AR - Management

1. Allergen avoidance
2. Pharmacotherapy
   - Antihistamines
   - Intranasal corticosteroids (INCS)
   - Other medications
3. Immunotherapy
2. Management - Pharmacotherapy

- **Intermittent AR**
  - Sneeze, Itching
  - Minimal drainage
  - **Oral Antihistamine**
    - +/- Saline spray
  - **Immunotherapy**
    - If Mild/Mod/No Asthma

- **Persistent AR**
  - Congestion, Drainage
  - +/- Sneeze, Itching
  - **Nasal Corticosteroid**
    - Antihistamine prn
  - **Nasal Corticosteroid**
    - + Regular Antihistamine
    - + Saline spray

- **If Mild/Mod/No Asthma**
  - **Immunotherapy**
  - **Nasal Corticosteroid**
  - **Antihistamine** prn
2. Management - Pharmacotherapy

- Antihistamines (second generation)
  - Blocks H1 receptor
  - Suspension
    - Cetirizine (Zyrtec) >12mo
    - Loratidine (Claratyne) >12mo
    - Desloratadine (Aerius) > 12mo; >6mo for hives
  - Effective against symptoms mediated by histamine
    - Rhinorrhoea, sneezing, nasal itching and eye symptoms
    - Less effective against nasal congestion

Bousquet et al. ARIA 2008. Allergy 2008: 63 (Sup 86): 8-160
2. Management - Pharmacotherapy

- **Intranasal Corticosteroid**
  - **Efficacy**
    - Acts by suppressing inflammation at multiple points in the inflammatory cascade\(^1\)
    - The most efficacious drug available for both allergic and non-allergic rhinitis\(^2\)
    - High concentrations can be achieved at the nasal mucosa receptor sites with minimal systemic side effects\(^2\)
    - Effective against both nasal congestion and ocular symptoms\(^2\)
  - Meta-analysis shows intranasal steroids are superior to antihistamines\(^3,4\)

2. Management - Pharmacotherapy

- Intranasal Corticosteroid
  - Over-the-counter
    - Budesonide (Rhinocort aqueous) 32 mcg
    - Fluticasone propionate (Beconase Allergy & Hayfever 24) 50 mcg
  - Prescription only
    - Budesonide (Rhinocort) 64 mcg
    - Mometasone (Nasonex) 50 mcg
    - Fluticasone furoate (Avamys) 27.5 mcg
  - Onset of action
    - 7-8 hours after dosing, but maximum efficacy takes up to 2 weeks
    - (Mometasone >) Budesonide > Fluticasone

Bousquet et al. ARIA 2008. Allergy 2008: 63 (Sup 86): 8-160
2. Management - Pharmacotherapy

- Intranasal Corticosteroid
  - Side effects
    - Long-term use is free of concerns a/w oral steroids\(^1,2\)
      - Beclomethasone: Inhibited growth at 1yr by 1cm in 6-9yr olds
      - Budesonide, mometasone, fluticasone propionate: No effect on HPA axis or growth at 1 year
  - Local side effects\(^3,4\)
    - Dryness, nasal irritation, sore throat (10% of users)
    - Epistaxis due to spraying onto Little’s area – emphasise correct technique

2. Management - Pharmacotherapy

(a)
1. Shake bottle well
2. Look down
3. Using RIGHT hand for LEFT nostril put nozzle just inside nose aiming towards outside wall
4. Squirt once or twice (2 different directions)
5. Change hands and repeat for other side
6. DO NOT SNIFF HARD

2. Management - Pharmacotherapy

2. Management - Pharmacotherapy

- Other medications
  - Saline irrigation
    - Use prior to intranasal corticosteroids
    - Useful in clearing mucous and improving ciliary function
  - Leukotriene receptor antagonists
    - More effective than placebo, equivalent to oral antihistamines, but inferior to nasal steroids
  - Combination therapy
    - Limited data on oral antihistamines + intranasal steroids
    - Oral antihistamines + leukotriene antagonists = does not increase efficacy of any single drug (and not more effective than intranasal steroids)

References:
2. Management - Pharmacotherapy

- Other medications
  - **Cromones**\(^1,2\)
    - Inhibit the degranulation of sensitised mast cells, inhibiting the release of inflammatory and allergic mediators.
    - Cromoglycate and nedocromil are available in intranasal and ocular preparations
    - Weakly effective in rhinitis
  - **Anticholinergics**\(^1,2\)
    - Topical ipratropium bromide; needs to be used 3x/day
    - Decreases rhinorrhoea but no effect on other nasal symptoms
    - Useful for autonomic rhinitis with predominant watery rhinorrhoea; or persistent watery rhinorrhoea in AR despite intranasal steroids.

2. Management - Pharmacotherapy

- Other medications
  - **Decongestants (topical/oral)**\(^1,2\)
    - **Intranasal**: Alpha1-agonist (ephedrine) and alpha2-agonist (xylometazoline) are sympathomimetics that increase nasal vasoconstriction → effective for nasal obstruction in both AR and non-AR
    - **Oral**: Pseudoephedrine → weakly effective in reducing nasal obstruction. Not generally recommended.
    - Does not improve sneezing, nasal itching or rhinorrhea
    - Prolonged use (> 10 days) may lead to tachyphylaxis and rebound swelling of the nasal mucosa (‘drug-induced rhinitis’)

AR - Management

1. Allergen avoidance
2. Pharmacotherapy
   - Antihistamines
   - Intranasal corticosteroids (INCS)
   - Other medications
3. Immunotherapy
3. Management - Immunotherapy

- **What is it**\(^1\):
  - Gradual administration of gradual increasing quantities of an allergen extract to an allergic subject.
  - This ameliorates the symptoms associated with subsequent exposure to the causative allergen.

- **Possible mechanisms of immunotherapy**\(^2\):
  - Altered T-cell cytokine balance (switch from TH2 to TH1 response).
  - Induction of (blocking) IgG antibodies.
  - Reduction of allergen-specific IgE levels (long term).
  - Induction of regulatory T cells → secretes IL10 & TGF-beta.
  - T-cell anergy.
  - Reduced recruitment of effector cells.

---

3. Management - Immunotherapy

- Subcutaneous injections
  - Weekly injections for 12-16 weeks (updosing)
  - Monthly injections for 3 years
  - 30-60 minute period of observation after each injection
  - Cost to patient ~$250-$300/allergen/year (pricing based on Stallergenes products)

- Sublingual
  - ‘Sublingual-swallow’: allergen drops/tablets are held under the tongue for 1-2 mins, then swallows
  - Daily dose for 11 days (updosing)
  - Maintenance drops 3x/week or every day
  - Cost to patient ~ $600-$750/allergen/year (pricing based on Stallergenes products)
3. Management - Immunotherapy

- **Eligibility**
  - Clinical history of allergy
  - Documented allergen-specific sensitisation
  - Allergen used for immunotherapy must be clinically relevant to clinical history
  - Poor response to pharmacotherapy

- **Contraindications**
  - Unstable/severe asthma
  - Concomitant illness
    - Autoimmune disease
    - Malignancy
    - Severe heart disease
    - Severe pulmonary disease
  - Pregnancy
  - Beta-blocker treatment
  - Poor adherence

3. Management - Immunotherapy

● **Safety**
  
  ● Localised reaction
    
    ● SCIT: Swelling/discomfort at site; nodules at site
    
    ● SLIT: Oral mucosa reactions
  
  ● Systemic
    
    ● Urticaria, angioedema, anaphylaxis
    
    ● In UK between 1957-1986: 26 fatal reactions were caused by immunotherapy. Indication for treatment documented in 16 out of 17 cases cited asthma.

2. Canonica et al. Allergy 2009. 64 (Supp 91): 1-59
### 3. Management - Immunotherapy

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>SCIT</th>
<th>SLIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local reactions</td>
<td></td>
<td>Up to 75%</td>
</tr>
<tr>
<td>Systemic reactions</td>
<td>0.05-3.2% of doses</td>
<td>0.06% of doses</td>
</tr>
<tr>
<td>Serious adverse reactions</td>
<td></td>
<td>1.4 per 100,000 doses.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 per 285 patients.</td>
</tr>
<tr>
<td>Near-fatal event *</td>
<td>5.4 per 1 million doses</td>
<td></td>
</tr>
<tr>
<td>Fatalities</td>
<td>1 in 2-2.5 million doses</td>
<td>None reported.</td>
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</table>

*Defined as severe respiratory compromise and/or fall in BP requiring emergency adrenaline treatment.

### SUMMARY OF IMMUNOTHERAPY

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AR</strong></td>
<td></td>
</tr>
<tr>
<td>• <strong>Effective</strong> for seasonal AR (Calderon 2007, Cochrane review)</td>
<td></td>
</tr>
<tr>
<td><strong>SCIT</strong></td>
<td></td>
</tr>
<tr>
<td>• Children: <strong>inconclusive</strong> (Roder 2008, systemic review of RCTs)</td>
<td></td>
</tr>
<tr>
<td><strong>SLIT</strong></td>
<td></td>
</tr>
<tr>
<td>• <strong>Effective</strong> for AR (Wilson 2003, Cochrane review)</td>
<td></td>
</tr>
<tr>
<td>• Children: <strong>possibly effective</strong> (Penagos 2006, meta-analysis)</td>
<td></td>
</tr>
</tbody>
</table>

2. Roder et al. Pediatric Allergy and Immunology 2008;19:197-207.
SCIT for seasonal AR

Calderon et al. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database of Systematic Reviews 2007. [DBPCCRT]

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment N</th>
<th>Mean(SD)</th>
<th>Control N</th>
<th>Mean(SD)</th>
<th>Std. Mean Difference IV,Random,95% CI</th>
<th>Weight</th>
<th>Std. Mean Difference IV,Random,95% CI</th>
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<tbody>
<tr>
<td>Balda 1998</td>
<td>49</td>
<td>6.56 (1.43)</td>
<td>56</td>
<td>9.07 (8.19)</td>
<td></td>
<td>9.3%</td>
<td>-0.27 [-0.65, 0.12]</td>
</tr>
<tr>
<td>Bodtger 2002</td>
<td>16</td>
<td>2.2 (1)</td>
<td>17</td>
<td>3.3 (1.4)</td>
<td></td>
<td>5.7%</td>
<td>-0.88 [-1.60, -0.16]</td>
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<tr>
<td>Bousquet 1990</td>
<td>20</td>
<td>63.6 (32.5)</td>
<td>18</td>
<td>108.6 (33.2)</td>
<td></td>
<td>5.8%</td>
<td>-1.34 [-2.05, -0.63]</td>
</tr>
<tr>
<td>Brewezynski 1999</td>
<td>10</td>
<td>59.5 (32.6)</td>
<td>8</td>
<td>122.4 (85.13)</td>
<td></td>
<td>3.8%</td>
<td>-0.98 [-1.97, 0.02]</td>
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<tr>
<td>Corrigan 2005</td>
<td>77</td>
<td>166.5 (114.93)</td>
<td>77</td>
<td>218 (135.39)</td>
<td></td>
<td>10.1%</td>
<td>-0.41 [-0.73, -0.09]</td>
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<tr>
<td>Drachenberg 2001</td>
<td>74</td>
<td>0.75 (0.44)</td>
<td>50</td>
<td>0.95 (0.41)</td>
<td></td>
<td>9.6%</td>
<td>-0.46 [-0.83, -0.10]</td>
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<tr>
<td>Ferrer 2005</td>
<td>22</td>
<td>0.44 (0.32)</td>
<td>20</td>
<td>0.8 (0.54)</td>
<td></td>
<td>6.5%</td>
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<td>Frew 2006</td>
<td>187</td>
<td>3.31 (2.42)</td>
<td>89</td>
<td>4.59 (2.93)</td>
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<td>10.8%</td>
<td>-0.49 [-0.75, -0.24]</td>
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<tr>
<td>Jutel 2005</td>
<td>29</td>
<td>3.93 (3.28)</td>
<td>28</td>
<td>5.82 (3.44)</td>
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<td>7.6%</td>
<td>-0.55 [-1.08, -0.02]</td>
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<td>Meriney 1986</td>
<td>10</td>
<td>3.51 (2.97)</td>
<td>10</td>
<td>8.43 (4.24)</td>
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<td>3.9%</td>
<td>-1.29 [-2.27, -0.30]</td>
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<tr>
<td>Orlolani 1984</td>
<td>8</td>
<td>2.01 (0.57)</td>
<td>7</td>
<td>5.86 (1.63)</td>
<td></td>
<td>1.8%</td>
<td>-3.06 [-4.69, -1.43]</td>
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<td>Orlolani 1994</td>
<td>18</td>
<td>0.61 (0.12)</td>
<td>17</td>
<td>2.3 (0.98)</td>
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<td>4.5%</td>
<td>-2.40 [-3.29, -1.51]</td>
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<td>Varney 1991</td>
<td>19</td>
<td>1531 (1875)</td>
<td>16</td>
<td>2230 (856)</td>
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<td>6.1%</td>
<td>-0.46 [-1.13, 0.22]</td>
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<td>Walker 2001</td>
<td>17</td>
<td>-1212 (2632)</td>
<td>13</td>
<td>-115 (1159)</td>
<td></td>
<td>5.6%</td>
<td>-0.50 [-1.24, 0.23]</td>
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<td>Zenner 1997</td>
<td>41</td>
<td>82.24 (64.38)</td>
<td>40</td>
<td>115.98 (83.67)</td>
<td></td>
<td>8.6%</td>
<td>-0.45 [-0.89, -0.01]</td>
</tr>
</tbody>
</table>

Total (95% CI) 597
Heterogeneity: $\tau^2 = 0.12; \chi^2 = 38.05, df = 14 (P = 0.00051); I^2 = 59\%$
Test for overall effect: $Z = 6.10, P < 0.000001$

100.0% -0.73 [-0.97, -0.50]

Favours treatment
Favours control
SCIT for seasonal AR
Calderon et al. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database of Systematic Reviews 2007. [DBPCRT]

1. No studies exclusively in children
2. 9 studies extended age range to subjects < 18yo, but no data assessing specific outcomes were reported
2008 Systemic review of RCT (6 trials)

<table>
<thead>
<tr>
<th>Article</th>
<th>Efficacy demonstrated</th>
<th>Methodological quality</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous immunotherapy</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sanders (1966) (11)</td>
<td>Yes</td>
<td>H*</td>
<td>Conflicting</td>
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<tr>
<td>Möller et al. (2002) (3)</td>
<td>Yes</td>
<td>L*</td>
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<tr>
<td>Fontana et al. (1966) (12)</td>
<td>No</td>
<td>L*</td>
<td></td>
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<tr>
<td>Weisnagel (1979) (13)</td>
<td>No</td>
<td>L*</td>
<td></td>
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<tr>
<td>Dreborg et al. (1986) (14)</td>
<td>No</td>
<td>L*</td>
<td></td>
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<tr>
<td>Urbanek et al. (1991) (15)</td>
<td>No</td>
<td>L*</td>
<td></td>
</tr>
</tbody>
</table>
## SLIT FOR AR

Wilson et al. Sublingual immunotherapy for allergic rhinitis.
Cochrane Database Syst Rev. 2003 [DBPCCRT]

<table>
<thead>
<tr>
<th>Study or subgroups</th>
<th>SLIT</th>
<th>Placebo</th>
<th>Mean Diff (95% CI)</th>
<th>21 trials</th>
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<td>Andre 2002</td>
<td>55</td>
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<td>3.32 (2.69)</td>
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<td>Artner 2001</td>
<td>10</td>
<td>1.8 (3.76)</td>
<td>30</td>
<td>5.34 (2.57)</td>
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<td>Bahreroder 2001</td>
<td>40</td>
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<td>10</td>
<td>0.4 (0.3)</td>
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<td>Casasnovas 1999</td>
<td>9</td>
<td>5.46 (3.50)</td>
<td>6</td>
<td>10.58 (6.13)</td>
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<td>D’Ambrosio 1996</td>
<td>15</td>
<td>2.9 (2.59)</td>
<td>15</td>
<td>408.9 (15.35)</td>
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<tr>
<td>D’Ambrosio 1999</td>
<td>14</td>
<td>5.9 (3.4)</td>
<td>16</td>
<td>887.06 (67.83)</td>
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<td>10</td>
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<td>Hirsh 1997</td>
<td>15</td>
<td>0.98 (0.13)</td>
<td>15</td>
<td>0.5 (0.47)</td>
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<td>Hordhi 1998</td>
<td>25</td>
<td>3.2 (0.95)</td>
<td>36</td>
<td>5.13 (4.9)</td>
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<td>La Fora 1999</td>
<td>21</td>
<td>1.21 (1.66)</td>
<td>21</td>
<td>1.41 (1.65)</td>
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<td>Li’s 2002</td>
<td>26</td>
<td>24.64 (23.26)</td>
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<td>26.65 (15.57)</td>
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<td>Hugan 1999</td>
<td>15</td>
<td>9.5 (6.45)</td>
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<td>0.47 (0.53)</td>
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<td>Nilson 1993</td>
<td>20</td>
<td>12.15 (6.86)</td>
<td>21</td>
<td>10.32 (3.56)</td>
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<td>Pardiag 1998</td>
<td>40</td>
<td>2 (0.46)</td>
<td>32</td>
<td>1.2 (0.75)</td>
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<td>Pelella 1999</td>
<td>15</td>
<td>6 (0.3)</td>
<td>15</td>
<td>15 (0.3)</td>
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<td>Predil 1999</td>
<td>31</td>
<td>2.33 (0.6)</td>
<td>32</td>
<td>2.05 (0.2)</td>
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<tr>
<td>Teli 1990</td>
<td>34</td>
<td>8 (0.5)</td>
<td>32</td>
<td>12 (0.5)</td>
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<tr>
<td>Travell 1995</td>
<td>25</td>
<td>87 (0.5)</td>
<td>15</td>
<td>102 (0.9)</td>
</tr>
<tr>
<td>Velander 2001</td>
<td>15</td>
<td>1.3 (1.58)</td>
<td>15</td>
<td>0.8 (0.5)</td>
</tr>
<tr>
<td>Velander 1998</td>
<td>34</td>
<td>1.36 (2.61)</td>
<td>32</td>
<td>1.67 (0.69)</td>
</tr>
</tbody>
</table>

Total (95% CI) | 484 | 475 | 100.0 % | -0.42 (-0.69, -0.35) |

Heterogeneity Test $\chi^2 = 7.37; df = 26; P = 0.0001; I^2 = 73%$

Test for overall effect $z = 3.85; P = 0.0001$
For children, no significant reduction in scores, but numbers were too small to make a reliable conclusion.
3. Management - Immunotherapy

● Efficacy

● SLIT for AR in paediatric patients (Meta-analysis 2006)¹
  ● Age 4-18 years
  ● 10 trials and 484 subjects
  ● SLIT significantly more effective than placebo
  ● However studies were heterogenous (study design, duration, outcome measures and inclusion criteria variability)

● However, 2 recent studies demonstrated no effect
  ● Grass pollen SLIT for children (low dose used)²
  ● HDM SLIT (reduction of allergic response to HDM)³

3. Management - Immunotherapy

- Immunotherapy in children with AR may
  - Reduce the development of new allergen sensitisation $^{1,2,3}$
  - Reduce the risk of developing asthma $^4$

Pollen immunotherapy reduces the risk of asthma (PAT study)

Referral to Allergist Immunologist

1. Medication is ineffective despite 3-6 month trial or causes adverse reaction.
2. Allergic rhinitis is complicated by a polyp.
3. Allergen desensitization is required.
4. Ongoing symptoms despite optimal topical nasal corticosteroid therapy and allergen avoidance.
5. Other severe allergic disease also presents (e.g. eczema, food allergy, asthma).
6. Refer all children under 3 years old.

Talk Overview

1. Background
2. Allergic rhinitis
3. Asthma
Asthma

1. AR and asthma
2. Management
   - Intranasal corticosteroids for AR
   - HDM avoidance
   - Subcutaneous immunotherapy
   - Sublingual immunotherapy
Asthma

1. AR and asthma
2. Management
   - Intranasal corticosteroids for AR
   - HDM avoidance
   - Subcutaneous immunotherapy
   - Sublingual immunotherapy
1. Of patients without rhinitis, asthma prevalence is $<2\%^1$
2. Of patients with rhinitis, 10-40% have asthma$^1$
3. Of patients with asthma, majority (75-80%) have rhinitis$^{2,3}$

AR increases the risk of developing asthma

  - Presence of doctor-diagnosed AR in infants was independently associated with a doubling of the risk of developing asthma by 11 years of age

  - 23-year follow-up of college students
  - Significantly more (10.5%) of the students originally diagnosed with AR went onto develop asthma
  - Compared with just 3.6% of those who did not originally have rhinitis
  - Rhinitis increased the risk of asthma development by 3 times more in both atopic and non-atopic subjects
AR is a RF for asthma control

- Compared to subjects with asthma alone, adults and children with asthma and AR:¹-⁶
  - Have ↑ asthma-related hospitalisations
  - Have ↑ GP visits
  - Incur higher asthma drug costs
  - Have ↑ absence from work and decreased productivity

‘One airway, one disease’

Bousquet et al. ARIA 2008. Allergy 2008; 63 (Sup 86): 8-160
Allergens and asthma

- Most allergens are a/w nasal and bronchial symptoms, but differences have been observed
  - House dust mite and cat dander is a risk factor for both asthma and rhinitis
  - Pollen allergy, however, is not usually associated with asthma
  - Chest symptoms are not more commonly found in patients with seasonal AR than in non-rhinitis patients
- Asthma and bronchial hyper-responsiveness are more common and severe in perennial compared to seasonal rhinitis.

Asthma

1. AR and asthma
2. Management
   - Intranasal corticosteroids for AR
   - HDM avoidance
   - Subcutaneous immunotherapy
   - Sublingual immunotherapy
Does treatment of AR improve asthma symptoms and control?
14 SB/DBPCCR trials involving 477 subjects assessed

Meta-analysis for asthma outcomes did not show statistically significant benefit of INCS in asthma

However, favouring a beneficial effect of INCS treatment, were asthma symptom scores and FEV₁
Taramarcaz P, Gibson PG. Intranasal corticosteroids for asthma control in people with coexisting asthma and rhinitis. Cochrane Database of Systematic Reviews 2003, Issue 3.

### Analysis 1.5. Comparison 1 Intranasal Corticosteroids versus Intranasal Placebo: all rhinitis and asthma, Outcome 5 Asthma Symptom Score.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV, Fixed, 95% CI</td>
<td>IV, Fixed, 95% CI</td>
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<td>Corren 1992</td>
<td>10 -2.78 (2.68)</td>
<td>8 -2.64 (2.2)</td>
<td>-0.05 [-0.98, 0.88]</td>
<td>48.8 %</td>
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</tr>
<tr>
<td>Pedersen 1998</td>
<td>12 2.67 (1.07)</td>
<td>11 1.09 (1.39)</td>
<td>1.24 [0.33, 2.14]</td>
<td>51.2 %</td>
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</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>22</td>
<td>19</td>
<td>100.0 %</td>
<td>0.61 [-0.04, 1.26]</td>
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</tr>
<tr>
<td>Heterogeneity: Chi² = 3.78, df = 1 (P = 0.05); I² = 74%</td>
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<tr>
<td>Test for overall effect: Z = 1.83 (P = 0.067)</td>
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<td>2 Cross-over Study</td>
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<td>0</td>
<td>0.0 %</td>
<td>0.0 [0.0, 0.0]</td>
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<tr>
<td>Heterogeneity: not applicable</td>
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<td>Test for overall effect: not applicable</td>
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<td><strong>Total (95% CI)</strong></td>
<td>22</td>
<td>19</td>
<td>100.0 %</td>
<td>0.61 [-0.04, 1.26]</td>
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<td>Heterogeneity: Chi² = 3.78, df = 1 (P = 0.05); I² = 74%</td>
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<td>Test for overall effect: Z = 1.83 (P = 0.067)</td>
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</table>
Taramarcaz P, Gibson PG. Intranasal corticosteroids for asthma control in people with coexisting asthma and rhinitis. Cochrane Database of Systematic Reviews 2003, Issue 3.

Analysis 1.1. Comparison of Intranasal Corticosteroids versus Intranasal Placebo: all rhinitis and asthma, Outcome 1 FEV1.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
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<th>Weight</th>
<th>Std. Mean Difference</th>
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<td>N Mean(SD)</td>
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<td>N/Fixed, 95% CI</td>
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<td>1 Parallel Study</td>
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<td>10 3.17 (0.66)</td>
<td>8 2.88 (0.45)</td>
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<tr>
<td></td>
<td></td>
<td>17 80 (15)</td>
<td>19 84 (19)</td>
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<td>27.6 %</td>
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<tr>
<td></td>
<td></td>
<td>11 114 (10)</td>
<td>10 102 (16)</td>
<td>-</td>
<td>14.5 %</td>
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<tr>
<td></td>
<td></td>
<td>20 103.1 (5.5)</td>
<td>11 100.4 (5.3)</td>
<td>-</td>
<td>21.3 %</td>
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<tr>
<td></td>
<td></td>
<td>25 102.8 (8)</td>
<td>11 100.4 (5.3)</td>
<td>-</td>
<td>23.4 %</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>83 59</td>
<td>100.0 %</td>
<td>0.31 [-0.04, 0.65]</td>
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<tr>
<td></td>
<td></td>
<td>83 59</td>
<td>100.0 %</td>
<td>0.31 [-0.04, 0.65]</td>
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</table>

5 parallel studies
Asthma

1. AR and asthma
2. Management
   - Intranasal corticosteroids for AR
   - HDM avoidance
   - Subcutaneous immunotherapy
   - Sublingual immunotherapy
54 randomised trials and 3002 patients

- Physical methods (n=36)
  - Mattress encasings (n=26)
- Chemical methods (n=10)
- Physical & chemical methods (n=8)
Gøtzsche PC, Johansen HK. House dust mite control measures for asthma. Cochrane Database of Systematic Reviews 2008, Issue 2.
Gøtzsche PC, Johansen HK. House dust mite control measures for asthma. Cochrane Database of Systematic Reviews 2008, Issue 2.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Std Mean Difference (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chemical Mites</td>
<td>24 (24)</td>
<td>14 (15)</td>
<td>1.44 (0.56)</td>
<td>12.3</td>
</tr>
<tr>
<td>2. Mite Extermination</td>
<td>26 (27)</td>
<td>18 (18)</td>
<td>2.13 (0.75)</td>
<td>2.51</td>
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<tr>
<td>3. Mite Eradication</td>
<td>28 (28)</td>
<td>20 (20)</td>
<td>2.89 (1.1)</td>
<td>1.82</td>
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<tr>
<td>4. Mite Reduction</td>
<td>30 (30)</td>
<td>22 (22)</td>
<td>3.33 (2.5)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

**Subtotal (50%)**

**Subtotal (50%)**

**Total (100%)**

**Effect of treatment**

**Effect of control**
Gøtzsche PC, Johansen HK. House dust mite control measures for asthma. Cochrane Database of Systematic Reviews 2008, Issue 2.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Mean (SD)</th>
<th>Control</th>
<th>Mean (SD)</th>
<th>Std. Mean Difference (W, Fixed, 95% CI)</th>
<th>Weight</th>
<th>Std. Mean Difference (W, Fixed, 95% CI)</th>
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<tbody>
<tr>
<td>1 Chemical methods</td>
<td>Dietemann 1993</td>
<td>11</td>
<td>2 (0.35)</td>
<td>12</td>
<td>1.54 (0.45)</td>
<td>2.6%</td>
<td>0.69 (0.62, 1.75)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>11</td>
<td>12</td>
<td>-2.0%</td>
<td>-0.89 (0.92, 1.75)</td>
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<tr>
<td>2 Physical methods - parallel group studies</td>
<td>Davies 2007</td>
<td>63</td>
<td>473 (441)</td>
<td>63</td>
<td>496 (420)</td>
<td>12.5%</td>
<td>-0.04 (-0.09, 0.01)</td>
</tr>
<tr>
<td></td>
<td>Dharmage 2006</td>
<td>18</td>
<td>6.26 (9.16)</td>
<td>18</td>
<td>6.6 (9.22)</td>
<td>2.0%</td>
<td>0.26 (0.10, 0.32)</td>
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<tr>
<td></td>
<td>Halken 2003</td>
<td>26</td>
<td>227 (93)</td>
<td>21</td>
<td>291 (60)</td>
<td>4.6%</td>
<td>-0.28 (-0.55, 0.01)</td>
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<tr>
<td></td>
<td>Huss 1992</td>
<td>26</td>
<td>4.38 (3.71)</td>
<td>26</td>
<td>5.53 (3.79)</td>
<td>5.1%</td>
<td>-0.22 (-0.77, 0.32)</td>
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<tr>
<td></td>
<td>Walshaw 1985</td>
<td>22</td>
<td>2.18 (1.8)</td>
<td>20</td>
<td>3.56 (3.61)</td>
<td>4.6%</td>
<td>-0.48 (-1.10, 0.13)</td>
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<tr>
<td></td>
<td>Woodcock 2003</td>
<td>31</td>
<td>2.23 (2.93)</td>
<td>31</td>
<td>2.24 (2.81)</td>
<td>61.8%</td>
<td>-0.01 (-0.16, 0.15)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>464</td>
<td>456</td>
<td>9.9%</td>
<td>-0.07 (-0.20, 0.06)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Physical methods - crossover studies</td>
<td>Antonelli 1991</td>
<td>9</td>
<td>0.62 (0.05)</td>
<td>9</td>
<td>0.03 (0.06)</td>
<td>1.8%</td>
<td>-0.17 (-1.10, 0.75)</td>
</tr>
<tr>
<td></td>
<td>Versil 1988</td>
<td>12</td>
<td>6.81 (6.73)</td>
<td>13</td>
<td>9.13 (6.28)</td>
<td>2.5%</td>
<td>-0.30 (-1.07, 0.47)</td>
</tr>
<tr>
<td></td>
<td>Warner 1992</td>
<td>14</td>
<td>0.48 (0.67)</td>
<td>14</td>
<td>0.53 (0.94)</td>
<td>2.8%</td>
<td>-0.05 (-0.60, 0.56)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>36</td>
<td>71.1%</td>
<td>-0.37 (-0.64, 0.29)</td>
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<td></td>
<td></td>
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<tr>
<td>Total (95% CI)</td>
<td>511</td>
<td>504</td>
<td>100.0%</td>
<td>-0.06 (-0.18, 0.07)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Author’s conclusion

- “No effect of the interventions were found”
- “Chemical and physical methods aimed at reducing exposure to HDM allergens cannot be recommended”
Gøtzsche PC, Johansen HK. House dust mite control measures for asthma. Cochrane Database of Systematic Reviews 2008, Issue 2.

- Controversies and criticisms
  - 2 questions:
    - How effective are physical/chemical methods at reducing HDM levels in the environment?
    - Does reduction of HDM in the environment correspond with improved asthma control?
  - No subgroup analysis was performed on methods whereby actual reduction of HDM levels was achieved\(^1\)
    - Dust mite reduction achieved in only 17 of 54 trials
    - Dust mite reduction unsuccessful in 24 of 54 trials
    - Not measured/reported in 13 of 54 trials

This is relevant given the large range of methods employed to reduce dust mite

- **Physical (n=16):** protective encasements (impermeable/semi-permeable/plastic), hot water washes, HEPA-filters, vacuum cleaning, removal of reservoirs, removal of carpets, frequent linen-change, damp dusting, sun exposure and ventilation, steam cleaning, temperature and humidity control, airing bedroom, electrostatic precipitator, laminar airflow system, ioniser.

- **Chemical (n=6):** acaricides (natamycin, benzyl benzoate tannic acid, esdepallethin/piperonyl butoxide, pyrethrinoid/piperonyl butoxide; foam/spray/solution), liquid nitrogen, detergent.
Gøtzsche PC, Johansen HK. House dust mite control measures for asthma. Cochrane Database of Systematic Reviews 2008, Issue 2.

- Controversies and criticisms
  - Cochrane review excluded a large study by Morgan 2004 (NEJM) which reported positive results
  - 937 children used HDM impermeable covers, high filtration vacuum cleaners and were also advised to avoid passive smoking where appropriate. Children in intervention group had significantly more symptom-free days (3.39 vs 4.20 days/fortnight, p<0.001) and reduced ER visits
  - Authors excluded this because: not blinded, subjective positive results were given over the phone, intervention group had more home visits, objective outcomes like FEV1 and PEFR were similar in both groups, HDM allergen levels decreased by < 50%.


WATCH THIS SPACE……
Asthma

1. AR and asthma
2. Management
   - Intranasal corticosteroids for AR
   - HDM avoidance
   - Subcutaneous immunotherapy
   - Sublingual immunotherapy
Abramson MJ, Puy RM, Weiner JM. SCIT for asthma. Cochrane Database of Systematic Reviews 2003, Issue 4

- 75 randomised controlled trials and 3506 subjects
- Allergens
  - HDM 36, pollens 20, animal dander 10, Cladosporium mould 2, latex 1, multiple allergens 6
- Overall significant benefit found for
  - Reducing asthma symptoms, medication use and improvement of bronchial hyperreactivity.
Abramson MJ, Puy RM, Weiner JM. SCIT for asthma. Cochrane Database of Systematic Reviews 2003, Issue 4

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunotherapy</th>
<th>Placebo</th>
<th>Std. Mean Difference (95% CI)</th>
<th>No. of studies</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mucous hypersecretory</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
</tr>
<tr>
<td>2. Non-responsive</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
</tr>
<tr>
<td>3. High dose</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
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<tr>
<td>4. Low dose</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
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<tr>
<td>5. Moderate dose</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
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<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
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<tr>
<td>3. High dose</td>
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<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
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<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
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<td>5. Moderate dose</td>
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<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
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<td>0.3 (0.1-0.5)</td>
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<td>0.3 (0.1-0.5)</td>
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<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
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<tr>
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<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.1-0.5)</td>
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</table>
Abramson MJ, Puy RM, Weiner JM. SCIT for asthma. Cochrane Database of Systematic Reviews 2003, Issue 4

### Summary of Findings

#### Asthma medication scores

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunotherapy</th>
<th>Placebo</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
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<tbody>
<tr>
<td><strong>1</strong> Mite immunotherapy</td>
<td>Paranos 1997</td>
<td>7</td>
<td>1 (0.58)</td>
<td>7</td>
<td>2.43 (1.13)</td>
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<td>Franco 1995</td>
<td>24</td>
<td>0.5 (0.7)</td>
<td>25</td>
<td>0.8 (1.7)</td>
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<td>Torres Cost 1996</td>
<td>11</td>
<td>1 (0.9)</td>
<td>11</td>
<td>2.7 (1.5)</td>
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<td>Machiels 1999a</td>
<td>24</td>
<td>92.72 (7.87)</td>
<td>24</td>
<td>111.44 (9.18)</td>
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<td></td>
<td>Price 1984</td>
<td>13</td>
<td>91.2 (144.9)</td>
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<td>168.6 (144.9)</td>
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<td></td>
<td>Mundan 1999</td>
<td>10</td>
<td>3.9 (0)</td>
<td>11</td>
<td>5.24 (0)</td>
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<td>Sin 1996</td>
<td>7</td>
<td>1.57 (1.39)</td>
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<td>6.13 (3.04)</td>
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<td>Tabar 1999</td>
<td>44</td>
<td>0.6 (3.67)</td>
<td>19</td>
<td>4.09 (6.93)</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>140</td>
<td>102</td>
<td>-1.06 [-1.61, -0.52]</td>
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#### Pollen immunotherapy

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<th>Mean (SD)</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
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<tr>
<td><strong>2</strong> Pollen immunotherapy</td>
<td>Hill 1984</td>
<td>11</td>
<td>5.09 (3.78)</td>
<td>9</td>
<td>2.44 (3.13)</td>
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<td></td>
<td>Bousquet 1989</td>
<td>46</td>
<td>0.57 (0.9)</td>
<td>46</td>
<td>1.56 (1.3)</td>
</tr>
<tr>
<td></td>
<td>Dolz 1996</td>
<td>18</td>
<td>33.84 (33.89)</td>
<td>18</td>
<td>61.6 (32.88)</td>
</tr>
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<td></td>
<td>Cretecos 1996</td>
<td>37</td>
<td>19 (48.66)</td>
<td>40</td>
<td>43 (50.6)</td>
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<tr>
<td></td>
<td>Sin 1996</td>
<td>9</td>
<td>1.89 (2.37)</td>
<td>7</td>
<td>7.43 (2.3)</td>
</tr>
<tr>
<td></td>
<td>Walker 2000</td>
<td>22</td>
<td>357 (1621.2)</td>
<td>22</td>
<td>1851 (2573)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>143</td>
<td>107</td>
<td>-0.69 [-1.16, -0.21]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Other immunotherapy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunotherapy</th>
<th>Placebo</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3</strong> Other immunotherapy</td>
<td>Addinckson 1997</td>
<td>61</td>
<td>3.5 (0.61)</td>
<td>60</td>
<td>3.8 (1.52)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>61</td>
<td>60</td>
<td>-0.26 [-0.62, 0.10]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Total (95% CI)

<table>
<thead>
<tr>
<th>Immunotherapy</th>
<th>Placebo</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>264</td>
<td>264</td>
<td>0.68 [-1.13, -0.48]</td>
<td></td>
</tr>
</tbody>
</table>

**Favors immunotherapy**

-10 10

**Favors placebo**

-10 10

Heterogeneity: Tau^2 = 0.22; Chi^2 = 37.67, df = 13 (P = 0.000033); I^2 = 65%

Test for overall effect: Z = 4.88 (P < 0.000001)
Abramson MJ, Puy RM, Weiner JM. SCIT for asthma.
Cochrane Database of Systematic Reviews 2003, Issue 4

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunotherapy n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maische 1989</td>
<td>5/30</td>
<td>4/11</td>
<td>4.5%</td>
<td>0.33 [0.32, 2.14]</td>
<td></td>
</tr>
<tr>
<td>Bousquet 1995</td>
<td>5/20</td>
<td>7/0</td>
<td>7.4%</td>
<td>0.32 [0.14, 0.74]</td>
<td></td>
</tr>
<tr>
<td>Orahovc 1986</td>
<td>3/14</td>
<td>10/13</td>
<td>7.8%</td>
<td>0.28 [0.10, 0.79]</td>
<td></td>
</tr>
<tr>
<td>Ohman 1994</td>
<td>2/9</td>
<td>3/8</td>
<td>2.4%</td>
<td>0.59 [0.13, 2.70]</td>
<td></td>
</tr>
<tr>
<td>Alvarez 1994</td>
<td>1/12</td>
<td>4/7</td>
<td>3.5%</td>
<td>0.15 [0.02, 1.04]</td>
<td></td>
</tr>
<tr>
<td>Machida 1990a</td>
<td>3/11</td>
<td>5/8</td>
<td>4.4%</td>
<td>0.44 [0.14, 1.32]</td>
<td></td>
</tr>
<tr>
<td>Bruce 1977</td>
<td>2/13</td>
<td>8/18</td>
<td>3.1%</td>
<td>0.37 [0.13, 2.04]</td>
<td></td>
</tr>
<tr>
<td>Van Marwijk 1988</td>
<td>1/11</td>
<td>7/10</td>
<td>5.6%</td>
<td>0.13 [0.02, 0.81]</td>
<td></td>
</tr>
<tr>
<td>Sundin 1990</td>
<td>2/15</td>
<td>11/15</td>
<td>9.2%</td>
<td>0.15 [0.04, 0.56]</td>
<td></td>
</tr>
<tr>
<td>Machida 1993</td>
<td>6/14</td>
<td>7/7</td>
<td>7.5%</td>
<td>0.46 [0.25, 0.85]</td>
<td></td>
</tr>
<tr>
<td>Van Bever 1992</td>
<td>4/9</td>
<td>8/9</td>
<td>6.1%</td>
<td>0.50 [0.23, 1.08]</td>
<td></td>
</tr>
<tr>
<td>Yakovleva 1994</td>
<td>5/12</td>
<td>10/12</td>
<td>5.3%</td>
<td>0.72 [0.38, 1.41]</td>
<td></td>
</tr>
<tr>
<td>Malling 1986</td>
<td>3/11</td>
<td>8/11</td>
<td>6.1%</td>
<td>0.38 [0.13, 1.05]</td>
<td></td>
</tr>
<tr>
<td>Taylor 1978</td>
<td>2/4</td>
<td>1/5</td>
<td>0.7%</td>
<td>2.59 [0.26, 18.62]</td>
<td></td>
</tr>
<tr>
<td>Warner 1978</td>
<td>12/22</td>
<td>14/24</td>
<td>10.3%</td>
<td>0.94 [0.56, 1.56]</td>
<td></td>
</tr>
<tr>
<td>Cremers 1996</td>
<td>6/25</td>
<td>13/24</td>
<td>10.3%</td>
<td>0.57 [0.25, 1.33]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 239 [191] 100.0% 0.51 [0.41, 0.63]
1. AR and asthma
2. Management
   - Intranasal corticosteroids for AR
   - HDM avoidance
   - Subcutaneous immunotherapy
   - Sublingual immunotherapy
SLIT for Asthma

- Calamita 2006 (Systematic review)\(^1\)
  - 25 studies and 1706 patients
  - SLIT demonstrated a small benefit for the treatment of asthma

- Canonica 2009 (WAO position paper)\(^2\)
  - 8 studies were specifically designed to assess the effect of SLIT on asthma
  - Majority confirmed a significant effect on symptoms and/or medication intake

2. Canonica et al. Allergy 2009;64(Suppl.91):1-59
SLIT for Asthma in children

- Penagos 2008 (Meta-analysis)
  - 9 DBPC trials and 441 patients
  - Age 3-18 years
  - Allergens: HDM 6, grass mix 1, Olea Europaea 1, pollen mix 1
  - Significant effect of SLIT on
    - Asthma symptoms (SMD -1.14, p=0.02, 9 trials)
    - Rescue medication (SMD -1.63, p=0.007, 7 trials)
  - Heterogeneity of trials was very large

Summary

- **Allergic rhinitis**
  - Consider allergic and non-allergic causes
  - Inspect the nose for nasal turbinate oedema
  - Patients with moderate/severe/persistent AR should be treated with *intranasal corticosteroids*
  - Patients with mild/intermittent AR can be treated with second generation *oral H1-antihistamines*
  - Those who failed treatment should be referred for consideration of specific allergen immunotherapy (subcutaneous or sublingual)
Summary

- Asthma
  - Majority (75-80%) have rhinitis
  - Patients with rhinitis have more frequent asthma symptoms
  - Treatment of rhinitis with intranasal corticosteroids is likely to benefit asthma control
  - Always ask about rhinitis in patients with asthma
Summary

- House dust mite avoidance
  - Has not been shown to provide a statistically significant benefit for either AR or asthma, in 2 recent Cochrane reviews.
  - In AR – acaricide sprays and extensive bedroom based environmental programmes may be of some benefit.
  - In asthma – subgroup analysis was not performed on methods with regards to successful/unsuccessful reduction of HDM levels. This may be relevant given the vast number of different physical & chemical methods used to reduce HDM in these studies.
# SUMMARY OF IMMUNOTHERAPY

<table>
<thead>
<tr>
<th>SCIT</th>
<th></th>
<th>SCIT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AR</strong></td>
<td>Effective for seasonal AR (Calderon 2007, Cochrane review)</td>
<td>Children: inconclusive (Roder 2008, systemic review of RCTs)</td>
<td><strong>Asthma</strong></td>
</tr>
</tbody>
</table>

2. Roder et al. Pediatric Allergy and Immunology 2008;19:197-207.
Short break...