Roles of Staphylococcal superantigens in allergic airway diseases

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Background

• The prevalence of current asthma is common among the elderly.

**Fig. 1.** Prevalence of current wheezing by questionnaire, bronchial hyper-responsiveness to methacholine and current asthma according to age. BHR, bronchial hyper-responsiveness to methacholine.
Background

- Adult-onset asthma is frequently non-atopic, but eosinophilic in nature.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Eosinophils</th>
<th>Skin Tests</th>
<th>Predicted Values*</th>
<th>Measured Lung Volumes†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sputum</td>
<td>Blood (cells/mm²)</td>
<td>FEV₁</td>
<td>VC</td>
</tr>
<tr>
<td>1</td>
<td>++</td>
<td>200</td>
<td>Pos.</td>
<td>2.85</td>
</tr>
<tr>
<td>2</td>
<td>++</td>
<td>780</td>
<td>Neg.</td>
<td>1.90</td>
</tr>
<tr>
<td>3</td>
<td>++</td>
<td>270</td>
<td>Neg.</td>
<td>2.94</td>
</tr>
<tr>
<td>4</td>
<td>++</td>
<td>480</td>
<td>Neg.</td>
<td>3.03</td>
</tr>
<tr>
<td>5</td>
<td>++</td>
<td>1,390</td>
<td>Neg.</td>
<td>3.00</td>
</tr>
<tr>
<td>6</td>
<td>++</td>
<td>390</td>
<td>Neg.</td>
<td>2.75</td>
</tr>
<tr>
<td>7</td>
<td>++</td>
<td>630</td>
<td>Neg.</td>
<td>1.71</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>280</td>
<td>Neg.</td>
<td>3.02</td>
</tr>
<tr>
<td>9</td>
<td>++</td>
<td>240</td>
<td>Neg.</td>
<td>2.50</td>
</tr>
<tr>
<td>10</td>
<td>++</td>
<td>880</td>
<td>Pos.</td>
<td>3.33</td>
</tr>
<tr>
<td>11</td>
<td>++</td>
<td>460</td>
<td>Neg.</td>
<td>2.70</td>
</tr>
<tr>
<td>12</td>
<td>No sputum</td>
<td>0</td>
<td>Neg.</td>
<td>2.78</td>
</tr>
<tr>
<td>13</td>
<td>++</td>
<td>930</td>
<td>Pos.</td>
<td>2.80</td>
</tr>
<tr>
<td>14</td>
<td>++</td>
<td>210</td>
<td>Neg.</td>
<td>2.05</td>
</tr>
<tr>
<td>15</td>
<td>+</td>
<td>100</td>
<td>Neg.</td>
<td>1.85</td>
</tr>
</tbody>
</table>

Lee and Stretton. *BMJ* 1972

- What underlies the pathophysiology of adult asthma?
Staphylococcal enterotoxin-specific IgE (SE-IgE)

Specific IgE against *Staphylococcus aureus* enterotoxins: An independent risk factor for asthma

Claus Bachert, MD, PhD, a, * Kristel van Steen, PhD, b, c, e Nan Zhang, MD, a Gabriele Holtappels, a Tom Cattaert, PhD, b, c Bärbel Maus, PhD, b, c, e Roland Buhl, MD, PhD, d Christian Taube, MD, PhD, d, i Stephanie Korn, MD, d Marek Kowalski, MD, f Jean Bousquet, MD, PhD, g and Peter Howarth, MD, h Ghent and Liège, Belgium, Lodz, Poland, Mainz, Germany, Montpellier, France, Southampton, United Kingdom, and Leiden, The Netherlands

**FIG 2.** Multiple correspondence analyses factor map with 95% confidence ellipses situating relationships between parameters and disease severity. SE IgE is situated near severe asthma, whereas GP and HDM IgEs are situated near nonsevere asthma.

**FIG 3.** Categorical Bayesian network results suggest that SE IgE and GP IgE affect disease severity directly and are not mediated through an effect on tIgE. SE IgE was associated with more severe disease, and GP IgE was associates with less severe disease.

Bachert et al. *JACI* 2012
Roles of Staphylococcal enterotoxins (SE)

- Strong immune modulator
- Enterotoxins act as superantigen
- Promoting allergen sensitization (tolerance breakdown)

- Enterotoxin-specific IgE: SE act like allergens?

Fig. 1. SAg cross-linking of MHC class II receptor on APC and TCR on T lymphocyte. Left: conventional antigen presentation with processing and presentation by the MHC II within the peptide binding groove. Right: SAg cross-linking MHC II and TCR, without being processed.

Huvenne et al. Int Arch Allergy Immunol 2013
Research questions

1. Could SE-IgE be a risk factor for asthma?

2. If so, which characteristics (phenotypes) of asthma could be related with SE-IgE sensitization?

3. What is the origin of SE-related allergic diseases?
Could SE-IgE be a risk factor for adult asthma?

- Systematic review
- No general adult population studies
*Staphylococcus aureus* enterotoxin-specific IgE is associated with asthma in the general population: a GA²LEN study

P. Tomassen1,*, D. Jarvis2,*, R. Newson2, R. Van Ree3, B. Forsberg4, P. Howarth5,6, C. Janson7, M. L. Kowalski8, U. Krämer9,10, P. M. Matricardi11, R. J. M. Middelveld12, A. Todo-Bom13, E. Toskala14, T. Thilsing15, G. Brožek16, C. Van Drunen17, P. Burney2 & C. Bachert1
Associations in general populations

SE-IgE and asthma relationships in Korean populations

Intrinsic = allergic to *S aureus*?
Asthma heterogeneity

Onset

Clinical marker of severity

Inflammatory characteristics

SE-IgE in elderly asthma cohort

Elderly asthma cohort (n=1,031):
Asthma patients recruited from 9 referral hospitals
(diagnosis based on clinical history and reversible airway obstruction)

Patients recruited at SNUH and SNUBH (n=370)

Excluded (n=661):
Patients recruited at other institutions and did not undergo nasal endoscopy

Patients with baseline serum (n=311)

Excluded (n=59):
No serum collection

Exclusion criteria by comorbid conditions (n=292)

Excluded (n=19):
Eczema (n=7), congestive heart failure (n=3), malignancy (n=3), anti-IgE therapy (n=3), other systemic steroid therapy (n=3)

Successful follow-up for 1 year (n=249)

Excluded (n=43):
Not followed-up

Patients included in this analysis (n=249)

Song et al. Clin Exp Allergy 2016
## SE-IgE in late-onset elderly asthma

<table>
<thead>
<tr>
<th></th>
<th>Elderly control (n=98)</th>
<th>Elderly asthma (n=249)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>68.4</td>
<td>66.3</td>
<td>0.708</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70.6±4.8</td>
<td>71.5±5.1</td>
<td>0.168</td>
</tr>
<tr>
<td>Asthma onset age (years)</td>
<td></td>
<td>64.3±8.7</td>
<td></td>
</tr>
<tr>
<td>Total IgE (kU/L)</td>
<td>91.5 (28.9–218.2)</td>
<td>83.3 (31.4–220.0)</td>
<td>0.934</td>
</tr>
<tr>
<td>Serum SE-IgE (kU/L)</td>
<td>0.10 (IQR 0.01–0.19)</td>
<td>0.16 (IQR 0.04–0.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SE-IgE sensitization (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (&lt;0.10 kU/L)</td>
<td>48.0</td>
<td>37.8</td>
<td>0.008</td>
</tr>
<tr>
<td>Moderate (0.10–0.35 kU/L)</td>
<td>35.7</td>
<td>29.3</td>
<td></td>
</tr>
<tr>
<td>High (≥ 0.35 kU/L)</td>
<td>16.3</td>
<td>32.9</td>
<td></td>
</tr>
</tbody>
</table>

Song et al. *Clin Exp Allergy* 2016
Clinical correlations of SE-IgE in asthma

**Sputum eosinophils %**

- Scatter plot showing the relationship between Log10 SE-IgE and sputum eosinophils (%).
- Sputum eosinophil (%) and 95% CI indicated.
- Fitted values shown.

**Comorbid CRS**

- Box plots for No CRS, CRSsNP, and CRSwNP.
- Comparison of CRS status across different conditions.

**OCS rescue**

- Scatter plot showing the relationship between Log10 SE-IgE and OCS rescue.
- OCS rescue and 95% CI indicated.
- Fitted values shown.

**Asthma severity**

- Box plots for Non-severe asthma and Severe asthma.
- Comparison of asthma severity across different conditions.
Severe eosinophilic asthma with CRS

Song et al. *Clin Exp Allergy* 2016
Cluster analysis of CRS phenotypes

Inflammatory mediators in nasal tissues

What is the origin of SE-related allergic airway diseases?
Nasal colonization of *S aureus* on asthma

**Staphylococcus aureus** colonization is associated with wheeze and asthma among US children and young adults

| Table II. Adjusted associations between *S aureus* nasal colonization and asthma and wheeze |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **Outcomes, OR [95% CI]**        | **Whole population (age 6 to 85 y)** | **Age 6 to 30 y** | **Age 31 to 85 y** | **S aureus and age interaction** |
| **Sample size**                  | n = 16,234                         | n = 8,703                   | n = 7,531                   |                                  |
| **Wheeze outcomes:**             |                                  |                              |                              |                                  |
| Wheeze in the past year†         | 1.02 [0.87, 1.20]                 | 1.35 [1.06, 1.73]*          | 0.85 [0.68, 1.06]            | *P* = .006                      |
| Wheeze during exercise†          | 1.00 [0.82, 1.19]                 | 1.27 [0.95, 1.70]           | 0.84 [0.67, 1.08]            | *P* = .06                       |
| Nocturnal wheeze§                 | 1.05 [0.84, 1.34]                 | 1.52 [1.15, 2.00]**         | 0.79 [0.53, 1.18]            | *P* = .01                       |
| Emergency room visit for wheezing‡| 1.28 [1.00, 1.62]*                | 1.50 [1.10, 2.03]*          | 1.11 [0.70, 1.78]            | *P* = .26                       |
| Wheeze limits activities‡        | 1.11 [0.89, 1.38]                 | 1.41 [1.05, 1.90]*          | 0.97 [0.72, 1.29]            | *P* = .03                       |
| Medication for wheezing§         | 0.93 [0.75, 1.14]                 | 1.52 [1.08, 2.14]*          | 0.64 [0.48, 0.84]**          | *P* < .001                      |
| Miss work or school due to wheeze‡¶ | 1.03 [0.77, 1.39]                | 1.42 [1.04, 1.94]*          | 0.61 [0.32, 1.20]            | *P* = .01                       |
| **Asthma outcomes:**             |                                  |                              |                              |                                  |
| Asthma diagnosis ever†           | 1.07 [0.92, 1.23]                 | 1.25 [0.99, 1.56]           | 0.92 [0.76, 1.11]            | *P* = .04                       |
| Current asthma†                  | 1.08 [0.87, 1.35]                 | 1.27 [0.95, 1.70]           | 0.93 [0.71, 1.22]            | *P* = .06                       |
| Asthma attack in past year§      | 1.37 [1.03, 1.83]*                | 1.42 [0.92, 2.19]           | 1.31 [0.94, 1.84]            | *P* = .64                       |
| Emergency room visit for asthma| 1.44 [0.89, 2.31]                 | 1.97 [1.05, 3.73]**         | 0.85 [0.37, 1.94]            | *P* = .09                       |

OR are (odds for colonized)/(odds for noncolonized).
Adjusted models use survey weighting and account for gender, ethnicity, obesity, smoking in the home, episode of flu, number of health care visits, poverty income ratio, and household size.
Whole-population and within-age-stratum models use age as a continuous variable.
Models with the *S aureus* × age interaction term use age as a binary variable.

*Davis et al. JACI 2014*
Allergic disease and *Staphylococcus aureus* carriage in adolescents in the Arctic region of Norway

Martin Sørensen¹,², Magnus Wickman³,⁴, Johanna U. E. Sollid⁵, Anne-Sofie Furberg⁶,⁷ & Claus Klingenberg¹,²

Table 4: Associations between allergic disease and nasal *S. aureus* carriage

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>Severe Asthma</th>
<th>Eczema</th>
<th>Severe Eczema</th>
<th>Allergic rhinitis (AR)</th>
<th>Severe Allergic rhinitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR  95% CI</td>
<td>OR  95% CI</td>
<td>OR  95% CI</td>
<td>OR  95% CI</td>
<td>OR  95% CI</td>
<td>OR  95% CI</td>
</tr>
<tr>
<td>Univariable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal <em>S. aureus</em> carriage</td>
<td>1.19  0.77–1.83</td>
<td>3.34  1.33–8.37</td>
<td>1.77  1.11–2.83</td>
<td>2.43  1.29–4.60</td>
<td>1.26  0.92–1.73</td>
<td>1.65  1.06–2.55</td>
</tr>
<tr>
<td>Multivariable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal <em>S. aureus</em> carriage</td>
<td>1.17  0.75–1.82</td>
<td>3.47  1.37–8.82</td>
<td>1.79  1.11–2.91</td>
<td>2.49  1.29–4.80</td>
<td>1.24  0.90–1.72</td>
<td>1.71  1.09–2.66</td>
</tr>
</tbody>
</table>
Intramucosal presence of *S. aureus*

**A. Staphylococcus aureus colonization (%)**

**B. Presence of specific IgE to SAE in tissue (%)**

Van Zele et al. JACI 2004; and Sachse et al. Allergy 2010
*S. aureus* within mast cells in nasal polyp tissues

Intracellular residency of *Staphylococcus aureus* within mast cells in nasal polyps: A novel observation

Hayes S et al. JACI 2015
**Hypothetical pathway**

- **S. aureus** → **Nasal colonization**
  - *Promoting superantigens*
  - Aging
  - Smoking
- 
  + **IgE sensitization**
  - Direct superantigen effects
  - **CRSwNP Th2 phenotype & persistent severity**
  - **Severe eosinophilic asthma in non-atopic adults**
Staphylococcal serine protease–like proteins are pacemakers of allergic airway reactions to *Staphylococcus aureus*  

Sebastian Stentzel, PhD, Andrea Teufelberger, Maria Nordengrün, Julia Kolata, PhD, Frank Schmidt, PhD, Koen van Crombruggen, PhD, Stephan Michalik, PhD, Jana Kumpfmüller, PhD, Sebastian Tischer, Thomas Schweder, PhD, Michael Hecker, PhD, Susanne Engelmann, PhD, Uwe Völker, PhD, Olga Krysko, PhD, Claus Bachert, MD, PhD, and Barbara M. Bröker, MD

Greifswald, Braunschweig, and Jena, Germany; Ghent, Belgium, Utrecht, The Netherlands, and Stockholm, Sweden

![Graphs showing IgE binding to SplA, SplB, SplD, and SplE](image)

**FIG 3.** Increased IgE binding to Spls in asthmatic patients. Serum IgE binding to SplA, SplB, SplD, and SplE was determined by using ELISA. Asthmatic patients (*n* = 50) had significantly more Spl-specific IgE than healthy adults (*n* = 40). Medians and interquartile ranges are depicted. *P* < .05 and ***P* < .001.
Intratracheal Spl-D administration in mice

A

**eosinophils lungs**

![Graph showing eosinophils lungs](image)

% viable cells

PBS | OVA | SplD

F

**SplD IgE serum**

![Graph showing SplD IgE serum](image)

OD (450nm)

PBS | OVA | SplD

Stentzel et al. *JACI* 2016
Hypothetical pathway

S. aureus → Nasal colonization

*Driven by Spl?*

- Aging
- Smoking

+ IgE sensitization

*Local IgE
  Systemic IgE

- Direct superantigen effects

- CRSwNP Th2 phenotype & persistent severity
- Severe eosinophilic asthma in non-atopic adults
Summary

• SE-IgE sensitization as a risk factor for asthma and CRS:
  - more related to late-onset severe eosinophilic asthma phenotype

• Nasal colonization of *S aureus* might be the origin of SE-related allergic airway diseases.

• Further questions:
  - major determinants (virulence factors and environmental interaction)?
  - direct cause, or disease modifier?
  - therapeutic implication?
Acknowledgement

- Seoul National University
  College of Medicine, Korea
  - Prof Sang-Heon Cho
  - Prof Min-Ho Choi
  - Prof Yoon-Seok Chang
  - Prof Heung-Woo Park
  - Prof Sae-Hoon Kim
  - Prof Min-Suk Yang
  - Ji-Won Lee

- Ghent University, Belgium
  - Prof Claus Bachert
Thank you very much for your attention.