12month cumulative tropomysin dose of 146 μg.
- Prior to SLIT-1 OFC resulted in OAS, dyspnea & OAS after 1 year; 1 shrimp OFC – OAS only
- Ate shrimp in small quantities at home without problems
- Change in shrimp SPT and sIgE but no other parameters


<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before SLIT</th>
<th>After SLIT</th>
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<tbody>
<tr>
<td>Dermatophagoides far prick mm</td>
<td>12.00</td>
<td>6.00</td>
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<tr>
<td>Dermatophagoides far IgE KU</td>
<td>55.10</td>
<td>70.50</td>
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<tr>
<td>Dermatophagoides far IgG mg/ml</td>
<td>18.20</td>
<td>21.50</td>
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<tr>
<td>Dermatophagoides far IgG4 mg/ml</td>
<td>0.17</td>
<td>0.16</td>
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<tr>
<td>Pen A1 IgE KU/ml</td>
<td>45.50</td>
<td>53.10</td>
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<tr>
<td>Pen A1 IgG mg/ml</td>
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<td>2.00</td>
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<tr>
<td>Pen A1 IgG4 mg/ml</td>
<td>0.03</td>
<td>0.07</td>
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<td>Shrimp IgE KU</td>
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<tr>
<td>Shrimp IgG mg/ml</td>
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<td>4.20</td>
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<tr>
<td>Shrimp IgG4 mg/ml</td>
<td>0.12</td>
<td>0.18</td>
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</tbody>
</table>
CRD Utility in Diagnostic Testing

• **Shrimp tropomysin** specificity (92.8%) was > than shrimp-slgE (75%) and SPT (64.2%)<sup>1</sup>

• **Bee and wasp venom** dual sensitivity to both insect venoms vs. cross-reactive carbohydrate determinants (CCDs) e.g., bromelain<sup>2</sup>

• **Wheat**: slgE to omega-5 gliadin can be used as an accurate alternative to wheat food challenges in monitoring WA.<sup>3</sup>

• **Kiwi**: Act d 1 kiwi monosensitized vs Bet v 1 homolog and profilin Act d 8 and 9 involved pollen-related kiwifruit allergy.<sup>4</sup>

1. Yang et al, JACI. 2010;125(4):872-8
Can CRD make specific immunotherapy more specific?

Soy positivity due to cross-reactivity (CCD, Profilin...)?
Ragweed and Mugwort sage
Allergen Proteins from Allergen.org (Jorgen Larson, ALK-Abello)
International Union of Immunological Societies, Allergen Nomenclature Sub-Committee

<table>
<thead>
<tr>
<th>Species name</th>
<th>Allergen name</th>
<th>Biochemical id or obsolete name</th>
<th>MW kDa SDS-PAGE</th>
<th>IgE Prevalence</th>
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<tr>
<td><strong>A. Weeds</strong></td>
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<td>Asterales</td>
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<td><strong>Ambrosia artemisiifolia</strong></td>
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<td>short ragweed</td>
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<td>Amb a 1 homologue, antigen K</td>
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<td>Amb a 5</td>
<td>Ra5</td>
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<td></td>
<td>Amb a 8</td>
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<td>39%</td>
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<tr>
<td></td>
<td>Amb a 9</td>
<td>polcalcin</td>
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<td>19%</td>
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<td></td>
<td>Amb a 10</td>
<td>polcalcin</td>
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<td>23%</td>
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<td><strong>Ambrosia trifida</strong></td>
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<tr>
<td>giant ragweed</td>
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<td>Ra5G</td>
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<td><strong>Artemisia vulgaris</strong></td>
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<td>mugwort</td>
<td>Art v 1</td>
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<td></td>
<td>Art v 2</td>
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<td>Art v 3</td>
<td>lipid transfer protein</td>
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<td>Art v 4</td>
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<td>Art v 5</td>
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<td>Art v 6</td>
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# Allergen Proteins from Allergen.org

## Bermuda and Northern Pasture Grass

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<thead>
<tr>
<th>Species name</th>
<th>Allergen Name</th>
<th>Biochemical ID</th>
<th>MW kDa SDS-PAGE</th>
<th>IgE Prevalence</th>
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<tbody>
<tr>
<td><em>Cynodon dactylon</em></td>
<td>Cyn d 1</td>
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<td>32</td>
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<td>Bermuda grass</td>
<td>Cyn d 2</td>
<td>Expansin C-term</td>
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<td>Cyn d 4</td>
<td>Berberine bridge enzymes</td>
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<td></td>
<td>Cyn d 7</td>
<td>polcalcin</td>
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<td>Cyn d 12</td>
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<td>Cyn d 13</td>
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<td><em>Phleum pratense</em></td>
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<td>Phl p 13</td>
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<td>55-60</td>
<td>36-50%</td>
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Schmid-Grendelmeier P. [Recombinant allergens. For routine use or still only science?]. Hautarzt. 2010 Nov;61(11):946-53
CRD and Allergy Immunotherapy Outcome

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Major+ Minor+</th>
<th>Major+ Minor-</th>
<th>Major- Minor+</th>
<th>Major- Minor-</th>
<th>Total</th>
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<td>None</td>
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<td>13</td>
<td>41</td>
<td>6</td>
<td>84</td>
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<td>28</td>
<td>26</td>
<td>3</td>
<td>166</td>
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<tr>
<td>Good</td>
<td>123</td>
<td>137</td>
<td>9</td>
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<td>269</td>
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<tr>
<td>Very good</td>
<td>74</td>
<td>147</td>
<td>6</td>
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<tr>
<td>Total</td>
<td>330</td>
<td>325</td>
<td>82</td>
<td>9</td>
<td>746</td>
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</table>

 Tested major allergens: Bet v 1 and/or Phl p 1/Phl p 5. Tested minor allergens: Bet v 2/Bet v 4 or Phl p 7/Phl p 12.

73% efficacy in patients sensitized to major allergens vs. 16% efficacy in patients sensitized exclusively to minor allergens

Schmid-Grendelmeier P. [Recombinant allergens. For routine use or still only science?]. Hautarzt. 2010 Nov;61(11):946-53
Improved Clinical Outcome in SIT Dosing with CRD:
689 patients with birch and grass pollinosis after 2 years of SIT

Clinical Symptom Improvement
- <30%
- 30-50%
- 50-75%
- 80-100%

IgE abs to Major components alt. Cross-reacting components
Molecular profiles of IgE to Phleum pratense in children with grass pollen allergy: Implications for specific immunotherapy

- Investigate the profiles of IgE sensitization to *Phleum pratense* in children with grass pollen allergy
- Among the 176 children with IgE sensitization to *P pratense* extract, 39 profiles of sensitization to the 8 allergenic molecules tested
- Profiles matched against an experimental SIT preparation containing Phl p 1, Phl p 2, Phl p 5, and Phl p 6.

Molecular profiles of IgE: Implications for SIT

- Potential suitability of a molecularly designed SIT mixture of Phl p 1, Phl p 2, Phl p 5a and Phl p 5b, and Phl p 6.15
- Only 7 (4%) of 176 patients had sensitization profile matching proposed mixture

<table>
<thead>
<tr>
<th>Patient's profile: APCS code</th>
<th>Example patient's profile</th>
<th>Molecular SIT profile</th>
<th>Example molecular overlapping</th>
<th>Patient's immunization category</th>
<th>Frequency by category n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>218</td>
<td>1 2</td>
<td>1 2</td>
<td>1 2</td>
<td>Matching</td>
<td>7/176 (4%)</td>
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<td>217, 218, 244</td>
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<td>1 2</td>
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<td>Type 1 mismatch underpowered immunization</td>
<td>50/176 (29%)</td>
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<tr>
<td>39, 49, 64, 120</td>
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<td>1 2</td>
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<td>Type 2 mismatch overpower immunization</td>
<td>57/176 (32%)</td>
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<td>69, 70, 120, 150</td>
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<td>1 2</td>
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<td>Type 3 mismatch underpower immunization</td>
<td>53/176 (30%)</td>
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<td>0, 22, 74</td>
<td></td>
<td>1 2</td>
<td></td>
<td>Type 4 mismatch unrelated immunization</td>
<td>0/176 (5%)</td>
</tr>
</tbody>
</table>

Clinical implications: Trials are needed to test whether different molecular sensitization profiles to grass pollen underlie different clinical responses to the same SIT preparation. Registration rules for molecularly designed SIT preparations should consider the extreme heterogeneity of sensitization profiles in populations.
Identification of Der p 23, a peritrophin-like protein, as a new major Dermatophagoides pteronyssinus allergen associated with the peritrophic matrix of mite fecal pellets.


A Hypoallergenic Vaccine Obtained by Tail-to-Head Restructuring of Timothy Grass Pollen Profilin, Phl p 12, for the Treatment of Cross-Sensitization to Profilin

Kerstin Westrithsching, Birgit Linhart, Margarete Focke-Tejkl, Tea Pavkov, Walter Keller, Tanja Ball, Adriano Mari, Anulf Hartl, Angelika Stöckdinger, Sandra Scheidlhofer, Josef Thalhammer, Fatima Ferreira, Stefan Vieths, Lothar Vogel, Alexandra Böhm, Peter Valent and Rudolf Valenta

*J Immunol.* 2007 Dec 1;179(11):7624-34.
Molecular Allergy Diagnostic Testing

- *May* allow patients’ sensitization profiles to be characterized in greater detail
- *May* assess the clinical risk for reactions (both mild and severe)
- *May* help differentiate between symptoms caused by true allergy and symptoms caused by cross-reactivity in suspected food allergy patients
- *May* help select patients for food challenge and targeted immunotherapy
"You're not allergic to molds or pollen, but you are interest-rate sensitive."
Accelerated Immunotherapy Schedules
Learning Objectives

• At the end of the session attendees will be able to
  – Compare safety of rush, cluster and conventional immunotherapy schedules
  – Discuss the effects of premedication on accelerated immunotherapy schedules
  – Discuss the onset of immunotherapy efficacy with accelerated immunotherapy schedules
• **SCIT SR rate** varies greatly depending on several factors: allergen dose, extract type, induction schedule, premeditation, extract type, etc.

• **SR rate**: review of SCIT studies that reported SR rate from 1995-2010:*
  
  – Per injection frequency was ~0.2%
  
  – Per patient rate of 2% to 7% in US studies with conventional schedules

• Purported advantage of accelerated schedules
  
  – Reduced number of visits to target dose BUT
  
  – Possible with increased risk of SR
    
    • Rush increased risk with aerollergen but not venom (except fire ant)
    
    • Cluster risk may be the same or increased

AAAAI/AACAI Surveillance Study of SCIT Safety: 10.2 SRs per 10,000 injection visits (0.1% for all 3 years)

About 8 million injections visits per year

Per injection SR rate & number (%) practices reporting

- **Grade 1 mild SR:**
  - 1 per 1,287 (.07% injection visits)
  - 613 (76%) practices

- **Grade 2 moderate SR:**
  - 1 per 4,166 (.02% injection visits)
  - 436 (54%) practices

- **Grade 3 severe SR:**
  - 1 per 30,566 (.003%)
  - 144 (18%) practices

Bernstein et al, Ann Allergy Asthma Immunol 2010;104:530-5.
of Onset
2,105 total # of SRs, 289 (14%) began after 30 minutes

Severity of SRs

## Advantages & Disadvantages of Accelerated Immunotherapy Schedules

**TABLE 1. Comparison of different immunotherapy build-up schedules for aeroallergens**

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Rush immunotherapy</th>
<th>Cluster immunotherapy</th>
<th>Conventional immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of visits during build-up phase</td>
<td>1-3</td>
<td>8*</td>
<td>30*</td>
</tr>
<tr>
<td>No. of injections</td>
<td>8†</td>
<td>18*</td>
<td>30*</td>
</tr>
<tr>
<td>Time to reach maintenance dose</td>
<td>1-3 d</td>
<td>5 wk*</td>
<td>15 wk at a frequency of 2 times per week or 7.5 mo if injections administered once a week</td>
</tr>
<tr>
<td>Premedication‡</td>
<td>Recommended in the AIPP but no specific protocol provided. H1 antihistamine and corticosteroids were used in all protocols§ in addition to other medications (eg, H2 antihistamines, leukotriene antagonists, theophylline, and ketotifen).</td>
<td>Antihistamine recommended by AIPP with notation that 2 hours before has been shown to decrease SR and local reactions.</td>
<td>Not routinely recommended but rarely studied: one study found reduced frequency of severe SR and increased the proportion of patients who achieved the target dose with fexofenadine premedication.</td>
</tr>
<tr>
<td>Range of SRs‡</td>
<td>Without premedication 15% to 100% of patients</td>
<td>3% to 79% of patients (100% in 1 study classified as cluster, but protocol had 5 injections per visit; allergen: <em>Cladosporium sp.</em></td>
<td>8.4% to 28.6% of patients; mean, 12.9%; SD, 10.8%§</td>
</tr>
<tr>
<td>With premedication</td>
<td>14.7% to 38% of patients</td>
<td>0 to 33% of patients</td>
<td>NA</td>
</tr>
</tbody>
</table>

Experience with Accelerated Immunotherapy Schedules Utilizing Multiple and Single Allergen Extracts in a Private Practice Setting.

- 2 day modified RIT with a target dose of 0.25 ml vial 2
- 3 groups: No premedication (n=26), Premedicated 3 meds prednisone, ranitidine and loratidine (n=6) and 4 meds (previous plus zafirlukast ) (n=25).

**Systemic reaction rate:**

- 9/26 (35%) pts without premedication
- 1/31 (3% of premedicated pts (pt was premedicated with 3 drug regimen)
- All pts who had SR during the modified RIT had at least one allergen with wheal of ≥14 mm on prick skin testing (ALK Lancet, ALO or Greer extract)

**High degree of STR associated with greater SR risk with Modified RIT**

Cox L, ACAAI Annual Meeting 1996 & 1998 Abstract Presentations
Dear Dr. Cox:

United HealthCare Insurance Company has received and reviewed your appeal and supporting documentation for reimbursement for RUSH immunotherapy under the US Airways benefit plan.

There is a lack of peer reviewed literature to support “RUSH” immunotherapy. It is considered of an unproved technique. There is no indication as to why standard immunotherapy would not have been effective in this case. Therefore, benefits are no available under the plan.

or treatment of a specified condition according to general medical standards or the medical community at large.

We can find no reference to the RUSH immunotherapy in any standard allergy textbook, which suggests this is a novel treatment, not generally accepted by the medical community. As such, no benefits are available under the plan for RUSH immunotherapy.
ACCELERATED AIT SCHEDULES
DATE BACK TO EARLY 1900’S

“In 1909, Noon and I began inoculating hay-fever patients with a grass pollen extract.... inoculations were given weekly merely because our out-patients at St. Mary’s Hospital were in the habit of coming every week.

Dr. Freeman noted the inconvenience of the weekly build-up and began experimenting with more rapid schedules. He concluded the advantages of the “rush” method were: the saving of time, convenience and patient compliance.

“Rush desensitization” with associated SR

7 year-old girl with horse-asthma desensitized over 4 days but developed urticaria, fluttering heat and felt “funny” and dose was decreased. Able to ride her pony without discomfort.
Subcutaneous Rush Schedule

- RIT incremental doses of allergen at intervals varying between 15 and 60 minutes over 1 to 3 days until the target therapeutic dose is achieved.
- RIT schedules for inhalant allergens can be associated with a greater risk of SR, particularly in high-risk patients and premedication appears to reduce the risk associated with aeroallergen RIT.
- However, venom RIT does not appear to a similar high incidence of systemic reactions and premedication does not appear to be necessary.
- Conflicting data with fire ant in terms of premedication.

Risk Factors for Rush Systemic Reactions

**FEV<sub>1</sub> & STR**

**Protocol:** 125 mite-allergic asthma pts (age 4 - 57) underwent a 3-day RIT.

Target dose: 3000 BU (4 µg of Der p 1) in subjects > 10 yrs and 1500 BU in < 10 yrs

<table>
<thead>
<tr>
<th>DAY 1</th>
<th>Hour</th>
<th>BU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>9:30</td>
<td>30</td>
<td>150</td>
</tr>
<tr>
<td>11</td>
<td>60</td>
<td>300</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DAY 2</th>
<th>Hour</th>
<th>BU</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>1200</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DAY 3</th>
<th>Hour</th>
<th>BU</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>3000</td>
<td></td>
</tr>
</tbody>
</table>

**Adverse reactions:** Severe SR in 34.4%.

35 pts had asthma SR, 8 pts had anaphylaxis and 5 pts had > 1 SRs.

The two significant differences between pts with severe SR and those with mild or no SR were:

- Skin prick end point titration
- FEV<sub>1</sub> (p<0.001) before RIT

73% of pts with FEV1 < 80% had asthma rx during RIT vs. 12.6 % of pts with FEV1 > 80%.

Bousquet et al, J Allergy Clin Immunol 1989; 83 (4) 797-801
RIT Modifying Risk with Premedication and Protocol Adjustments

**Method:** 1152 mite-allergic pts and 454 pollen allergen (age 3 to 65) years with asthma ± rhinitis positive by RAST or PST

- Premedication protocol: Day 1 of RIT:
  - Methylprednisone (0.5mg/kg) 9 AM only,
  - Ketotifen (1 mg) 9 AM and 7 PM,
  - Long acting theophylline 9 AM & 7 PM.

**4 groups**

1. RIT
2. RIT with 3 days of premedication
3. RIT with premedication with preventative measures excluding patients with FEV1 <70% and ↓ rate with LLR >10cm.

4. **Step protocol:** 6 visits over 2 weeks to reach maintenance

1. Hejjaoui A et al. J Allergy Clin Immunol 1989; 83 (4) 797-8017
Reduced SR and Severe SR with Premedication and Preventive Measure

Table 1. Systemic Reactions According to Immunotherapy Schedule, Premedication, and Prevention Measures in Dust Mite and Pollen Allergic Patients With Allergic Rhinitis With or Without Asthma

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Allergen</th>
<th>SR per patient, %</th>
<th>SR per injection, %</th>
<th>Asthma reactions, %</th>
<th>Anaphylaxis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A: 3-day RIT, 290 patients</td>
<td>Dust mite, 290 patients</td>
<td>36</td>
<td>3.8</td>
<td>30.6</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>Pollen, 74 patients</td>
<td>31.3</td>
<td>3.1</td>
<td>9.7</td>
<td>5.8</td>
</tr>
<tr>
<td>Group B: RIT plus premedication†</td>
<td>Dust mite, 160 patients</td>
<td>16.2</td>
<td>2.0</td>
<td>13.7</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Pollen, 102 patients</td>
<td>14.7</td>
<td>3.1</td>
<td>5.8</td>
<td>5.8</td>
</tr>
<tr>
<td>Group C: RIT plus premedication and preventive measure‡</td>
<td>Dust mites, 478 patients</td>
<td>7.3</td>
<td>0.8</td>
<td>6.9</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Pollen 200 patients</td>
<td>7.5</td>
<td>2.3</td>
<td>2.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Group D: step protocol with premedication and preventive measure§</td>
<td>Dust mites, 223 patients</td>
<td>5.1</td>
<td>0.6</td>
<td>5.0</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Pollen, 78 patients</td>
<td>2.8</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Rush Immunotherapy: multiple allergens with & without premedication one and two day protocols

1st study (11 pts): 2 day RIT with no premedication. SR in 55% of pts; Grades 3 to 5. All SR at dose > 0.3 ml 1:1000 w/v

- LR did not predict SR
- Correlation between severity of SR and number of positive ST/cumulative size

Table 1. Schedule for Administration of 1-Day Rush Immunotherapy

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume, mL</th>
<th>Dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:00</td>
<td>0.30</td>
<td>1:100,000</td>
</tr>
<tr>
<td>09:30</td>
<td>0.10</td>
<td>1:10,000</td>
</tr>
<tr>
<td>10:00</td>
<td>0.30</td>
<td>1:10,000</td>
</tr>
<tr>
<td>10:30</td>
<td>0.05</td>
<td>1:1000</td>
</tr>
<tr>
<td>11:00</td>
<td>0.15</td>
<td>1:1000</td>
</tr>
<tr>
<td>12:00</td>
<td>0.30</td>
<td>1:1000</td>
</tr>
<tr>
<td>13:00</td>
<td>0.05</td>
<td>1:100</td>
</tr>
<tr>
<td>14:00</td>
<td>0.10</td>
<td>1:100</td>
</tr>
<tr>
<td>Total</td>
<td>0.20</td>
<td>1:100</td>
</tr>
</tbody>
</table>

* Total is the cumulative dose given over 6 hours.

Grading of SRs:
2= cutaneous only, rash;
3= generalized pruritus, sneezing, mouth itchiness;
4= wheezing, shortness of breath;
5= anaphylaxis

Rush Immunotherapy: multiple allergens with & without premedication one and two day protocols

2nd study (22 pts) Premedication reduced SR rate: 27% of premed group vs. 73% of placebo premedication ($p=0.047$).

- Best predictor for SR was STR before and after premedication.
- Noted increase STR in placebo before SR

3rd study: 22 pts: one day RIT with premedication. SR in 23%.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Day 0*</th>
<th>Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astemizole</td>
<td>15 mg twice a day</td>
<td>10 mg twice a day</td>
<td>5 mg</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>150 mg BID on all 3 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>30 mg a day on all 3 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Portnoy et al Ann Allergy 1994; 73: 409-18
2. Sharley et al Ann Allergy 1996; 76: 175-80
Fastest SCIT Rush Schedule for Inhalant Allergens

- The most accelerated schedule for inhalant allergens: 7 injections administered over day 4 hours in a one day protocol. Premedication 1 day before and morning of RIT
  - Prednisone 40 mg, cetirizine 10 mg, ranitidine 300 mg and montelukast 10 mg/zafirlukast 40mg
  - 38% SR Rate

---

**Table 1. Rush Immunotherapy Protocol**

<table>
<thead>
<tr>
<th>Injection No.</th>
<th>Time, min</th>
<th>Concentration, volume:volume</th>
<th>Volume, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>1:10,000</td>
<td>0.3</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>1:1,000</td>
<td>0.3</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>1:100</td>
<td>0.1</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>1:100</td>
<td>0.3</td>
</tr>
<tr>
<td>5</td>
<td>120</td>
<td>1:10</td>
<td>0.1</td>
</tr>
<tr>
<td>6</td>
<td>180</td>
<td>1:10</td>
<td>0.2</td>
</tr>
<tr>
<td>7</td>
<td>240</td>
<td>Undiluted concentrate</td>
<td>0.05</td>
</tr>
</tbody>
</table>

88% of reactions

Symptomatology of Moderate to Severe Systemic Reactions

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Reaction</th>
<th>Severity</th>
<th>Eliciting Dose</th>
<th>Treatment</th>
<th>Time to reaction, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Lip swelling, nasal congestion, chest tightness, abdominal cramping, nausea, vomiting</td>
<td>Moderate</td>
<td>0.2 mL 1:10</td>
<td>Hydroxyzine, 75 mg; levocabastine, 2 gtt s OU; epinephrine, 0.3 mg s.c.; loratadine, 10 mg; albuterol, 2 puffs</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>Facial and trunk flushing, abdominal cramping, palmar pruritus</td>
<td>Moderate</td>
<td>0.05 mL concentrate</td>
<td>Epinephrine, 0.3 mg s.c.; cetirizine, 10 mg</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>Nasal congestion, sneezing, axillary pruritus and erythema, decreased FEV₁</td>
<td>Moderate</td>
<td>0.1 mL concentrate</td>
<td>Albuterol, 5 puffs; albuterol nebulizer, 0.5 mL; ipratropium, 4 puffs; prednisone, 40 mg; cetirizine, 10 mg</td>
<td>35</td>
</tr>
<tr>
<td>22</td>
<td>Severe abdominal cramping</td>
<td>Moderate</td>
<td>0.2 mL 1:10</td>
<td>Epinephrine, 0.3 mg s.c.; rofecoxib, 50 mg</td>
<td>45</td>
</tr>
<tr>
<td>31</td>
<td>Cough, wheezing, chest tightness, facial flushing, palmar pruritus</td>
<td>Moderate</td>
<td>0.05 mL concentrate</td>
<td>Epinephrine, 0.3 mg s.c.; cetirizine, 10 mg; albuterol, 2 puffs</td>
<td>40</td>
</tr>
<tr>
<td>65</td>
<td>Hypotension (systolic blood pressure 50 mm Hg), urticaria, pruritus, facial angioedema</td>
<td>Severe</td>
<td>0.1 mL 1:10</td>
<td>Epinephrine, 0.6 mg intramuscularly 2 times; intravenous fluids, 1 L; cetirizine, 10 mg; prednisone, 40 mg; ranitidine, 150 mg</td>
<td>55 (mild), 150 (severe)</td>
</tr>
</tbody>
</table>

Mild reaction at 55, severe at 150 minutes

“29-year-old woman who began developing pruritus on her neck 55 minutes after the third-to-last injection of the protocol. The next injection was held, but she developed urticaria that was treated with cetirizine and prednisone. Ninety minutes after the onset of her symptoms, the patient acutely worsened and became hypotensive. She was treated with 2 doses of epinephrine, 0.5 mg, administered intramuscularly with prompt resolution of her hypotension. Her course after RIT was uneventful, and she reached a maintenance dose of 0.5 mL of concentrate.”

Modified One Day Protocol: Reduced SR Rate When Target Dose Decreased to 0.1 ml of 1:10v/v

Comparison of RIT protocols with different final target doses*

Dose ≥ 0.2 ml of 1:10 v/v: SR 18.1% (n=72):
Dose 0.1 ml of 1:10 v/v : SR 7.2% (n=111):, all mild (no epinephrine)

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Concentration (volume:volume)</th>
<th>Volume (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1:10,000</td>
<td>0.3</td>
</tr>
<tr>
<td>30</td>
<td>1:1,000</td>
<td>0.3</td>
</tr>
<tr>
<td>60</td>
<td>1:100</td>
<td>0.1</td>
</tr>
<tr>
<td>90</td>
<td>1:100</td>
<td>0.3</td>
</tr>
<tr>
<td>120</td>
<td>1:10</td>
<td>0.1</td>
</tr>
</tbody>
</table>

All patients observed 90 minutes after final dose

*Alvares M et al. AAAAI 2012 Orlando
Slide provided and modified with permission David Khan. MD
**Recommended AIT build-up protocol following 2 hour RIT**

<table>
<thead>
<tr>
<th>Week</th>
<th>Concentration</th>
<th>Volume (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (Day of RIT)</td>
<td>1:10 v:v</td>
<td>0.1</td>
</tr>
<tr>
<td>1</td>
<td>1:10 v:v</td>
<td>0.1</td>
</tr>
<tr>
<td>2</td>
<td>1:10 v:v</td>
<td>0.2</td>
</tr>
<tr>
<td>3</td>
<td>1:1 v:v (concentrate)</td>
<td>0.05</td>
</tr>
<tr>
<td>4</td>
<td>1:1 v:v</td>
<td>0.1</td>
</tr>
<tr>
<td>5</td>
<td>1:1 v:v</td>
<td>0.2</td>
</tr>
<tr>
<td>6</td>
<td>1:1 v:v</td>
<td>0.3</td>
</tr>
<tr>
<td>7</td>
<td>1:1 v:v</td>
<td>0.4</td>
</tr>
<tr>
<td>8</td>
<td>1:1 v:v</td>
<td>0.5</td>
</tr>
<tr>
<td>10</td>
<td>1:1 v:v</td>
<td>0.5</td>
</tr>
<tr>
<td>13</td>
<td>1:1 v:v</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Pre-med of prednisone 40 mg for 1st post RIT dose

Generally recommend all pts take AH during build-up

Maintenance dose at 8 weeks with weekly post-RIT build-up (4 weeks with twice weekly build-up)

---

Alvare M et al. AAAAI 2012 Orlando
Slide provided and modified with permission David Khan. MD
Subcutaneous Venom Rush Schedule (VIT)

- Ultrarush stinging insect protocols achieve the maintenance dose in 2.5 to 4 hours
- VIT not associated with a higher incidence of SR as inhalant RIT
- May be well tolerated in ‘high-risk’ patients (e.g. SR with conventional venom IT) \(^1,2\)
- Conflicting data on safety of fire ant (FA) RIT without premedication
  - 1-day FA RIT: 37 pts without premedication reported 24.3% experienced SR most being urticaria and pruritus.\(^3\)
  - “Further studies are needed to clarify the risk of fire ant rush immunotherapy, and premedication might be considered.” *(from the 2011 Allergen Immunotherapy Practice Parameter 3rd Update)*

Subcutaneous Cluster Schedule

- Cluster entails administering several injections at increasing doses (generally 2-3 per visit) sequentially in a single day of treatment on nonconsecutive days.
- Cluster schedule associated with the same or a slightly increased frequency of SRs compared with conventional schedules.
- Few studies compare safety and most used single allergen: *can safety be extrapolated to multiallergen?*

---

APPENDIX 5. Example of a cluster immunotherapy schedule

<table>
<thead>
<tr>
<th>Visit</th>
<th>Dose (mL)</th>
<th>Concentration as dilution of maintenance vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.10</td>
<td>1:1000 vol/vol</td>
</tr>
<tr>
<td></td>
<td>0.40</td>
<td>1:100 vol/vol</td>
</tr>
<tr>
<td></td>
<td>0.10</td>
<td>1:100 vol/vol</td>
</tr>
<tr>
<td>2</td>
<td>0.20</td>
<td>1:100 vol/vol</td>
</tr>
<tr>
<td></td>
<td>0.40</td>
<td>1:100 vol/vol</td>
</tr>
<tr>
<td></td>
<td>0.07</td>
<td>1:10 vol/vol</td>
</tr>
<tr>
<td>3</td>
<td>0.10</td>
<td>1:10 vol/vol</td>
</tr>
<tr>
<td></td>
<td>0.15</td>
<td>1:10 vol/vol</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>1:10 vol/vol</td>
</tr>
<tr>
<td>4</td>
<td>0.35</td>
<td>1:10 vol/vol</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>1:1 vol/vol</td>
</tr>
<tr>
<td>5</td>
<td>0.07</td>
<td>1:1 vol/vol</td>
</tr>
<tr>
<td></td>
<td>0.10</td>
<td>1:1 vol/vol</td>
</tr>
<tr>
<td>6</td>
<td>0.15</td>
<td>1:1 vol/vol</td>
</tr>
<tr>
<td></td>
<td>0.20</td>
<td>1:1 vol/vol</td>
</tr>
<tr>
<td>7</td>
<td>0.30</td>
<td>1:1 vol/vol</td>
</tr>
<tr>
<td></td>
<td>0.40</td>
<td>1:1 vol/vol</td>
</tr>
<tr>
<td>8</td>
<td>0.50</td>
<td>1:1 vol/vol</td>
</tr>
</tbody>
</table>

Example of a 8 visit 18 injection schedule in the 2nd and 3rd ITPP updates*

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Studies Comparing Cluster and Conventional Immunotherapy Schedule

- DBPC study of 239 pts with dust mite AR ± asthma comparing 6-week cluster with a 12-week conventional schedule found:\(^1\)
  - No differences between the 2 schedules in terms of AEs
  - Improved clinical and objective parameters in the cluster 6 weeks before conventional group

Randomized study of 96 patients with dust mite AR comparing 6 week cluster with 14 week conventional found:\(^2\)
- Cluster reduced time to maintenance dose by 57%
- Earlier symptom/medication reduction.
- No differences in SRs compared with conventional schedule.

Systemic reactions with aeroallergen cluster immunotherapy in a clinical practice

**Methods:** A retrospective, observational review in a large, multicenter group regarding cluster IT safety

Maintenance dose based on AIPP guidelines, most premedicated

**Results:** Data from 441 cluster patients. 48 patients (10.9%) experienced SRs

Based on the WAO SCIT SR Grading System,

- 18 grade 1 reactions (38.3%),
- 23 grade 2 reactions (48.9%),
- 5 grade 3 reactions (10.6%),

Compared with clinics conventional IT during 2-yr period with 12,963 receiving SIT:

SR rate 0.043% of IT visits and 2.2% of patients

Higher systemic reaction rate with aeroallergen cluster immunotherapy in a clinical practice

- **Risk factors** for a systemic reaction included: female sex, asthma, age 21 to 40 years, and inclusion of certain allergens in the immunotherapy vaccine (grass, weed, cat, & dog).

- **Conclusions** Cluster buildup may lead to a higher rate of systemic reactions. Identifying risk factors for systemic reactions will help improve the safety of cluster immunotherapy.

**Table 7. Concentration of Immunotherapy Extract Leading to Systemic Reactions**

<table>
<thead>
<tr>
<th>Concentration of extract (vol:vol)</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1,000</td>
<td>0 (0)</td>
</tr>
<tr>
<td>1:100</td>
<td>6 (12.5)</td>
</tr>
<tr>
<td>1:10</td>
<td>25 (52.1)</td>
</tr>
<tr>
<td>1:1</td>
<td>17 (35.4)</td>
</tr>
</tbody>
</table>

**Table 8. Time from Eliciting Injection until Onset of Reaction**

<table>
<thead>
<tr>
<th>Time until onset of reaction (minutes)</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15</td>
<td>6 (13.3)</td>
</tr>
<tr>
<td>15–30</td>
<td>14 (31.1)</td>
</tr>
<tr>
<td>31–60</td>
<td>12 (26.7)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>13 (28.8)</td>
</tr>
</tbody>
</table>

Multiallergen Cluster SR Rate vs. Conventional Schedule in Patients with a High Degree of STR

**Study:** Controlled retrospective analysis of SR rate in a sample of cluster versus conventional schedule SCIT pts.

Patients had high degree of STR: had to have at least ≥ 5mm wheal on PST to dust mites, cat, dog, or ragweed, plus at least one additional inhalant allergen.

AR ± controlled asthma: PEFR and pre-injection questionnaire before AIT administration

Cluster schedule 8 visits and 18 step protocol from ITPP 2nd Update

Both groups premedicated with an antihistamine and montelukast at least 2 hours prior to AIT injection with exception of one conventional pt pretreated with monteleukast alone.

Systemic Reactions in a Sample of Multiallergen Cluster vs. Conventional Schedule Patients

• Total of 2,157 injections between the two groups, 634 in the cluster group and 1,523 in the conventional group.
• No statistically significant difference in the proportion of SR between the cluster group as compared to the conventional group per patient ( p=0.414)
  • Cluster (21): 4 SR in 3 patients.
    • 14.3% of patients and 0.6% of injections
  • Conventional (20): 6 SR in 6 patients.
    • 30% of patients and 0.3% of injections
• Office historical SR rate (2008): 9 SR in ~4,160 injections- 0.2% per injection.

Premedication with accelerated immunotherapy schedules.

Summary Statement 57: Premedication before cluster and rush immunotherapy with aeroallergens might reduce the rate of systemic reactions. Combination therapy is effective in reducing systemic and local reactions during accelerated immunotherapy build-up protocols. A


Procedure for Rush and Cluster Immunotherapy

Premedication

**Rush Immunotherapy (RIT)**

Patients receiving 1 or 2-day RIT should receive premedication starting 2 days prior to the procedure to reduce the likelihood of a systemic reaction.

- **H-1 Antagonist**
  - Cetirizine
  - Fexofenadine
  - Diphenhydramine

- **H-2 Antagonist**
  - Ranitidine

- **Corticosteroid**
  - Prednisone
  - Leukotriene receptor antagonist
  - Montelukast
Measures to Improve Safety Premedication

Antihistamines

– Studies with RIT & cluster suggest decreased incidence of local and SRs with inhalant and VIT

– Conventional IT:
  • One DBPC study found premedication with fexofenadine reduced # of severe SRs, ↑ number of pts who reached TMD & ↓ time to TMD

Leukotriene receptor antagonist

– Anecdotal reports of reductions in SR rates. One DBPC study demonstrated ↓ LLR during venom RIT with moneleukast

1. Ohashi et al, Ann Allergy Asthma Immunol 2006; 96
2. Wohrl et al., Int Arch Allergy Immunol 2007;144:137-42
Premedication with montelukast reduces local reactions of allergen immunotherapy

- **Methods:** 15 pts with hymenoptera anaphylaxis received 19 injections administered over 5 consecutive days. Counted # of injections until an LR of >3 cm occurred. Randomized to 3 treatment groups: premedication with placebo, 10 mg montelukast or 5 mg of desloratadine.

- **Results:** Compared with placebo, LRs (>3 cm) was significantly delayed by montelukast (p < 0.01) but not by desloratadine (p = 0.19).
  - Difference between montelukast and desloratadine was close to significant (p = 0.054).

- **Conclusion:** Montelukast can be useful in the prevention of LRs after specific immunotherapy.

Wohrl et al, Int Arch Allergy Immunol 2007; 144:137-142
Effectiveness of antihistamine premedication in specific cluster immunotherapy: A DBPC study.

**Methods:** DBPCS of 45 pts with grass or birch pollen SAR. Pts randomized to receive either loratadine 10 mg (N=21) or placebo (N=24) 2 hours before the first injection of each visit. Injections given once a week.

Target dose: 23 µg of *Bet v 1* or 25 µg *Phl p 5*

**Results:** SR in 33% of loratadine and 79% placebo groups. SR more severe in placebo group. Local reactions were significantly smaller in the loratadine group between 30 minutes.

**Conclusion:** The authors noted that one would expect a higher degree of severe SR if antihistamines were masking mild reactions and no dose modifications were made.

• **Summary Statement 58:** Omalizumab pretreatment has been shown to improve the safety and tolerability of cluster and rush immunotherapy schedules in patients with moderate-persistent asthma and allergic rhinitis, respectively. Additionally, omalizumab used in combination with immunotherapy has been shown to be effective in improving symptom scores compared to immunotherapy alone. A

Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced SAR

Methods: DBPC study of adult ragweed-AR treated with 9 weeks of omalizumab or placebo, then by 1-day RIT or placebo IT and 12 week follow-up

Results:

– Omalizumab resulted in a 5-fold decrease risk of anaphylaxis caused by RIT (OR, 0.17; P = .026).
– On an ITT basis, patients IT plus omalizumab showed a significant improvement in severity scores compared with IT alone (P = .044).

Conclusion: Omalizumab pretreatment may allow rapid and higher doses of IT to be given more safely and with greater efficacy to patients with allergic diseases.

Effect of pretreatment with omalizumab on the tolerability of SIT in allergic asthma

DBPC study 248 patients with at least moderate persistent allergic asthma inadequately controlled with inhaled corticosteroids randomized to receive with omalizumab or placebo, followed by SIT to at least 1 of 3 perennial allergens (cat, dog, & HDM)

FIG 1. Study design.

Effect of 16 week pretreatment with omalizumab on the tolerability of SIT in moderate persistent allergic asthma

- Significantly fewer and less severe SRs in omalizumab t group
- Antihistamine did not effect SR rate in either group
- Significantly higher proportion of patients reached TMD: 87.3% vs. 72.1% of control p = 0.004

Accelerated Immunotherapy Schedules
Onset of Efficacy

Time course of improvement. Summary Statement 22: Clinical and physiological improvement can be demonstrated very shortly after the patient reaches a maintenance dose. A

Effect of RIT on airway inflammation and AHR after bronchoprovocation with allergen in asthma.

- **Protocol:** 8 dust mite-allergic asthma pts treated with RIT vs. 6 untreated controls. Protocol included premedication with antihistamine and dose increment modified for LR> 8 cm.

- **Efficacy parameters studied:** Laboratory studies performed at baseline and 6 months after RIT : total & EG2 eosinophils, sputum ECP

- **Results:** All of the parameters studied after 6 months of RIT were significantly changed in the RIT group.

- **Symptoms scores** improved significantly after one month from baseline and showed progressive improvement through 6 months. Similar pattern seen in PEF measurements.

Kohno et al, J Allergy Clin Immunol 1998; 102 (6) 927-9349
Cluster Immunotherapy: Immunological changes at 5 weeks predictive of 52 weeks

- 3 studies (28 pts each) that investigated dose response of cat or dog extract compared placebo, 0.5, 3 and 15 mcg of Fel d 1\(^1,2\) or Can f 1\(^3\)
- Found 15 mcg had the greatest/most consistent efficacy in terms of objective parameters
- Immunological changes at 5 weeks reflective of 52 weeks
- Loaratadine, Loratadine + zafirlucast or loratadine +zafirluscast 2 hrs before: 1 SR in 3 studies-urticaria 1\(^{st}\) dose in vial 1 (loratadine +zafirlucast) \(^2\)

1. Ewbank JACI 2003; 111: 155-161
2. Nanda et al, JACI; 2005 114: 1339-1344
3. Lent et al, JACI 2006 118: 1249-125
Cat Immunotherapy Objective Parameters: Dose and Timing

**Titrated Nasal Challenge**

**End Point Dose of Cat Extract of Titrated Prick Skin Tests**

**Cat-Specific IgG₄**

Dose Response:
- 5 weeks $p = 0.014$
- 1 year $p < 0.0001$

Maintenance dose of Fel d 1
Effects of different up-dosing regimens for hymenoptera venom immunotherapy on serum CTLA-4 and IL-10

Methods: to assess the effects on CTLA-4 of 94 pts who received VIT via different induction protocols: conventional (6 weeks) 50 pts, rush (3 days) 20 pts or ultra rush (1 day) 24 pts. Sera collected at baseline and at the end of the induction phase.

Results: Soluble CTLA-4 significantly decreased at the end of the induction, irrespective of protocol. In parallel, IL-10 significantly increased at the end of the induction.

Summary: Alternative Schedules & Premedication

• **Aeroallergen RIT** - greater risk, cluster - data conflicting

• **Venom RIT** appears as safe as conventional with no predmedication - but verdict out on fire ant

• **Risk Factors For Systemic Reaction With Accelerated AIT**
  - Degree of skin test reactivity
    - Portnoy et al found that the most important predictor of a systemic reaction was the initial wheal size.
    - Bousquet et al found a correlation with STR & SR
  - FEV$_1$ < 80% predicted
  - Dose: increased SR with > vial 2 (1:10 v/v) 0.1 ml

• Premedication reduced SR rate in RIT & Cluster aeroallergen studies

• Premedication does not increase severity or frequency of SR by masking early warnings.

• Clinical efficacy can be seen early with accelerated AIT
We received a request to review services provided to you on 06/11/2012 - 07/16/2012 by Allergy & Asthma Center 5333 N Dixie Hwy Ste 210 Oakland Park, FL 33334-3454. We have denied this request after thoroughly reviewing all available information.

This decision was based on:

- A physician review.

Based on Medical Director review of the submitted information, rapid desensitization CPT 95180 (a form of allergy treatment) is determined to be not Medically Necessary. Per review of Humana Medical Coverage Policy/Allergy Treatment, which can be viewed at www.humana.com, treating allergic rhinitis does not meet the coverage criteria. Humana members MAY be eligible under the Plan for rapid desensitization (e.g., rush or cluster immunotherapy) for the following indications: • Hymenoptera (insects such as wasps, hornets, bees, fire ants) hypersensitivity; OR • IgE antibodies to a medically necessary drug that cannot be treated with alternative medications. Your Plan contains a direct exclusion for services that are not Medically Necessary. Therefore, this request has been denied.