Allergic Rhinitis
Update 2008

Prof. Ralph Mösges
Otorhinolaryngologist and Allergologist
University Hospital of Cologne
Augustus  Claudius  Britannicus
Review article

Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update
(in collaboration with the World Health Organization, GA²LEN* and AllerGen**)
Definition and classification of allergic rhinitis

- Allergic rhinitis is clinically defined as a symptomatic disorder of the nose induced after allergen exposure by an IgE-mediated inflammation.
- Allergic rhinitis is subdivided into IAR or PER disease.
- The severity of allergic rhinitis can be classified as ‘mild’ or ‘moderate/severe’.
- Allergic rhinitis impairs QOL, sleep, school and work.
- Many nonallergic triggers induce nasal symptoms which mimic allergic rhinitis. They include drugs (aspirin and other nonsteroidal anti-inflammatory agents), occupational agents, foods, physical, emotional and chemical factors and viral infections.
Allergic Rhinitis Update 2008

• Epidemiology
• Etiology
• Mechanisms
• Management
C. von Pirquet

Allergie

Von C. v. Pirquet

In den letzten Jahren ist eine Reihe von Tatzen gesammelt worden, welche in das Bereich der Immunität gehörten, aber unter den Namen schlecht passen. Sie haben viel von Ueberempfindlichkeit am immunisierten Organismus.¹)

Diese beiden Ausdrücke scheinen gegenständig; unter immunnen den wir uns doch einen Organismus vor, welcher gegen eine Krankheit geschützt ist, von ihr nicht mehr angegriffen wird; und der soll gleichzeitig gegen derselben Krankheit überverschränkt sein?

Diesen Widerspruch hat schon v. Behring gefühlt, als er den Tod von gegen Tetanus hoch immunisierten Tieren bei kleinen Mengen desselben Toxins mit "paradoxe Reaction" bezeichnete.

Eine "Paradoxe" können wir doch nur als Ausnahmefall gelten lassen; je mehr man aber in diesem Gebiete eindringt, desto weiter reicht die Genauigkeit, und wir können schon die leisten große Züge der Krankheitsprozesse, bei denen Symptome von Ueberempfindlichkeit angetroffen werden. Hier gehören:


Sind aber wirklich Immunität und Ueberempfindlichkeit mit einander verkehren, oder sind es die Prozesse, bei denen Symptome von Ueberempfindlichkeit angetroffen werden, werden hier die "paradoxe Reaction" erklären.

²) Zentralb. f. Bakteriologie, Bd. 27, 1904; Münch. med. Wochenbl. 1906, No. 5; Das Heilser, München, Lehmann 1906.
Are we trading one epidemic against another one?

The Inverse Association Between Tuberculin Responses and Atopic Disorder

SCIENCE • VOL. 275 • 3 JANUARY 1997
Asthma prevalence, children and young adults

Year

%
The problem
Prevalence of atopic conditions in 12-13 year olds

Asthma

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>1973</td>
<td>4%</td>
</tr>
<tr>
<td>1988</td>
<td>9%</td>
</tr>
<tr>
<td>1996</td>
<td>30%</td>
</tr>
</tbody>
</table>

Rhinitis

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973</td>
<td>9%</td>
</tr>
<tr>
<td>1988</td>
<td>15%</td>
</tr>
<tr>
<td>1996</td>
<td>30%</td>
</tr>
</tbody>
</table>

Doubling every 8 years

* Burr et al 1989 Arch Dis Child 64: 1452
** Kaur et al 1997 Brit Med J
Allergy is more present in the medical field

AAAAI News: August 2007

*CIF continues steady climb*
*JACI citation impact factor reaches 8.829*

The *Journal of Allergy and Clinical Immunology* (JACI) is the most highly cited journal in the area of allergy and clinical immunology with a 2006 citation impact factor (CIF) of 6.829. The CIF measures the frequency with which the average article from the previous two years has been cited in the previous year and reflects a journal’s relative importance.

"We are very pleased with the progress that has been made this year, as it is a big step toward our goal of raising the impact factor to 10 or higher," said Donald Y.M. Leung, MD, PhD, FAAAAI, Editor-in-Chief. "We are thankful to everyone who has helped contribute to the success of the Journal, including all of our editors, reviewers, authors and readers."

As a part of its ongoing commitment to a standard of excellence, the JACI will add a number of new features this year:

- To ensure that the JACI content remains relevant to the practicing allergist/immunologist, the AAAAAI Board of Directors has endorsed adding a professional medical editor to the JACI team. This individual will be charged with editing selected articles to make them more viable to the clinical audience, and drafting content such as article summaries and Beyond Our Pages reviews that highlight material of particular interest to clinicians.
Rhinitis prevalence in the east of Germany

doubling every 3 years
The cohort effect

"allergy decreases with age"
When does Allergy begin?

**Figure 1.** Age of onset (years) in 794 adults with self-reported hay fever out of a population-based sample of 4261 subjects (mean 26 years).
Allergy is an transmissible disease!

Original article

Does my partner cause my allergy?

Background: The study of partners can help to understand the impact of environmental influences on the development of allergies. We aimed to test the hypothesis that subjects whose partners have hay fever are at increased risk for the same disease and that the risk increases with the time subjects live together with an affected partner.

Methods: A nested unmatched case-control study was performed in a random sample of 4261 inhabitants, aged 25–74 years, of the City of Augsburg, Germany, and two adjacent counties. Using standardized computer-assisted face-to-face interviews, we determined the risk of doctor-diagnosed hay fever in subjects who lived together with a partner having the same disease as opposed to subjects living with an unaffected partner. Furthermore, the risk of doctor-diagnosed hay fever depending on the time the subjects had lived together with an affected partner was calculated.

Results: After adjustment for age, sex, parental predisposition and social status, the risk of hay fever was more than double in subjects who lived together with a partner having the same disease (odds ratio, ORadj, 2.41; 95% confidence interval, CI, 1.48–3.92). If subjects lived together with an affected partner, the risk of developing the disease increased with the time the partners lived together (1–11 years, OR 1; 12–23 years, OR 1.8; 24–35 years, OR 7.4; 36–54 years, OR 13.7).

Conclusion: The risk of developing hay fever is significantly elevated in subjects who live together with a partner having the same disease. The risk further increases with the time the partners live together. This points to important shared environmental influences or behaviours and raises speculations on a transmissible cause.

T. Schäfer1, J. Merkt2, E. Klemm3, H.-E. Wichmann3, J. Ring2, KORA Study Group

1Department of Social Medicine, Medical University Schleswig-Holstein, Lübeck; 2Department of Dermatology and Allergy, and Division of Environmental Dermatology and Allergology, GSF Technical University Munich, Munich; 3GSF National Research Center for Environment and Health, Institute of Epidemiology, Neuherberg, and Institute of Medical Data Processing, Biometrics, and Epidemiology, Ludwig Maximilian University, Munich, Germany

Key words: allergy; epidemiology; hay fever; partner.

Prof. Dr Torsten Schäfer
Department of Social Medicine
Medical University Schleswig-Holstein
Campus Lübeck
Beckergrube 43-47
23552 Lübeck
Germany

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### Table 3. Multiple logistic regression for actual doctor-diagnosed hay fever (occurring after the start of living together with a partner) and duration of living together with a partner with hay fever in 315 adults from the general population

<table>
<thead>
<tr>
<th>Variable (n)</th>
<th>OR*</th>
<th>95% CI†</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (25–34 years, 85; 35–44 years, 91; 45–54 years, 66; 55–64 years, 49; 65–74 years, 24)</td>
<td>0.53</td>
<td>0.24–1.20</td>
<td>0.13</td>
</tr>
<tr>
<td>Female sex (145)</td>
<td>1.55</td>
<td>0.62–3.89</td>
<td>0.35</td>
</tr>
<tr>
<td>Parental predisposition (70)</td>
<td>1.48</td>
<td>0.53–4.09</td>
<td>0.46</td>
</tr>
<tr>
<td>Length of school education</td>
<td>0.67</td>
<td>0.41–1.07</td>
<td>0.09</td>
</tr>
<tr>
<td>(no graduation, 2; 8 years, 136; 10 years, 74; 13 years, 32; 15 years, 67)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living together with an affected partner (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–11 (120)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12–23 (88)</td>
<td>1.80</td>
<td>0.44–7.35</td>
<td>0.41</td>
</tr>
<tr>
<td>24–35 (69)</td>
<td>7.44</td>
<td>1.01–55.21</td>
<td>0.049</td>
</tr>
<tr>
<td>36–54 (38)</td>
<td>13.73</td>
<td>0.78–241.95</td>
<td>0.07</td>
</tr>
</tbody>
</table>

* OR: odds ratio.
† CI: confidence interval.
The Causes of Allergic Rhinitis
Risk factors for allergic rhinitis

- Allergic rhinitis is a multifactorial disease induced by gene–environment interactions.
- Indoor and outdoor inhalant allergens cause allergic rhinitis.
- Major outdoor allergens include pollens and molds.
- Major indoor allergens include mites, animal danders, insects and molds.
- Food allergens are rarely the cause of isolated nasal symptoms.
- Occupational agents can cause rhinitis by allergic and nonallergic mechanisms.
- The role of indoor and outdoor air pollutants is probably of importance, but more data are needed to assess their effect.
- Socioeconomic differences are reported in allergic diseases, but more data are required before producing specific recommendations.
The Causes of allergic rhinitis

• Genes
• Hygiene
• Environmental exposure

• Vaccination studies!
The mechanisms
Allergen → B lymphocytes → T lymphocytes (mast cells) → Eosinophils

- Histamine
- Leukotrienes
- Prostaglandins
- Bradykinin, PAF

Immediate rhinitis symptoms:
- Itch, sneezing
- Watery discharge
- Nasal congestion

Chronic ongoing rhinitis:
- Nasal blockage
- Loss of smell
- "Nasal hyper-reactivity"
Some mediators of allergy

Histamine
Serotonin
Adenosine
Nitric oxide
Superoxide
Peroxynitrite

PGE_2
PGI_2
PGF_2α
PGD_2
TxA_2
LTD_4
HPETEs
di-HETES
Lipoxins
PAF

ACh
SP
NKA
NPK
GGRP
VIP
Gal
NPY

En dothelins
Bradykinin
Kallidin
C5a
C3a

IL-1β
IL-2
IL-3
IL-4
IL-5
IL-6
IL-7
IL-8
IL-9
IL-10
IL-11
IL-12
IL-13
IL-14
IL-15
IL-16
IL-17
IL-18
IL-19

TNF-α
GM-CSF
SCF
IFN-γ
Oncostatin
LIF

IL-8
RANTES
Eotaxin-1
Eotaxin-2
Eotaxin-3
MIP-1α
MCP-1
MCP-2
MCP-3
MCP-4
MDC
SDF-1α/β
TARC

PDGF
FGF
TGF-β
EGF
VEGF
BMP
IGF

Tryptase
Chymase
hNE
MMP-2
MMP-9

The mechanisms

- Dendritic cells
- T-reg cells
- Cytokines
- Chemokines
- Mediators
The management of AR

- Diagnosis
- Prevention
- Therapy
Diagnostics

- Anamnesis
- Skin test
- NPT / CPT
- Lab Test
  - IgE
  - Basophils
Diagnostics

• Micro-Array-Technology

Available ISAC® products

ISAC® Variants

ISAC®-CRD
Contains a variety of recombinant or purified allergens of animals (cat and dog), food (apple, barley, carrot, chicken egg, celery, cow’s milk, wheat), mites (Der. Farinae and Der. Pteronyssinus), moulds (Alternaria alternata), pollen (birch, timothy grass, black alder, hazel) and latex.

ISAC®-Latex
Contains especially selected allergens for the determination of latex-specific IgEs.

Custom ISAC®
Choose from our range of allergen components and design your personal allergen microarray. Or, bring your specific allergens and have your personal microarray assembled by a team of VBC-GENOMICS experts.
Overview

ISAC®-based allergy testing

ISAC® (Immuno Solid-phase Allergen Chip) is a microarray-based multianalyte test system for the detection of allergen-specific IgE antibodies contained in the serum of allergic patients. In contrast to conventional in-vitro diagnostic tests, ISAC® employs only purified allergenic components, either as recombinant proteins or in a natural form. Therefore, ISAC® represents the first commercially available test that has adopted the concept of component resolved diagnosis (CRD) of allergic diseases.

Quality-controlled ISAC manufacturing

The manufacturing of ISAC® is conducted under an ISO 9001:2000 and ISO 13485 certified quality management system. Since December 2003 ISAC® is approved as an in-vitro diagnostic medical device in the EU and each kit wears a CE-mark.

Multiple parallel allergen monitoring

Currently, several ISAC®-variants are available. They are distinguished by their respective allergen composition while more than 50 allergens can be analysed per assay. The current microarray design permits the analysis of three patients in a single run while using only 20 µl of serum. Allergen-specific binding of human IgE is detected by the addition of a fluorescence-labelled secondary anti-human IgE on each ISAC®, a calibration sample is assayed in parallel which allows the semi-quantitative analysis of allergen-specific and IgE-dependent fluorescence signals.
Prevalence of Allergies is Increasing

• >80 million people in Europe have some form of allergy\(^1\)

• Research worldwide shows a steep rise in prevalence of asthma and allergic rhinitis (AR)\(^2\)

• Allergic rhinoconjunctivitis affects about 20% of the population globally\(^3\)

• New sensitisations / Onset of allergic diseases also in elder patients

1. EFA. http://www.efanet.org/allergy/index.html;
2. Green RJ. *Current Allergy & Clinical Immunology* 2003;
Exposure to Novel Outdoor Allergens is also Increasing

- Spread of invasive, non-native plant species has increased
  - increase in ragweed and birch pollen allergen in Europe\textsuperscript{1, 2, 3}

1. Asero R. Allergy 2002
Evolution of Ambrosia pollen concentrations

1989

Pollination Concentration
for Ambrosia in 1989

very low
low
moderate
high
very high

1997

Pollination Concentration
for Ambrosia in 1997

very low
low
moderate
high
very high

2008
Exposure to Novel Outdoor Allergens - Consequences

• Previously non-allergic individuals may develop allergies

• Previously allergic individuals may become polysensitised
Allergic Rhinitis is often caused by polysensitisation

Valovirta E. Curr Opinion Allergy Immunol; in press
ARIA Classification

**Intermittent**
- ≤ 4 days per week
- or ≤ 4 weeks

**Mild**
- normal sleep
- & no impairment of daily activities, sport, leisure
- & normal work and school
- & no troublesome symptoms

in untreated patients

**Persistent**
- > 4 days per week and > 4 weeks

**Moderate-severe**
- one or more items
- abnormal sleep
- impairment of daily activities, sport, leisure
- abnormal work

in untreated patients
Allergic rhinitis complaints
ARIA Classification

- Intermittent Mild: 22.9%
- Intermittent Moderate/severe: 40.96%
- Persistent Mild: 5.35%
- Persistent Moderate/severe: 30.79%

Bachert C, Belgian Survey 2004
What is today’s situation?

**Rationale:** To assess the symptom burden of patients with rhinitis symptoms during an allergy season.

**Methods:** Population based cross-sectional survey. A brief screening questionnaire was mailed to 15,000 households (65.6% response rate). More detailed follow-up surveys were sent to 9,822 respondents during an allergy season (April 2004 to May 2004) of whom 7,112 (70%) responded.

**Results:** A total of 7,069 individuals with complete data were analyzed. 5,303 met the case definition of rhinitis sufferers (i.e., experienced at least one nasal/eye symptom in the past four weeks). Among rhinitis symptom sufferers, 40.8% rated their nasal symptoms as mild, 46.4% rated them as moderate, and 12.8% rated them as severe. The most commonly reported symptoms were runny nose/sniffing (52.3%), sneezing (51.1%), congested/blocking nose (38.1%), and tiredness (37.7%). In addition, nasal symptoms were reported to be completely controlled in 9.7%, well controlled in 29.5%, somewhat controlled in 44.1%, unchanged in 14.1%, worsened in 2.5% over the previous 4 weeks.

**Conclusions:** This large household survey shows that during an allergy season, rhinitis symptom sufferers have a large nasal symptom burden despite the availability of over the counter and prescription medication treatments.
Figure 1: Patients Self Rating of Rhinitis Severity

- Mild: 40.8%
- Moderate: 46.4%
- Severe: 12.8%
Original article

Relationship between ARIA classification and drug treatment in allergic rhinitis and asthma

**Introduction:** The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines provide a stepwise treatment to rhinitis, which classifies the disease according to its duration and severity.

**Objectives:** The aim of the study was to verify whether these variables influence drug prescriptions for rhinitis and asthma.

**Methods:** A multi-centre cross-sectional pharmaco-epidemiological survey was carried out on 1610 allergic rhinitis patients and the relationship between the clinical features of rhinitis and drug therapy for rhinitis and asthma was evaluated.

**Results:** A total of 1321 adult patients were enrolled. Mild intermittent rhinitis was diagnosed in 7.7% of the patients, moderate/severe intermittent in 17.1%, mild persistent in 11.6%, and moderate/severe persistent in 63.6%. A high level of rhinitis-asthma comorbidity (616/1321 = 46.6%) was found. The majority of patients (1060 (80.24%)) were treated. Significant associations between the severity of rhinitis and the presence of therapy (P = 0.008), and of oral antihistamines (P < 0.001), topical nasal steroids (P = 0.022), and systemic steroids (P = 0.005) were found. A weak association was found between features of rhinitis and the therapy for asthma, whereas the comorbidity with asthma increases the prescription of inhalants (P = 0.001) and oral steroids (P = 0.015) to treat rhinitis.

**Conclusion:** The severity of rhinitis influences patient request for rhinitis therapy and the type of medication more than the duration of these features of rhinitis seem to poorly influence asthma therapy. As the ARIA classification is able to reveal a relevant impairment notwithstanding therapy, its role in treated patients merits further study.


1 Allergy Unit, Department of Internal Medicine, Immuno-Allergic and Respiratory Diseases, Ospedali Riuniti di Ancona, Ancona; 2 Allergy and Clinical Immunology, Senigallia, Macerata Hospital, Genova; 3 Allergy Unit, Vicenza, Father Minor Hospital, Verona; 4 Internal Medicine, S. Giuseppe Hospital, Verona; 5 Biostatistics, University of Verona, Verona, Italy.

Keywords: ARIA; allergic asthma; allergic rhinitis; Italy; drug therapy.

L. Antonioelli
Allergy Unit
Department of Internal Medicine, Immuno-Allergic and Respiratory Diseases
Ospedali Riuniti di Ancona
Via Conca-Torrente
60200 Ancona
Italy

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Figure 3: Nasal Symptoms Control Over Last 4 Weeks

- Completely: 9.7%
- Well: 29.5%
- Somewhat: 44.1%
- Unchanged: 14.1%
- Worsened: 2.5%
Original article

Undertreatment of rhinitis symptoms in Europe: findings from a cross-sectional questionnaire survey

Background: Allergic rhinitis is a frequent disease affecting one in five Europeans with a significant impact on patient quality of life, health-care costs, and economic productivity. Although effective treatments exist, the disease often remains undiagnosed and not correctly treated, despite international diagnostic and therapeutic guidelines from WHO, EAACI (European Academy of Allergology and Clinical Immunology), and GALEN (Global Allergy and Asthma European Network). This study elucidates the reasons for this discrepancy in the patients’ point of view.

Methods: An internet and telephone survey was conducted with 2966 randomly selected adults with allergies from the general population in five major countries: UK, France, Germany, Italy, and Spain.

Results: The main reason why the majority of respondents consulted a medical professional for their rhinitis symptoms was because their symptoms became intolerable. The respondents had not seen a medical professional in the past year for their rhinitis symptoms in 52.6% of the cases, and 30.2% of the respondents preferred nonprescription medication because it did not require visiting a doctor. ‘Nontreaters’ and ‘homeopathic treaters’ together made up 26.2% of the respondents, and 40.2% of them gave the cost of medication as a reason they do not use allergy medications.

Conclusions: Allergic rhinitis remains widely undertreated in Europe with avoidable socioeconomic consequences. Effective treatment exists, but patients wait too long to seek medical advice, and health providers neglect to actively screen early for allergies.
Take your patient seriously!

Among the 295 matched patient-physician records, the physicians rated 4.8% of the patients as having severe allergic rhinitis, while 14.8% of the patients gave themselves such a rating. The physicians gave a rating of mild to 43.5% of patients, while 31.3% of patients self-rated their disease as mild. Moderate ratings were given by 51.7% of physicians and 54.0% of patients. Physicians reported sleep disturbance in 23.4%, compared with such reports by 47.2% of patients.
Figure 1: Drawings made by patients with AR showing how allergy symptoms make them feel.

"Big heavy head. Throbbing head. Puffy, irritable, painful, streaming eyes. Painful sinuses. Sore, runny nose, dry skin. Sad"

"Head feels huge (coz of congestion). Headache. Itchy, puffy, red, swollen, streaming eyes. Thumping sinus. Sore nose from blowing. Itchy throat"

"Thumping head. Puffball eyes. Gooey nose. Sinus ducts blocked. Face hurts. Throat feels like it needs to be cut"

"Clamp pressure. Nose is tender, feels huge. Feel like a zombie"
Distribution of Patients Tested by Number of Allergens and Competency in Allergy Diagnosis

- Total Number of Patients
- Physicians Experienced in Allergy Diagnosis
- Physicians Performing Allergy Diagnosis for the First Time

Number of Allergens

Number of Patients

0 1 2 3 4 5 6 7 8 9 10 More Than 10
Today’s Allergies Require New Treatment Strategies

Pollution

↑ Sensitisation
↑ Responsiveness
↑ Allergenicity

Indoor lifestyle / Novel Allergens

Perennial exposure
Polysensitisation

Neuroimmunological factors

↑ Sensitisation
↑ Manifestation

Severe symptoms

Persistent symptoms

Need for new treatment strategies
Therapy
Leukotriene receptor antagonists
Dekongestants
Allergen-specific Immunotherapy
Cromones
Antihistamines
Glukocorticosteroids
Leukotrienenreceptor-antagonists
Anti-IgE
Drug-therapy
Etablierte Therapien

immunologisch

Hyposensibilisierung

Experimentelle Therapien

Allergen

IFN als IL-4 Antagonist
löslicher IL-4 Rezeptor

Anti-IgE Antikörper
löslicher IgE-Rezeptor
Anti-IgE Rezeptor-Antikörper

pharmakologisch

Cromoglycat
Nedocromil

Antihistaminika

Beta-2-Mimetika
Theophyllin
Glukokortikoide

Mediatoren

PAF-Antagonisten
Leukotrienantagonisten
5-Lipoxygenase-Inhibitoren
selektive Phosphodiesterase-Inhibitoren

Zielzelle

Spätreaktion
Sofortreaktion
Treatment of allergic rhinitis (ARIA)

- Allergen and irritant avoidance
- Immunotherapy
- Intra-nasal decongestant (< 10 days) or oral decongestant
- Oral or local non-sedative H1-blocker
- Intra-nasal steroid
- Local cromone
- Mild intermittent
- Moderate severe intermittent
- Mild persistent
- Moderate severe persistent

ARIA guidelines
New ARIA Guideline

ARIA
At-A-Glance Pocket Reference
2007

1st Edition
Diagnosis of allergic rhinitis

Intermittent symptoms

Mild
- Not in preferred order
  - Oral H1-antihistamine
  - Intranasal H1-antihistamine
  - Decongestant
- In persistent rhinitis
  - Review the patient after 2-4 weeks
- If failure: step-up
- If improved: continue for 1 month

Moderate
- Not in preferred order
  - Oral H1-antihistamine
  - Intranasal H1-antihistamine
  - Decongestant
- In persistent rhinitis
  - Review the patient after 2-4 weeks
  - Step down and continue treatment for 1 month
  - Increase intranasal CS dose
  - Itch/sneeze
    - Add H1 antihistamine
    - Add decongestant or oral CS (short-term)
  - Rhinorrhea
    - Add ipratropium
    - Blockage
  - Failure
  - Surgical referral

Persistent symptoms

Moderate
- In preferred order
  - Intranasal CS
  - H1-antihistamine or LTRA
- Review the patient after 2-4 weeks
  - Improved
  - Failure
  - Review diagnosis
    - Query infections or other causes

In particular, in patients with asthma.

Allergen and irritant avoidance may be appropriate

If conjunctivitis
- Add:
  - Oral H1-antihistamine
  - Intracocular H1-antihistamine
  - Intracocular cromone
  - (or saline)

Consider specific immunotherapy
Meta-Analysis of placebo-controlled clinical trials
Monotherapy

Baseline value nasal sum score

Mean improvement of nasal sum score

p < 0.001

n=12708

n=1820

3.69

3.31

no comedication

comedication

0.00

1.00

2.00

3.00

4.00

5.00

6.00

7.00

8.00

9.00

0.00

1.00

2.00

3.00

4.00

5.00

6.00

7.00

8.00

9.00

Mean improvement of nasal sum score
Mean improvement of congestion

1+1=0.9

Spray or steroid
- 0,00
- 1,00

n=3405
n=4381
n=156
n=2592
n=210

n=2686
n=29
Prophylactic treatment
# Treatment Thresholds for Rhinitis

<table>
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<tr>
<th>Treatment</th>
<th>Benefit</th>
<th>NNT</th>
<th>Harm</th>
<th>NNH</th>
<th>Rx Threshold</th>
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<tr>
<td><strong>Antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetirizine</td>
<td>0.112</td>
<td>8.9</td>
<td>0.030</td>
<td>33.3</td>
<td>21%</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>0.066</td>
<td>15.2</td>
<td>0.013</td>
<td>76.9</td>
<td>16%</td>
</tr>
<tr>
<td>Desloratadine</td>
<td>0.056</td>
<td>17.9</td>
<td>0.021</td>
<td>48.0</td>
<td>27%</td>
</tr>
<tr>
<td>Loratadine</td>
<td>0.029</td>
<td>34.5</td>
<td>0.015</td>
<td>66.7</td>
<td>34%</td>
</tr>
<tr>
<td>Class Mean</td>
<td>0.066</td>
<td>15.2</td>
<td>0.020</td>
<td>50.7</td>
<td>23%</td>
</tr>
<tr>
<td><strong>Nasal Sprays</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>0.211</td>
<td>4.7</td>
<td>0.019</td>
<td>52.6</td>
<td>8%</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>0.168</td>
<td>6.0</td>
<td>0.015</td>
<td>66.7</td>
<td>8%</td>
</tr>
<tr>
<td>Budesonide</td>
<td>0.207</td>
<td>4.8</td>
<td>0.030</td>
<td>33.3</td>
<td>13%</td>
</tr>
<tr>
<td>Mometasone</td>
<td>0.330</td>
<td>3.0</td>
<td>0.019</td>
<td>52.6</td>
<td>5%</td>
</tr>
<tr>
<td>Class Mean</td>
<td>0.229</td>
<td>4.4</td>
<td>0.021</td>
<td>48.2</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Nasal Antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azalastine Qday</td>
<td>0.160</td>
<td>6.3</td>
<td>0.031</td>
<td>32.3</td>
<td>16%</td>
</tr>
<tr>
<td>Azalastine BID</td>
<td>0.200</td>
<td>5.0</td>
<td>0.046</td>
<td>21.7</td>
<td>19%</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monteleukast</td>
<td>0.070</td>
<td>14.3</td>
<td>0.006</td>
<td>166.7</td>
<td>8%</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>0.081</td>
<td>12.3</td>
<td>0.080</td>
<td>12.5</td>
<td>50%</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>0.218</td>
<td>4.6</td>
<td>0.072</td>
<td>13.9</td>
<td>25%</td>
</tr>
</tbody>
</table>

Portnoy J, VanOsdoi T, Williams PB. *Current Allergy and Asthma Reports.* 2004; 4: 439-46
Immuntherapie gegen Allergien hilft am besten
Tabletten ersetzen die Injektionsbehandlung

DÜSSELDORF. Das Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Iqwig) hat die neuesten unabhängigen Forschungsarbeiten zu Allergien analysiert, um herauszufinden, welche Therapien oder vorbeugenden Maßnahmen tatsächlich wirken. Das Ergebnis: Die spezifische Immuntherapie gegen allergische Beschwerden kann vielen Menschen helfen.

Bei dieser auch Hyposensibilisierung genannten Behandlung wird der Wirkstoff, ein Allergenextrakt, als Spritze unter die Haut oder in Form von Tropfen, Tabletten oder Spray unter die Zunge (sublingual) gegeben. Die Therapie wird immer häufiger eingesetzt: Der Arzneiverordnungs-Report 2007 zeigt, dass mehr als ein Dutzend dieser Extrakte mittlerweile zu den 3 000 Medikamenten zählen, die in Deutschland am häufigsten verschrieben werden. Gleichzeitig ist der Einsatz von so genannten Antihistaminika in den letzten Jahren zurückgegangen. Diese können Allergiesymptome zwar lindern, haben häufig aber unerwünschte Wirkungen.

„Besonders die sublinguale Immuntherapie wird in Europa immer beliebter“, sagt der Leiter des Iqwig, Peter Sawicki. Die Forschung habe gezeigt, dass sie bestimmte allergische Reaktionen bei Erwachsenen verringern kann und weniger unerwünschte Wirkungen auslöst als die Injektionsbehandlung. „Wir sind noch nicht völlig sicher, ob die Therapie genau so wirksam ist wie die Behandlung mit Spritzen, und ob sie auch bei Kindern wirkt“, so Sawicki. Studien, die diese Fragen derzeit untersuchen, könnten aber bald Antworten liefern.
SIT vs symptomatic drugs
Efficacy of symptomatic drugs in rhinitis
(improvement vs placebo)

Source: Wilson study quoted by S. Duham (JACI 2006)
The immune privilege of the oral mucosa

Natalija Novak¹, Jörg Haberstok², Thomas Bieber¹ and Jean-Pierre Allam¹

¹Department of Dermatology and Allergy, University of Bonn, Sigmund-Freud-Str. 25, 53105 Bonn, Germany
²Division of Cranio-Maxillofacial Surgery, University Hospital Basel, Spitalstr. 21, 4031 Basel, Switzerland
Sublingual immunotherapy with once-daily grass allergen tablets: A randomized controlled trial in seasonal allergic rhinoconjunctivitis

Stephen R. Durham, MD, a William H. Yang, MD, b Martin R. Pedersen, MS-Pharm, c Niels Johansen, MS-Chef Eng, d and Sabina Rak, MD d London, United Kingdom, Ottawa, Ontario, Canada, Horsholm, Denmark, and Gothenburg, Sweden

Background: Specific immunotherapy is the only treatment modality that has the potential to alter the natural course of allergic diseases. Sublingual immunotherapy has been developed to facilitate access to this form of treatment and to minimize serious adverse events.

Objective: To investigate the efficacy and safety of sublingual grass allergen tablets in seasonal allergic rhinoconjunctivitis.

Methods: A multinational, multicenter, randomized, placebo-controlled trial conducted during 2002 and 2003. Fifty-five centers in 8 countries included 825 participants age 18 to 65 years who gave a history of grass pollen–induced allergic rhinoconjunctivitis and had a positive skin prick test and elevated serum allergen-specific IgE to Phleum pratense. Participants were randomized to 2500, 25,000, or 75,000 SQ-T grass allergen tablets (GRAZAX; ALK-Abelló, Horsholm, Denmark) or placebo for sublingual administration once daily. Mean duration of treatment was 18 weeks.

Results: Average rhinoconjunctivitis scores during the season showed moderate reductions of symptoms (16%) and medication use (28%) for the grass allergen tablet 75,000 SQ-T (P = .0710; P = .0470) compared with placebo. Significantly better rhinoconjunctivitis quality of life scores (P = .006) and an increased number of well days (P = .041) were also observed. Efficacy was increased in the subgroup of patients who completed the recommended preseasonal treatment of at least 8 weeks before the grass pollen season (symptoms, 21%; P = .0020; and medication use, 29%, P = .0120). No safety concerns were observed.

Conclusion: This study confirms dose-dependent efficacy of the grass allergen tablet. Although further studies are required, the greater tolerability of the tablet may permit immunotherapy to be available to a much broader group of patients with impaired quality of life caused by grass pollen allergy.

Clinical implications: For patients with grass pollen allergy, sublingual immunotherapy is well tolerated and can reduce symptoms and improve quality of life. (J Allergy Clin Immunol 2006;117:802-9.)

Key words: Specific immunotherapy, sublingual immunotherapy, grass allergen tablets

Allergic rhinoconjunctivitis represents a global health problem. A recent community-based survey in 6 countries in Western Europe revealed an average prevalence of 23% (range, 17% to 29%). Allergy to grass pollen is one of the most common inhalant allergies leading to impaired quality of life and increased expenditures in the healthcare system. The current recommended treatment for allergic rhinitis is the use of topical nasal corticosteroids and antihistamines. However, these measures have been shown to be at best only partially effective in more than 40% of patients with hay fever evaluated in a general practice setting. In patients who fail to respond to these measures, controlled trials have documented the
Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis

Ronald Dahl, MD, a Alexander Kapp, MD, b Giselda Colombo, MD, c Jan G. R. de Monchy, MD, d Sabina Rak, MD, e Waltraud Emminger, MD, f Montserrat Fernández Rivas, MD, g Mette Ribel, MSc, h and Stephen R. Durham, MD Aarhus and Hørsholm, Denmark, Hannover, Germany, Milan, Italy, Groningen, The Netherlands, Gothenburg, Sweden, Vienna, Austria, Madrid, Spain, and London, United Kingdom

Background: Allergen immunotherapy (desensitization) by injection is effective for seasonal allergic rhinitis and has been shown to induce long-term disease remission. The sublingual route also has potential, although definitive evidence from large randomized controlled trials has been lacking.

Objective: The aim was to confirm the efficacy of a rapidly dissolving grass allergen tablet (GRAZAX, ALK-Abelló, Hørsholm, Denmark) compared with placebo in patients with seasonal rhinoconjunctivitis.

Methods: A longitudinal, double-blind, placebo-controlled, parallel-group study that included 51 centers from 8 countries. Subjects were randomized (1:1) to receive a grass allergen tablet or placebo once daily. A total of 634 subjects with a history of grass pollen–induced rhinoconjunctivitis for at least 2 years and confirmation of IgE sensitivity (positive skin prick test and serum-specific IgE) were included in the study.

Subjects commenced treatment at least 16 weeks before the grass pollen season, and treatment was continued throughout the entire season.

Results: The primary efficacy analysis showed a reduction of 30% in rhinoconjunctivitis symptom score (P < .0001) and a reduction of 38% in rhinoconjunctivitis medication score (P < .0001) compared with placebo. Side effects mainly comprised mild itching and swelling in the mouth that was in general well tolerated and led to treatment withdrawal in less than 4% of participants. There were no serious local side effects and no severe systemic adverse events.

Conclusion: Sublingual immunotherapy with grass allergen tablets was effective in grass pollen–induced rhinoconjunctivitis. The tablet was well tolerated with minor local side effects.

Clinical implications: The grass allergen tablet represents a safe alternative to injection immunotherapy suitable for home use. (J Allergy Clin Immunol 2006;118:434-40.)
Rhinitis, sinusitis, and ocular diseases

Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis

Alain Didier, MD, a Hans-Jörgen Malling, MD, b Margitta Worm, MD, c Friedrich Horak, MD, d Siegfried Jäger, PhD, e Armelle Montagut, PhD, f Claude André, MD, g Olivier de Beaumont, MD, g and Michel Melac, MD g Toulouse, Meylan, and Antony, France, Copenhagen, Denmark, Berlin, Germany, and Vienna, Austria

Background: Sublingual immunotherapy is well tolerated and data suggest its effectiveness for the treatment of allergic rhinitis in adults, but it lacks optimum dose definition.

Objective: To assess the efficacy, safety, and optimal dose of grass pollen tablets for immunotherapy of patients with allergic rhinoconjunctivitis.

Methods: In this multinational, randomized, double-blind, placebo-controlled study, 628 adults with grass pollen rhinoconjunctivitis (confirmed by positive skin prick test and serum-specific IgE) received 1 of 3 doses of a standardized 5-grass pollen extract, or placebo, administered sublingually using a once-daily tablet formulation. The treatment was initiated 4 months before the estimated pollen season and continued throughout the season. The primary outcome was Rhinoconjunctivitis Total Symptom Score; secondary outcomes included 6 individual symptom scores, rescue medication use, quality of life, and safety assessments.

Results: Both the 300-index of reactivity (IR) and 500-IR doses significantly reduced mean Rhinoconjunctivitis Total Symptom Score (3.58 ± 3.0, P = .0001; and 3.74 ± 3.1, P = .0006, respectively) compared with placebo (4.93 ± 3.2) in the intent-to-treat and per-protocol analyses. The 100-IR group (4.70 ± 3.1) score was not significantly different from placebo. Analysis of all secondary efficacy variables (sneezing, runny nose, itchy nose, nasal congestion, watery eyes, itchy eyes, rescue medication usage, and quality of life) confirmed the efficacy of the 300-IR and 500-IR doses. No serious side effects were reported.

Conclusion: In the first pollen season, the efficacy and safety of sublingual immunotherapy with grass tablets was confirmed. The 300-IR and 500-IR doses both demonstrated significant efficacy compared with placebo.

Clinical implications: The risk-benefit ratio favors the use of 300-IR tablets for clinical practice. (J Allergy Clin Immunol 2007;120:1338-45.)

Key words: Sublingual immunotherapy, grass pollen tablet, grass pollen allergy, allergic rhinoconjunctivitis, allergen, randomized, double-blind, placebo-controlled trial, dose response
Sublingual immunotherapy in pollen-induced seasonal rhinitis and conjunctivitis: a randomized controlled trial

R. Mösges, H. Brüning, H.-J. Hessler, G. Gerhardt, H.-G. Knaussmann, and study group

ABSTRACT

Background: Sublingual immunotherapy (SLIT) is a recognized and safe treatment for allergic rhinitis and conjunctivitis. The aim was to evaluate the efficacy and safety of tablets for grass and rye pollen-induced rhinitis and conjunctivitis.

Methods: A double-blind, randomized, placebo-controlled trial was carried out over 9 months. 105 patients received a standardized grass/rye mix extract or a placebo using sublingual drops during the build-up phase. Drops were replaced by sublingual tablets during the maintenance phase (300 IR/daily).

Results: In patients that received active treatment, a significantly lower total symptom score (rhinitis and conjunctivitis) compared to the placebo group was observed (p = 0.038). The investigators’ assessment revealed a significant improvement in favor of the active treatment group (p = 0.018). Skin reactivity to grass and rye pollen was significantly reduced in the active treatment group (p < 0.05). No statistical difference was observed between the two groups for serum-specific IgG4 levels. Side effects were local and mild, and no severe systemic reactions were reported.

Conclusion: This study indicates that tablet-based sublingual immunotherapy was safe and significantly improved grass/rye pollen-induced rhinoconjunctivitis symptoms. It was also associated with a significant inhibition of the immediate skin response.


4. Mösges et al.: Eigene Auswertung
<table>
<thead>
<tr>
<th>TABLE V. Summary of treatment-emergent adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment group</strong></td>
</tr>
<tr>
<td>Grass allergen tablet</td>
</tr>
<tr>
<td>N (%)</td>
</tr>
<tr>
<td>No. of subjects</td>
</tr>
<tr>
<td>All adverse events</td>
</tr>
<tr>
<td>Causality</td>
</tr>
<tr>
<td>Probable related</td>
</tr>
<tr>
<td>Possible related</td>
</tr>
<tr>
<td>Unlikely related</td>
</tr>
<tr>
<td>Severity</td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe*</td>
</tr>
</tbody>
</table>

*N. Number of subjects; E, number of events.
*Ten of the severe events were assessed by the investigator to be treatment-related. Because of the continuous blinding of the study, it is unknown whether they received active treatment. The severe related events were 2 oral pruritus, 4 edema mouth, 1 fatigue, 1 pharyngeal edema, 1 oral discomfort, and 1 nausea.

<table>
<thead>
<tr>
<th>TABLE VI. Treatment-emergent adverse events reported by ≥5% of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment group</strong></td>
</tr>
<tr>
<td>Grass allergen tablet</td>
</tr>
<tr>
<td>N (%)</td>
</tr>
<tr>
<td>No. of subjects</td>
</tr>
<tr>
<td>Oral pruritus</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>Edema mouth</td>
</tr>
<tr>
<td>Influenza</td>
</tr>
<tr>
<td>Ear pruritus</td>
</tr>
<tr>
<td>Throat irritation</td>
</tr>
<tr>
<td>Headache</td>
</tr>
</tbody>
</table>

improvements in favor of the active treatment for all endpoints tested. The grass allergen tablet resulted in a 30% decrease in sinonasal and mild symptoms in the face of an additional 38% reduction in the use of reliever medication (antihistamines and intranasal corticosteroid).
Most frequent related adverse events (AE)
Incidence of at least 5 % (safety population)

• No serious AE were related to treatment
Original article

Distribution of Langerhans cells and mast cells within the human oral mucosa: new application sites of allergens in sublingual immunotherapy?

Background: Sublingual immunotherapy (SLIT) represents an alternative to subcutaneous immunotherapy. While antigen-presenting cells such as Langerhans cells (LCs) are thought to contribute to the effectiveness of SLIT, mast cells (MCs) most likely account for adverse reactions such as sublingual edema. As little is known about LCs and MCs within the oral cavity, we investigated their distribution in search for mucosal sites with highest LCs and lowest MCs density.

Methods: Biopsies were taken simultaneously from human vestibulum, bucca, palatum, lingua, sublingua, gingiva, and skin. Immunohistochemistry and flow cytometry were used to detect MCs, LCs and high affinity receptor for IgE (FcεRI) expression of LCs. Mixed lymphocyte reactions were performed to assess their stimulatory capacity.

Results: Highest density of MCs was detected within the gingiva, while the lowest density of MCs was found within the palatum and lingua. However, sublingual MCs were located within glands, which might explain swelling of sublingual caruncle in some SLIT patients. Highest density of LCs was detected within the vestibular region with lowest density in sublingual region. Highest expression of FcεRI was detected on LCs within the vestibulum. Furthermore LCs from different regions displayed similar stimulatory capacity towards allogeneic T cells.

Conclusions: In view of our data, different mucosal regions such as the vestibulum might represent alternative SLIT application sites with potent allergen uptake. Our data might serve as a basis for new application strategies for SLIT to enhance efficiency and reduce local adverse reactions.
Figure 7. Cell suspension was obtained by oral mucosal tissue trypsinization. OLC were detected by CD1a expression. Dead cells were gated out manually by 7AAD staining. FcεRI is depicted on y-axis as percent of positive CD1a cells ± SD ($n = 6$). Histograms show one representative sample of FcεRI (numbers in upper right of each histogram represent % ± SD of $n = 6$). The highest FcεRI expression could be detected on oLC from the vestibulum.
Merkblatt

Durchbruch in der Allergie-Behandlung ! ?

Der Zürcher Dermatologe und Forscher Thomas Kündig (40) hat eine neuartige Impfmethode entwickelt, welche die Behandlung von Heuschnupfen und anderen Allergien revolutionieren könnte.
Intra-lymphnodal-IT

- Randomized controlled study
- n=154
- 3 injections à 1000 SQ
  as efficient as
- 3 years with injections of 4,000,000 SQ
- Less side effects
Figure 1. Inductive and effector sites in the oral mucosa versus the gut mucosa. (a) Because classical mucosa-associated lymphoid tissue (MALT), defined as the inductive site of the immune response, is absent from the oral mucosa, it has been hypothesized that dendritic cells (DCs) in the epithelium take up antigens (represented by light blue triangles), mature partially and migrate to the basal lamina, where they present the antigens to the oral lymphoid follicle to T cells to directly induce an effector response (i). DCs migrate to regional lymphoid organs such as tonsils to prime naïve T cells and to induce effector immune responses (ii). (b) By contrast, gut mucosal inductive sites for T and B cells are comprised of MALT with B cell follicles and M cell-containing lymphoid epithelium, which pass the uptake antigens to antigen presenting cells including DCs, macrophages, B cells and follicular dendritic cells. As in the oral mucosa, DCs migrate to regional lymphoid tissue to prime naïve T cells and induce effector immune responses. Memory B and T cells migrate by way of the blood to effector sites in the gut. The distribution of v, v, CD4 and CD8 positive T lymphocytes is depicted, as well as differentiation of B cells into IgA and IgM producing plasma cells. In addition, soluble IgA is generated. Abbreviations: B, B cell; DC, dendritic cell; FDC, follicular dendritic cell; HSP, heat shock protein; IgA, immunoglobulin A; MC, macrophage; P, plasma cell; T, T cell; Th1, T helper cell 1; Tr, T reg.
10 points to remember

1. Allergic rhinitis is a major chronic respiratory disease due to its:
   - prevalence
   - impact on quality of life
   - impact on work/school performance and productivity
   - economic burden
   - links with asthma

2. In addition, allergic rhinitis is associated with sinusitis and other co-morbidities such as conjunctivitis

3. Allergic rhinitis should be considered as a risk factor for asthma along with other known risk factors

4. A new subdivision of allergic rhinitis has been proposed:
   - Intermittent – persistent

5. The severity of allergic rhinitis has been classified as mild or moderate/severe depending on the severity of symptoms and quality of life outcomes
10 points to remember

6. Depending on the subdivision and severity of allergic rhinitis, a stepwise therapeutic approach has been proposed.

7. The treatment of allergic rhinitis combines:
   - Allergen avoidance (when possible)
   - Pharmacotherapy
   - Immunotherapy
   - Education

8. Patients with persistent allergic rhinitis should be evaluated for asthma by history, chest examination and, if possible and when necessary, the assessment of airflow obstruction before and after bronchodilator.

9. Patients with asthma should be appropriately evaluated (history and physical examination) for rhinitis.

10. A combined strategy should ideally be used to treat the upper and lower airway diseases in terms of efficacy and safety.
5 points to remember

• Think of allergy in sinusitis patients
• Longer treatment duration
• Continuous treatment
• Avoid combinations, they reduce patients’ compliance
• Use potent compounds
KISS – Keep It Simple & Small
Allergic Rhinitis
Update 2008

Ralph@Moesges.de

Prof. Ralph Mösges
Otorhinolaryngologist and Allergologist
University Hospital of Cologne